4. AIM AND OBJECTIVES

**AIM:**

To find out the role of anti-diabetic medications on cognitive functions and quality of life in patients with type 2 diabetes mellitus.

**OBJECTIVES:**

- To assess the role of antidiabetic medications on cognitive functions in T2DM patients with and/or without Hypertension and Dyslipidemia
- To assess the role of antidiabetic medications on quality of life in T2DM patients with and/or without Hypertension and Dyslipidemia
- To estimate the prevalence of cognitive impairment in T2DM patients and different factors associated with it.
- To find out the association between Cognitive functions and Quality of life
5. PLAN OF STUDY

The current study discusses the influence of antidiabetic therapy on cognitive functions and quality of life of type-2 diabetes patients associated with hypertension and/or dyslipidemia. The comparative efficacy of Glitins monotherapy and combination with other antidiabetic medication used in the treatment of type-2 diabetes in relation to their cognitive function and quality of life with glycemic and lipid profile will also be revealed. In our study population the prevalence of cognitive impairment and different factors associated with it will be investigated and finally the association between Cognitive functions and Quality of life will be studied.

Plan of study

The following procedures will be completed before enrolling the patients for the study

- Designing the protocol and the number of subjects required for the study will be analyzed by applying power calculation
- Getting the approval from the ethical committee.
- Written informed consent form will be collected from the study subjects prior to enrollment
- Enrolling the patients based on the study criteria
- Cognitive Functions Assessment will be carried out by administering Mini Mental State Examination. The quality of life of the subjects will be assessed by using SF12V2 test.

The study is carried out in the following phases

- The socio demographic details include age, gender, education, physical exercise and food habits, patient medical history like duration of T2DM, comorbidities such as hypertension and dyslipidemia and treatment received for diabetes is recorded
- Administering the Folstein’s Mini Mental State Examination and Short form health survey version 2 (SF12V2) questionnaire
- Certain laboratory tests such as fasting blood glucose, post prandial blood glucose, HbA1c, total cholesterol, HDL, LDL and triglyceride levels will be collected to assess biochemical, metabolic and glycemic status of the patients.
- Statistical analysis to compare the effect of antidiabetic drugs on cognition and quality of life using one way-ANOVA followed by Tukey post-hoc analysis will be evaluated. The association between independent variables and dependent variables will be tested using Chi-square test. Pearson’s approach will be used for correlation estimation.
Study site:

The study will be conducted in Kovai Diabetes Specialty Centre and Hospital, Coimbatore, Tamilnadu. It provides standard diabetic care and has well established out patients ward with a visit of 100 patients per day.

Study design:

It is a cross sectional, observational study on patients who are under anti-diabetic therapy associated with and/or without co-morbidities (hypertension and dyslipidemia).

Study duration:

The study will be carried out for 13 months June 2016 to June 2017.

Study subjects:

Approximately 500 study subjects in the age above 18 years fulfilling the patient recruitment criteria will be enrolled. The patients will be recruited according to the following Inclusion and Exclusion criteria.

Inclusion criteria:

- Male and Female patients above 18 years of age
- Known Type 2 Diabetes Mellitus associated with and without Hypertension and Dyslipidemia
- Patients who are taking the study drugs
- Patients who are able to give written informed consent form for study participation

Exclusion criteria:

- Subjects with Type 1 Diabetes Mellitus and other types of Diabetes
- Pregnancy and lactating women
- Patients with known hepatic and renal impairment and cerebrovascular accidents
- Patients under treatment with psychoactive/depressant drugs (anti-cholinergic, narcotics, antidepressants, benzodiazepines or major tranquilizers)
- History of pancreatitis
- Blindness, hearing impairment.
- Illiterate
Study drugs:

Anti diabetic drugs taken as monotherapy or in combination therapy

- Biguanides: Metformin.
- Sulphonylureas: Glimepiride, Gliclazide
- DPP4 Inhibitors: Sitagliptin, Saxagliptin, Linagliptin, Vildagliptin, Teneligliptin.
- Alfa-glucosidase Inhibitors: Acarbose, Voglibose.
- Insulin

Dosage: As directed by physician

Assessment of Cognition:

The Mini Mental State Examination which assesses orientation, registration attention and calculation, language and recall with a score range of 0-30 will be administered to evaluate the mental status. It takes only 5-10 minutes to administer. This test was introduced as a standard measure of global cognitive function to be used for both research and clinical purposes.

Assessment of Quality of life:

Quality of life will be assessed by twelve item short form health survey version 2 (SF-12v2) licensed by Optum. The Optum SF-12v2 Health Survey is a shorter version of the SF-36v2 Health Survey that uses just 12 questions to measure functional health and well-being from the patient’s point of view. It takes only two to three minutes to complete, the SF-12v2 is a practical, reliable and valid measure of physical and mental health and is particularly useful in large population health surveys or for applications that combine a generic and disease-specific health survey. Available in multiple language translations, the SF-12v2 covers the eight health domains scales contributing to Physical health [Physical Component Summary (PCS)] Physical Functioning, Role Physical, Bodily Pain, General Health and the scales contributing to Mental health [Mental Component Summary (MCS)] Social Functioning, Role Emotional, Vitality and Mental Health. It is a widely used tool for monitoring population health, comparing and analyzing disease burden and predicting medical expenses.

Type 2 Diabetes Mellitus Patient Selection:

Type-2 diabetes ascertained using a combination of medical history, drug use, and fasting plasma glucose. Participants who met to American Diabetes Association Criteria for diagnosis of diabetes mellitus, Fasting plasma glucose (FPG) level≥126mg/dl (fasting is defined as no calorie intake for atleast 8hours), Post prandial blood glucose ≥200mg/dl or a random plasma glucose concentration 200mg/dl in the presence of symptoms and the diagnosis of
diabetes must be conformed on the subsequent day by measuring anyone of the three criteria were characterized as having diabetes.

**Hypertension:**

Hypertension defined as systolic blood pressure (sBP) ≥140mmHg and/or diastolic blood pressure (dBP) ≥ 90mmHg or patients under antihypertensive treatment.

**Dyslipidemia:**

Dyslipidemia defined as total cholesterol ≥200mg/dl and/or HDL ≤ 45mg/dl and/or LDL ≥ 100mg/dl and/or triglycerides ≥ 150mg/dl and/or use of statins or fibrates. Triglycerides, HDL-C and LDL-C and total cholesterol will be measured using an auto analyzer (Flexer Junior Machine) and this data will be obtained from the medical records.

**Statistics**

The data obtained will be analyzed with the statistical package for social sciences version 21 software (SPSS). The prevalence of cognitive impairment will be calculated in percentage. The qualitative data will be expressed as frequencies and percentages, while the quantitative data will be summarized as means and standard deviations. The association between independent variables and dependent variables will be tested using Chi-square test. Pearson’s approach will be used for correlation estimation. Comparison of treatment effects will be carried out using Student’s t-tests or one way-ANOVA followed by Tukey post-hoc analysis. All p values are two tailed and values of p < 0.05 will be considered as statistically significant.
PLAN OF THE WORK

From Earlier studies

Formulating the research question

Aim and objectives

Literature Review

Structuring the study
- Scope and Plan of work
- Methodology
- Study Protocol
- Data Collection Forms

Ethical Committee Approval
- Protocol submission to Institutional Review Board
- Protocol Revision (if any)
- Study Approval

Study Initiation
- Informed Consent Process
- Subject recruitment

Assessment of Cognitive Functions by Mini Mental State Examination (MMSE)

Assessment of Quality of Life by twelve item short form health survey version 2 (SF-12v2)

Statistical Analysis of Data

Results and Discussion

Thesis writing
Presentations
Publications

Basis for Future Work
6. MATERIALS AND METHODS

MATERIALS

1. Ethical committee approval (Annexure I)
2. Patients informed consent form - English (Annexure II)
3. Patients informed consent form – Tamil (Annexure III)
4. Patient data collection form (Annexure IV)
5. Folstein Mini Mental State Examination – English (Annexure V)
6. Folstein Mini Mental State Examination – Tamil (Annexure VI)
7. Short form health survey version 2 (SF-12v2) - English (Annexure VII)
8. Short form health survey version 2 (SF-12v2) - Tamil (Annexure VIII)
9. Patient Medical History

METHODS

Study Design:

This is a cross sectional observational study performed from June 2016 to June 2017. It was carried out in a group of 542 type 2 diabetes mellitus outpatients attended at the diabetic clinic of Kovai Diabetes Specialty Centre and Hospital, Coimbatore, TamilNadu. The study was reviewed and approved by Institutional Ethics Committee of Kovai Diabetes Specialty Centre and Hospital, Coimbatore, TamilNadu. (Ref: ECR/233/Inst/TN/2013)

Patient Recruitment:

Type 2 diabetes mellitus patients who are under anti diabetic therapy associated with or without comorbidities (hypertension and/or dyslipidemia) aged 18 years and above of both sexes male and female were enrolled for the study. After initial evaluation by the physician during their scheduled routine visits they were approached for possible enrollment based on inclusion and exclusion criteria.

Inclusion Criteria:

- Male and Female patients above 18 years of age
- Known Type 2 Diabetes Mellitus associated with and without Hypertension and Dyslipidemia
- Patients who are taking the study drugs
- Patients who are able to give written informed consent form for study participation
Methodology

Exclusion Criteria:

- Subjects with Type 1 Diabetes Mellitus and other types of Diabetes.
- Pregnancy and lactating women
- Patients with known hepatic and renal impairment and cerebrovascular accidents
- Patients under treatment with psychoactive/depressant drugs (anti-cholinergic, narcotics, antidepressants, benzodiazepines or major tranquilizers)
- History of pancreatitis
- Blindness, hearing impairment
- Illiterate

Study drugs:

Anti diabetic drugs taken as monotherapy or in combination therapy

- Biguanides: Metformin.
- Sulphonylureas: Glimepiride, Gliclazide
- DPP4 Inhibitors: Sitagliptin, Saxagliptin, Linagliptin, Vildagliptin, Teneligliptin.
- Alfa-glucosidase Inhibitors: Acarbose, Voglibose.
- Insulin

Dosage: As directed by physician

INFORMED CONSENT AND PATIENT DATA COLLECTION

- Each study subject received a description of the study and they were informed about the purpose of the study. A full informed written consent was obtained from all patients.
- The patients were interviewed in a community room in comfortable environment. All the information regarding socio-demographic details, present physical health status, diabetes mellitus history and other medical history were collected.
- Socio demographic characteristics such as age, gender, years of study, physical exercise, food habits, and medical history of hypertension, dyslipidemia, duration of diabetes and treatment of diabetes were assessed.
Methodology

- Blood pressure measurement was taken to know the current health status of the study patients.

- Height and Weight were measured to the nearest 0.1 cm and 0.1 Kg respectively. Body mass index (BMI) (Kg/m²) was calculated using these measurements. In the current study we used BMI as a measure of obesity which was categorized according to the National Institutes of Health Obesity standards as underweight BMI less than 18.5, normal weight BMI 18.5-24.99, overweight BMI 25.00-29.99 and obese BMI greater than 30.

- Physical exercise was self reported by the patients and was defined as if subject was doing atleast 30 minutes of aerobic exercise/ walk (that means walking a mile in 13 minutes or less), he or she was considered as physically active otherwise sedentary.

- The level of education of the patients was self reported during the demographic interview and classified for the purpose of the study as less than or equal to 5 years of education, 6-12 years of education and greater than 12 years of education.

- We reviewed the electronic medical records of the subjects for patient medical history which included duration of T2DM, co morbidities such as hypertension and dyslipidemia and treatment received for diabetes.

- Certain laboratory tests such as fasting blood glucose, post prandial blood glucose, HbA1c, total cholesterol, HDL, LDL and triglyceride levels were collected to assess glycemic and lipid levels of the patients.

Type 2 Diabetes Mellitus:

Type-2 diabetes ascertained using a combination of medical history, drug use, and fasting plasma glucose. Participants who met to American Diabetes Association Criteria for diagnosis of diabetes mellitus, Fasting plasma glucose (FPG) level≥126mg/dl) (fasing is defined as no calorie intake for atleast 8hours), Post prandial blood glucose ≥200mg/dl or a random plasma glucose concentration 200mg/dl in the presence of symptoms and the diagnosis of diabetes must be conformed on the subsequent day by measuring anyone of the three criteria were characterized as having diabetes.

Hypertension:

Hypertension was defined as systolic blood pressure (sBP) ≥140 mmHg and/or diastolic blood pressure (dBP) ≥ 90 mmHg or any value in patients under antihypertensive treatment.
Dyslipidemia:

Dyslipidemia was defined as total cholesterol ≥ 200 mg/dl and/or HDL < 40 mg/dl and/or LDL ≥ 100 mg/dl and/or triglycerides ≥ 150 mg/dl and/or use of statins or fibrates.

Assessment of Cognitive Function:

Cognitive function was assessed by applying standardized Mini-Mental State Examination (MMSE) of Folstein [208]. MMSE scale ranges from 0 to 30, with lower scores indicating increasing severity of cognitive impairments in the domains of orientation, memory, attention, and executive functions. The MMSE consists of 19 questions designed to assess the patient’s mental status in the following 5 categories: 10 orientations questions (year, season, month, date, day, city, country, state, hospital and floor); 2 memories items (repeat the words watch, car and pencil and after delayed recall); 1 calculation item; 5 language items (naming the objects pointing to watch, then a pencil, repeat 3 words ‘No ifs, ands, or buts’ (adapted to Tamil language as ‘இந்தது எந்தவும் இல்லாமல்’, 3 step-command, read and follow the sentence ‘close your eyes’ and write a sentence) and 1 constructional item (copy overlapping pentagon) (Annexure V, VI). The patient was addressed in a friendly manner to make them comfortable once it is arranged the MMSE scale was administered. It takes only 5-10 minutes to administer Scores of 24–30 considered as to have normal cognition, 18–23 mild cognitive impairment and 0–17 severe cognitive impairment.

Assessment of Quality Of Life:

There are many health survey questionnaires to analyze the quality of life, among them we have selected SF-12 version 2 health survey questionnaire after obtaining license from Optum.

The SF-12v2 is having 12 questions which are selected from the SF-36v2. It measures the generalized quality of life in diabetic patients and is not an age specific and disease specific and requires less time to administer. It has a good validity and considered as an alternative to SF-36 version 2. It summarizes the general, physical and mental status of individual patients. It has 12 items and 8 different scales which includes Physical Functioning, Role Physical, Bodily Pain, General Health, Social Functioning, Role Emotional, Vitality and Mental Health. It provides the answer by combining both physical and mental component questions. The scores range from 0-100 where 0 indicates poor quality of life above 50 is considered as clinically significant quality of life.
### SHORT FORM HEALTH SURVEY VERSION 2 (SF-12V2) MODEL

<table>
<thead>
<tr>
<th>Sl.No.</th>
<th>ITEMS</th>
<th>SCALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>Moderate activities</td>
<td>Scale 1: Physical function (PF)</td>
</tr>
<tr>
<td>2b</td>
<td>Climb several flights</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>Accomplished less</td>
<td>Scale 2: Role Physical (RP)</td>
</tr>
<tr>
<td>3b</td>
<td>Limited in kind</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Pain impact</td>
<td>Scale 3: Bodily Pain (BP)</td>
</tr>
<tr>
<td>1</td>
<td>Health in general</td>
<td>Scale 4: General Health (GH)</td>
</tr>
<tr>
<td>6b</td>
<td>Lot of energy</td>
<td>Scale 5: Vitality (VT)</td>
</tr>
<tr>
<td>7</td>
<td>Social impact</td>
<td>Scale 6: Social Function (SF)</td>
</tr>
<tr>
<td>4a</td>
<td>Accomplished less</td>
<td>Scale 7: Role Emotional (RE)</td>
</tr>
<tr>
<td>4b</td>
<td>Did work less careful</td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>Felt calm</td>
<td>Scale 8: Mental Health (MH)</td>
</tr>
<tr>
<td>6c</td>
<td>Felt downhearted</td>
<td></td>
</tr>
</tbody>
</table>

#### DIMENSIONS

- **PHYSICAL HEALTH**
- **MENTAL HEALTH**

---

**Methodology**
Statistical Analysis:

The data obtained were analyzed with the statistical package for social sciences version 21 software (SPSS). The prevalence of cognitive impairment was calculated in percentage. The qualitative data were expressed as frequencies and percentages, while the quantitative data were summarized as means and standard deviations. The association between independent variables and dependent variables was tested using Chi-square test. Pearson's approach was used for correlation estimation. Comparison of treatment effects was carried out using Student's t-tests or one way-ANOVA followed by Tukey post-hoc analysis. All p values were two tailed and a value of p < 0.05 was considered as statistically significant.