5. MATERIALS & METHODS

5.1 Materials

- Institutional Review Board Approval *(Annexure-I)*
- Patient informed consent form – English *(Annexure-II)*
- Patient informed consent form – Tamil version *(Annexure-III)*
- Patient data collection form and Follow up visit form *(Annexure-IV)*
- Structured interview guide for the Hamilton depression rating scale – English version *(Annexure-V)*
- Structured interview guide for the Hamilton depression rating scale – Tamil version *(Annexure-VI)*
- Patient Education Leaflet for Diabetes Mellitus in Tamil *(Annexure-VII)*
- Diet chart for Diabetes Mellitus in Tamil version *(Annexure-VIII)*
- Patient Information Leaflet on Diabetes Mellitus in English *(Annexure-IX)*
- Patient medical dairy
- Patient medication order/ prescription
5.2 Methodology

5.2.1 Ethical Consideration: The protocol of the study was approved by the ‘Institutional Review Board’ of JSS College of Pharmacy, Udhagamandalam. The study was conducted in compliance with the good clinical practice guidelines.

5.2.2 Study Design: Prospective open label study

5.2.3 Study Site: Government District Head Quarters Hospital, Ooty

5.2.4 Subjects: Type 2 diabetes mellitus patients

5.2.5 Sample size (n): 401

5.2.6 Study Duration: 3 years

5.2.7 Study Criteria:

➢ Inclusion Criteria:

❖ Male and female patients above 18 years of age

❖ Known Type 2 Diabetes Mellitus with or without co-morbidities

❖ Patients who are able to give written informed consent for study participation

❖ Patients who are taking the study drugs

➢ Exclusion Criteria:

❖ Contraindication to study drugs

❖ Pregnancy and lactating women

❖ Type 1 Diabetes mellitus and other type of Diabetes

❖ Patients with type 2 diabetes mellitus longer than 15 years duration

❖ Patient with known hepatic and renal impairment

❖ Patients with medications which can significantly affect the glycemic control
5.2.8 Study procedure

➢ Informed Consent

Study details were explained to the patients and written informed consent form was obtained.

➢ Patient Data Collection

Patients’ data including demographic, past medical and medication history, present medications, biochemical test results and other parameters were collected in a structured data collection form. The severity of depression was found out by administration of structured interview guide for Hamilton depression rating scale (SIGH D) in Tamil version. SIGH D is a 17 item interviewer – administered questionnaire in local language where scorings are done in five or three points scale. Out of 17-items, nine are scored on a five-point scale, ranging from zero to four. A score of zero represents an absence of the depressive symptom being measured, a score of one indicates doubt concerning the presence of the symptom, a score of two indicates mild symptoms, a score of three indicates moderate symptoms, and a score of four represents the presence of severe symptoms. The remaining eight items are scored on a three-point scale, from zero to two, with zero representing absence of symptom, one indicating doubt, and two representing clear presence of symptoms. For the 17-item version, scores can range from 0 to 54. Final scores between 0 and 6 indicate a normal person, scores between 7 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression.
5.2.9 Groups: The allocation of the patients according to their therapy was done as follows

<table>
<thead>
<tr>
<th>Groups</th>
<th>Medicament Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Subjects who received only MMC</td>
</tr>
<tr>
<td>Group II</td>
<td>Subjects who received only NKC</td>
</tr>
<tr>
<td>Group III</td>
<td>Subjects who received only Glibenclamide</td>
</tr>
<tr>
<td>Group IV</td>
<td>Subjects who received only Glimepiride</td>
</tr>
<tr>
<td>Group V</td>
<td>Subjects who received only Metformin</td>
</tr>
<tr>
<td>Group VI</td>
<td>Subjects who received MMC + Metformin</td>
</tr>
<tr>
<td>Group VII</td>
<td>Subjects who received MMC + Glibenclamide</td>
</tr>
<tr>
<td>Group VIII</td>
<td>Subjects who received MMC + Glimepiride</td>
</tr>
<tr>
<td>Group IX</td>
<td>Subjects who received NKC + Metformin</td>
</tr>
<tr>
<td>Group X</td>
<td>Subjects who received NKC + Glibenclamide</td>
</tr>
<tr>
<td>Group XI</td>
<td>Subjects who received NKC + Glimepiride</td>
</tr>
<tr>
<td>Group XII</td>
<td>Subjects who received Metformin + Glibenclamide</td>
</tr>
<tr>
<td>Group XIII</td>
<td>Subjects who received Metformin + Glimepiride</td>
</tr>
<tr>
<td>Group XIV</td>
<td>Subjects who received Metformin + Glibenclamide + MMC</td>
</tr>
<tr>
<td>Group XV</td>
<td>Subjects who received Metformin + Glimepiride + MMC</td>
</tr>
<tr>
<td>Group XVI</td>
<td>Subjects who received Metformin + Glibenclamide + NKC</td>
</tr>
<tr>
<td>Group XVII</td>
<td>Subjects who received Metformin + Glimepiride + NKC</td>
</tr>
</tbody>
</table>

Further the individuals in each groups are subgrouped (random allocation) into Pharmaceutical care and without pharmaceutical care using Quickcals (http://www.graphpad.com/quickcalcs/rand Menu/).
5.2.10 Monitoring Parameters

There were totally of twenty four follow up visits each separated by a gap of 7 days. During the follow up visits the patients are assessed for the following as per the frequency mentioned in brackets

1. Fasting blood glucose levels (once in 15 days)
2. Post prandial blood glucose levels (once in 15 days)
3. Random blood glucose levels (once in 7 days)
4. Dosage of the MMC, NKC, Metformin, Glibenclamide, Glimepiride
5. HbA1c (At baseline and week 12 for SM group)
6. Lipid Profiles (once in 15 days)
7. Blood pressure (once in 7 days)
8. Body Mass Index
9. Food Habits, Exercise (strictly monitored during the study period)
10. Adverse effects (eg. Hypoglycemia, weight gain etc)
11. Consumption of any other herbal / allopathic / OTC drugs
12. Problems in following diabetes care plan for the patients in pharmaceutical care intervention group
13. Review of the patient medical dairy
14. Counseling for patients in the pharmaceutical care group
5.2.11 Pharmaceutical Care

Patients in the pharmaceutical care group received diabetic medication counseling, printed educational material (Annexure VI) and instructions on dietary regulation (Annexure VII), advice on exercise and lifestyle modifications (Annexure VIII), while the patients under without pharmaceutical care group did not receive any counseling till the end of the study.

5.2.11.1 Diabetes knowledge counseling

The counseling points focused on and provided information about

- What is diabetes?
- Types of diabetes
- The risk factors for diabetes
- How to identify the Hypoglycemia and Hyperglycemia?
- What are the signs and symptoms of diabetes?
- Importance of controlling and managing diabetes
- Complications of diabetes

5.2.11.2 Diet Counseling

Dietary modification in addition to exercise and medication is essential for controlling and managing diabetes. Through dietary modifications, type 2 DM patients can also attain and maintain their ideal body weights. The modifications suggested to the patients included reducing the intake of fats, increasing the intake of high-fiber carbohydrates, reducing the intake of refined sugars and salts, restricting alcohol
consumption, spacing meals evenly (4-5 h apart), maintaining regular eating habits and eating fruits in moderate amounts (preferably raw and partially ripe fruits).

The patient education material and dietary chart was prepared in Tamil for the convenience of the patients. The dietary chart contains information on the list of food items on vegetables, fruits, dairy products, poultry etc in measured quantities that can be consumed by diabetic patients. The dietary chart also includes the time table for consumption of food with periodic timing at specific interval stating the type and amount of food that can be consumed.

5.2.11.3 Life style modification counseling

The study subjects belonging to pharmaceutical care group were advised to perform any one exercise regularly to improve blood sugar control, body weight control and to increase the sensitivity of insulin. Walking is one of the most convenient and easy exercises advised to start with. The patients were advised to go for a walk for 30- 45 min atleast three times a week.

5.2.11.4 Medication knowledge counseling

The patients were given following detailed counseling on medication and related aspects

- The names of the medication they consume for the diabetes
- When to take the medication i.e before or after meals?
- Route of administration
- Frequency of the administration
• Doses of the medication
• The time gap that should be maintained between medication and food
• How long the medications to be taken?
• The food or other medications that should be avoided while taking diabetic medicines.
• The adverse effects of the diabetic medications.
• In case of missed dose it should be taken immediately unless it is almost time to take the next dose and not to take the 2 doses at a time.
• Learning to recognize and manage hyperglycemia/hypoglycemia.
• All the study subjects were advised to keep sugar or sweet candy to consume immediately under hypoglycemic conditions, and were advised to always have someone with them who can detect symptoms of hypoglycemia.

5.2.11.5 Complications

The subjects were also given counseling about the complications that can arise due to persistent hyperglycemia. Diabetic retinopathy silently robs adults between the ages of 27 and 74 years of their sight making a leading cause of blindness. Uncontrolled diabetes can cause permanent damage to the eyes (retinopathy). In the intervention group, the subjects were advised to undergo scheduled yearly eye exams to ensure that diabetic eye diseases are detected before causing permanent loss of vision. Frequent blood pressure monitoring was advised to patients for the control of the blood pressure within normal limits and preventive measures such as avoiding smoking and alcoholism like risk factors were suggested to reduce the high blood pressure related
complications. The subjects in the intervention group were educated on protecting their feet to avoid gangrene and other foot infections. Patient education regarding foot hygiene, nail care and proper footwear was given to reduce the risk of an injury that can lead to ulcer formation. Risk factors and the symptoms for the diabetic foot were explained. The patients were advised to frequently check their feet with the help of doctor for the presence of foot ulcers. Diabetic nephropathy occurs in 20-40% of the patients with diabetes. Poor glycemic control and high blood pressure are the main risk factors for diabetic nephropathy. Patients were advised to control their blood sugar and blood pressure to avoid nephropathy. Patients usually will have the presence of proteins in the urine which is an indicative of the kidney damage. The patients were advised to take urine tests for the presence of microalbuminaria atleast once in 2 months.

5.2.11.6 General instructions to the patients

(a) Avoiding smoking and alcohol
(b) Understanding that therapy relieves symptoms but does not cure the disease
(c) Wearing or carrying medical identification regarding their diabetic status
(d) Avoiding other medications, including over-the-counter drugs, without medical approval.

The patients who are unable to follow the treatment, diabetes control and management plan were excluded from the study.
The subjects who were not under control for glucose levels with single / dual / triple therapy were selected and recruited (with their willingness) into stringent monitoring along with continuing their therapy and followed up for 3 months. The process involved in stringent monitoring is

<table>
<thead>
<tr>
<th>Selected subjects*</th>
<th>Restricted Diet</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not achieving target Glycemic levels</td>
<td><strong>Special food for breakfast (daily)</strong>(56,57)</td>
<td>Walking 30 mins every day for 5 times a week</td>
</tr>
<tr>
<td>Ingredients:</td>
<td></td>
<td>Blood Glucose level measurements</td>
</tr>
<tr>
<td>Fenugreek Seed – 4 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mung Dhal - 250g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samba Wheat Broken – 50 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onion, Green Chilli and Salt – for taste</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wash well the fenugreek seed and mung dhal, soak them overnight. Grind in a mixie, add samba wheat broken and continue grinding. Add onion, red chilli and salt for taste. Toast it</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consume 2 to 3 Adai every day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#The stringent monitoring performed through telephonic and personal follow up

*Reassessed once in every 2 weeks

A cross-sectional study was conducted from March 2012 to August 2012 in the study sites. Totally 150 Type 2 DM patients were assessed for 30 minutes regular exercise (RE) 3 to 5 times per week. Data were obtained through questionnaire and personal interview. The gender wise barriers towards regular exercise (RE) were assessed and ranking for the same were given.

Similarly a cross-sectional study was conducted from September 2012 to January 2013. Data were obtained from selected pharmacies from the districts namely Coimbatore, Nilgiris and Chennai.
The pharmacist role in the pharmacy was assessed for the following diabetes management services.\textsuperscript{58}

1. Patient education on disease by provision of relevant educational material (e.g., patient educational leaflet for diabetes, diabetes food chart)

2. Patient education on diabetes complications

3. Education aspects on diabetes self-care such as foot care, managing hypo - and hyperglycemia

4. Assessment on MNT

5. Education on the importance of Medical Nutritional Therapy (MNT)\textsuperscript{14,15,59}

6. Medication Adherence assessment and detection of drug-related problems (DRPs)

7. Education on importance of medication adherence

8. Encouragement for the usage of Self Monitoring Blood Glucose systems (SMBG)\textsuperscript{59}

9. Periodical support for blood pressure and lipid level monitoring

10. Reminder of regular follow up for prevention of possible complications related to diabetes

11. Patient referrals: Referring patients to other members of the diabetes care team (e.g., Diabetes educators, Dieticians, Ophthalmologists, Podiatrists, Cardiologist, Nephrologists, Dentists and Neurologist)\textsuperscript{60}

12. Assessment of the patients for the signs and symptoms of depression

13. Promoting and reminding about HbA1c testing once in 3 months

Many of these pharmacies were visited with diabetes prescription at their comfortable time (post lunch work time). Additional data collected include the pharmacist’s awareness about diabetes disorder and the importance of their involvement in diabetes management service.

5.2.12 Statistical analysis

The data was analyzed using GraphPad Prism statistical software version 6.04 and SPSS statistical package version 22. Mean and standard deviation for continuous variables and percentage for categorical variables are reported relevant. Significant differences between groups were evaluated using paired Student’s t test, unpaired Student’s t test, Repeated Measure two way ANOVA where ever appropriate. A p value of <0.05 was considered statistically significant.