PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MD DEGREE IN INTERNAL MEDICINE

Title of the Protocol: Effect of Tight Glycemic Control on Microvascular Complications in Type 2 Diabetes Mellitus: A Randomized Controlled Trial in an Egyptian Cohort
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Postgraduate Student: Ola Mohamed Mostafa Shaheen
Degree: Master of internal medicine- Faculty of Medicine – Ain Shams University

DIRECTOR: Dr. Manal Mohamed Abu Shady
Academic Position: Professor
Department: Internal Medicine, Endocrinology Department – Ain Shams University

Co-DIRECTOR: Dr. Mona Mohamed Abdelsalam
Academic Position: Professor
Department: Internal Medicine, Endocrinology Department – Ain Shams University

Co-DIRECTOR: Dr. Meram Mohamed Bekhet
Academic Position: Assistant Professor
Department: Internal Medicine, Endocrinology Department – Ain Shams University

Co-DIRECTOR: Dr. Salah Hussein Elhalawany
Academic Position: Lecturer
Department: Internal Medicine, Endocrinology Department – Ain Shams University

Co-DIRECTOR: Dr. Hany Khairy Mansour
Academic Position: Lecturer
Department: Internal Medicine, Endocrinology Department – Ain Shams University

Faculty of Medicine
Ain Shams University
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What is already known on this subject? AND

What does this study add?

Near normalization of blood glucose levels has been known to reduce the long-term risk of diabetic retinopathy. However, transient worsening of preexisting retinopathy has also been demonstrated when glucose control is intensified (**Bethel A. et *al.*, 2021).**

The pathophysiology of this phenomenon is not well understood. Furthermore, the circumstances under which it appears remain to be not fully elucidated. Since its discovery, early worsening has been described in patients with type 1 and type 2 diabetes, including those undergoing various diabetic therapies, those who have undergone bariatric surgery, and pregnant women (**Feldman-Billard *et al.*, 2018**).

Hence, this study will assessthe relationship between the glycemic control in patients with diabetes mellitus and the contemporary statements on the value of tight glycemic control, when compared with less tight control with regard to microvascular outcomes including diabetic retinopathy, nephropathy and neuropathy.

1.INTRODUCTION/ REVIEW

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia due to either insulin deficiency or resistance or both **(Goyal&Jialal 2021).** Hyperglycemia induces tissue damage through mitochondrial superoxide production, affecting retina, glomerulus, and neurons. It requires continuing medical care and ongoing self-care management to prevent and delay acute and long-term micro and macrovascular complications (**Fasil A *et al.*, 2019)**.

Chronic diabetes complications like retinopathy, nephropathy, neuropathy, self-reported chest pain, vision decrement, painful paresthesia, and psychiatric

events result in decrement of health-related quality of life (**Jacobson *et al.*, 2013)**.

Diabetic retinopathy (DR) is the most common microvascular complication of DM and is a leading cause of blindness in the working age population worldwide (**Leasher*et al.*, 2016**). It is a progressive sight-threatening eye disease caused by hyperglycemia, which damages the retinal microvasculature leading to vascular permeability, retinal ischemia, neovascularization, retinal detachment, and blindness (**Augustine *et al.*, 2020**).

After the DCCT (Diabetes Control and Complications Trial) found that tight glycemic control (a glycohemoglobin A1c (HbA1c) <7%) could prevent or slow the progression of nephropathy, retinopathy, and neuropathy in patients with diabetes mellitus, a consensus, extended to patients with type 1 and type 2 diabetes mellitus, emerged: normalizing glycemia prevents diabetes mellitus complications (**Garber *et al.*, 2013**). Guidelines, quality improvement interventions, quality-of-care measures and patient-directed marketing have since focused on achieving tight glycemic control. (**Rodriguez &Montori2016**).

Appropriate glycemic control and management is fundamental to prevent and delay DM complications. Poor glycemic control is highly correlated with high burden of diabetes complications. However, data are scanty regarding factors for poor glycemic control and the relationship between glycemic control and DM complications (**Fasil A *et al.*, 2019)**.

2.AIM / OBJECTIVES

This randomized controlled study will examine the relation between tight glycemic control and microvascular complications of Diabetes in comparison with patients with good (less tight) glycemic control.

Research question: Does tight glycemic control worsens microvascular complications of Diabetes?

3.METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods

- **Type of Study:**

Randomized controlled trial.

- **Study Setting:**

The study will be conducted at Ain Shams University Hospitals "outpatient diabetes clinic and inpatient department."

- **Study duration:**

This study will be conducted during the period from May 2022 to October 2023

- **Labs (see later), thorough clinical examination with special emphasis on microvascular complications (neurological and Fundus examination) will be done for every patient at time of recruitment and 6 months following glycemic control.**

- **Study Population:**

  - 80subjects with uncontrolled Diabetes Mellitus with HbA1c 8% or above all will receive standard medical care (nutritional therapy and pharmacological therapy) and will be divided into two groups:

    (a) Group (A) will undergo tight glycemic control (HbA1c <7%) done by nutritional education and medication adjustment.

    (b) Group (B)will undergo conventional glycemic control (HbA1c <7.5 %).

Subjects will be collected from patients with Diabetes Mellitus referred to Ain Shams University Hospitals for evaluation with the following criteria:

- **Inclusion criteria:**

1. Both sexes.
2. Age 18-60years old.
3. Patients diagnosed with Diabetes Mellitus (Type 2) according to ADA guidelines.
4. Patients willing to participate after signing a written consent to be enrolled in the study after being explained to them in an interview.
5. Diabetic patients with mild and moderate non proliferative diabetic retinopathy

Exclusion criteria:

1. Patients with age above 60 or below 18 years old.
2. Patients with severe non proliferative diabetic retinopathy up to advanced proliferative diabetic retinopathy.
3. Patients diagnosed with type 1 DM.
4. Patients with malignant tumors.
5. Patients with end stage renal disease and end stage liver disease.
6. Patients with history of myocardial infarction.
7. Patients with recurrent attacks of hypoglycemia and hypoglycemia unawareness.

Sampling Method:

Purposive sampling

Sample Size:

The study will be conducted on 80subjects.

Ethical and Safety Consideration:

This study will be done after approval of the Ethical Committee of the Department of Internal Medicine, Faculty of Medicine, Ain Shams University. Informed consent will be taken from all participants before recruitment in the study, and after explaining the purpose and procedures of the study. The investigator will retain the original signed informed consent form. All data will be collected confidentially. The study will be based on the investigator self-funding.

Study procedures and interventions:

1. After approval of study protocol, patients will be enrolled into the study according to inclusion and exclusion criteria.
2. All participants will sign written informed consent that is approved by the local ethics committee.
3. All patients will be subjected to:
   - **Detailed history taking of the patient medical condition.**
   - **Anthropometric and blood pressure measurements:**
     - ✓ Weight and height of all patients will be measured using a calibrated scale. Body mass index (BMI) will be calculated by dividing weight in kilograms by height in meters squared.

- ✓ Blood pressure will be measured in both standing and seated position after a 5-min rest using an aneroid sphygmomanometer and stethoscope.
- ✓ Basal heart rate measurement

➢ **Biochemical assays:**

- ✓ Laboratory measurements will include:
  - ❖ Fasting, 2 hour post prandial glucose levels and HbA1C.
  - ❖ Kidney function tests including serum urea and creatinine.
  - ❖ Albumin/creatinine ratio.
  - ❖ Estimated GFR calculation using MDRD 4 variable equation.
  - ❖ Complete blood count.

➢ **Fundus examination using Optomed aurora portable fundoscopy.**

➢ **Neurological assessment usingDN4 (Douleur Neuropathique 4 questions).**

- **Labs, neurological and Fundus examination will be done at time of recruitment and 6 months following glycemic control.**
- **Outcomes:**

Effect of tight glycemic control on microvascular complications of Diabetes.

- **Statistical analysis:**

To summarize characteristics of study patients based on TyG quartiles, one-way analysis of variance (ANOVA) and chi-square (c2) tests will be used, where appropriate. To determine the association of liver fibrosis with TyG, multivariable-adjusted odds ratios (ORs) will be applied. Two-sided significance at $P < 0.05$ will be significant.

Statistical Package:

Data will be analyzed with the use of IBM SPSS Statistics.

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