

Design Development and Implementation of Pharmacist Intervened Effective Programme on Screening and Management of Anaemia among Adolescent Student Population in the Suburban Area around Tamilnadu, India

Submitted in partial fulfillment of the requirements for the award of

Bachelor of Pharmacy

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Declaration

We do hereby declare that the work presented in the thesis entitled "**Design Development and Implementation of Pharmacist Intervened Effective Programme on Screening and Management of Anaemia Among Adolescent Student Population in the Suburban Area Around Tamilnadu, India**", submitted by us to the **Sathyabama Institute of Science & Technology, Chennai-600119** for the award of the degree of **Bachelor of Pharmacy (2019-2023)** by research is a original record of research work carried out by us under the supervision of **Dr. A. Porselvi, M. Pharm., PhD., PG Dip in Clin Pharm., Associate Professor, Department of Pharmacy**. The contents of this dissertation, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma, membership, fellowship, associateship etc.. In keeping with the general practice in reporting scientific observation, due acknowledgement has been made whenever the work described is based on the findings of other investigators.

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Abstract

Back ground:

Diabetes mellitus is a chronic metabolic disease that directly affects the well-being and possess a high morbidity risk. The management of type 2 diabetes mellitus is a complex, requiring continuous medical care by health care professionals and considerable self-care efforts by patients. Pharmacist interventions programs delivered by the pharmacists are known to help the patients with diabetes succeed in achieving treatment goals, improving outcomes.

Objectives:

To study the impact of pharmacist interventions on therapeutic outcomes, determined by hemoglobin A1c (HbA1c), and secondarily on blood glucose levels, blood pressure, medication adherence, self-care activities and health related quality of life.

Methods:

A Prospective randomized controlled study was conducted in Santhiram medical college and general hospital, Nandyal from July 2019 to November 2019, with 150 type 2 diabetic patients. Of those, 75 patients were in intervention group and 75 patients were in control group. The intervention group participated in the pharmacist interventions provided by the pharmacist over a period of 4 months, whereas control group do not. The main outcome measure was change in HbA1c and secondary outcomes were changes in fasting blood glucose, post prandial blood glucose, blood pressure, medication adherence, self-care activities and health related quality of life.

Results:

A total of 150 patients completed the study. The intervention patients showed a significant reduction in HbA1c values than the control group, and also the intervention group showed a greater reduction in fasting blood glucose, post prandial blood glucose levels and blood pressure levels between baseline and end of the 4 months than the control group. Improvements were observed in self-reported medication adherence and self-care activities in the intervention group.

Conclusion:

A pharmacist interventions program resulted in better glycemic control, quality of life, medication adherence and self-care in type 2 diabetic patients over a 4-month period.

Key words: Type 2 Diabetes, Pharmacist interventions, Glycosylated hemoglobin (HbA1c)

INTRODUCTION

1.1 DEFINITION:

The American Diabetes Association (ADA) defines Diabetes Mellitus as a group of metabolic diseases characterized by inappropriate hyperglycemia resulting from defects in Insulin secretion, insulin action or both [Leon Shargel et al., 2013] ^[33]. As per WHO ^[16], Diabetes Mellitus is defined as a heterogeneous metabolic disorder characterized by common feature of chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism [Harsh Mohan, 2010] ^[22].

1.2 EPIDEMIOLOGY:

It is noted as one of the leading causes of death and disability worldwide [Adhikari A.K. Vidyasagar et al., 2011] ^[1]. The incidence of T1DM is increasing worldwide, for unknown reasons. India has the highest number of diabetic patients in the world. It is speculated that environmental changes may be causing modification to the diabetes associated alleles. Also, since the introduction of Insulin in the 1930s, an increasing number of people with T1DM have had children. There are major ethnic and geographical differences in the prevalence and incidence of T1DM. Figures are highest in Caucasians (especially Scandinavians), while the disorder is rare in Japan and the Pacific area [Roger Walker et al., 2012] ^[17]. It is estimated that approximately 1% of population suffers from Diabetes Mellitus [Adhikari A.K. Vidyasagar et al., 2011] ^[1]. In northern Europe, the prevalence is approximately 0.3% in those under 30 years of age. T1DM may present at any age, but there is a sharp increase around the time of puberty and a decline thereafter. Approximately 50-60% of patients with T1DM will present before 20 years of age [Roger Walker et al., 2012] ^[17]. T2DM is much more common than T1DM, accounting for 90% of people with Diabetes. It usually occurs in those over the age of 40 years. Estimates in UK suggest that T2DM currently affects approximately 2.3 million people, and up to another 500,000 are thought to be undiagnosed [Roger Walker et al., 2012] ^[17]. In the United States, an estimated 8.3% of the population has DM and 35% of adults (age 20 years and older) have Prediabetes. Disparities exist in the diagnosis of diabetes across ethnic groups and minority populations, with Native Americans and Alaska Natives having the highest rates of diagnosed diabetes (16.1%), followed by Blacks (12.6) and Hispanics

(11.8) [Leon Shargel et al., 2013] ^[33]. It has been predicted that the prevalence of Diabetes in the adult population in India will be 6% (57.2 million cases) by the year 2025 [Adhikari A.K. Vidyasagar et al., 2011] ^[1]. According to International Diabetes Federation (IDF), 65.1 million adults in India suffered from Diabetes in the year 2013 [Sekhar Mandal et al., 2016] ^[20]. The number of people affected with Diabetes is projected to increase from 171 million in 2000 and 366 million in 2030. The most important demographic change to Diabetes prevalence globally appears to be the increase in the proportion of people above 65 years of age [Lisha Jenny John et al., 2012] ^[28]. The incidence of T2DM increases with age and with increasing obesity. In general, non-obese populations, the prevalence is 1-3%. In the more obese societies, there is a sharp increase in prevalence with estimates of 6-8% in the USA, increasing to values as high as 50% in the Pima Indians of Arizona. Diabetes is six times more common among Asian immigrants in the UK than in the indigenous population. World studies of immigrants have suggested that the chances of developing T2DM are between 2 and 20 times in well-fed populations than in lean populations of same race [Roger Walker et al., 2012] ^[17].

1.3 CLASSIFICATION:

There are four clinical classes of Diabetes. They are: Type-I, Type-II, Gestational and other specific types.

1.3.1 TYPE-I: Earlier called as Insulin-dependent or Juvenile-onset Diabetes. It is typically characterized by an absolute insulin deficiency attributed to an autoimmune destruction of the β -cells of the Islets of Langerhans. Affected individuals will have auto-antibodies to glutamic acid decarboxylase, pancreatic islet β -cells, and/or insulin. It may be diagnosed at any age, but it is most likely to be diagnosed prior the age of 30 years.

1.3.2 TYPE-II: Earlier called as Non-insulin dependent or maturity-onset Diabetes. It is the most common form of DM and is typically identified in individuals over the age of 30 years; however, it has become a more prominent diagnosis in adolescents of certain ethnic origins (e.g., Hispanic, African and American). Those diagnosed with T2DM are typically overweight or obese, have a positive family history of Diabetes, and/or exhibit signs of insulin resistance (e.g., truncal obesity, high triglycerides, low

HDL-C, acanthosis nigricans); auto-antibodies found in Type-I DM are absent in Type-II DM.

1.3.3 GESTATIONAL: It is a condition in which women first exhibit levels of elevated plasma glucose during pregnancy. Women previously diagnosed with Diabetes prior to pregnancy are excluded from this classification. After pregnancy, the diagnostic classification of GDM may be changed based on postpartum testing.

1.3.4 SECONDARY DIABETES: Earlier called as Maturity-onset diabetes of the young (MODY). Secondary Diabetes occur when the diagnosis of Diabetes is a result of other disorders (e.g., Cushing's syndrome, Acromegaly, cystic fibrosis, Down syndrome, pancreatic disorders) or treatments (e.g., Glucocorticoids, antipsychotics). Monogenic DM (formerly maturity-onset diabetes of the young) should be considered in children with an atypical presentation or response to therapy. Adults may present with Latent Autoimmune Diabetes of the Adult (LADA), which is a slow destruction of the pancreatic β -cells similar to T2DM, but auto-antibodies are present as in T1DM.

1.3.5 PREDIABETES: individuals who have elevated blood glucose levels that do not meet diagnostic criteria for Diabetes, but that are too high to be considered normal, are classified as having Prediabetes. Prediabetes is a high-risk category for the future development of T2DM [Leon Shargel et al., 2013]^[33].

1.4 ETIOLOGY:

1.4.1 TYPE-I: Genetic predisposition, environmental factors and autoimmunity have been proposed as causes that lead to progressive β -cell dysfunction and eventually, overt Diabetes Mellitus. This type is the result of immune-mediated destruction of the β -cells and is characterized by the abrupt onset of signs and symptoms.

a) Genetics: Human leukocyte antigens (HLAs) DQA and DQB appear to code for either disease susceptibility (DR3, DR4, HLA-DQA1*0301) or resistance (DRB1*04008-DQB1*0411-DQB1*0302). Greater than 90% Caucasians diagnosed with T1DM have HLA-DR3 and/or HLA-DR4 present, but 95% of these individuals have HLA-DQA1*0301 and HLA-DQA1*0302 present. However, in studies of identical twins, there is a 50% discordance rate, suggesting that other factors such as environment (e.g., infectious agents, chemical agents, dietary agents) may be contributing factors to disease development. The risk of developing T1DM is increased in the offspring of individuals diagnosed with Diabetes.

b) Environment: environmental triggers such as viral (e.g., rubella, Coxsackie B), chemical or dietary (e.g., cow's milk) have been suspected in the development of T1DM.

c) Autoimmunity: An auto-immune component, possibly triggered by an environmental factor, is involved in the development of T1DM. Anti-insulin or β -cell antibodies are present in the blood of most individuals at the time of diagnosis of T1DM. Antibodies to glutamic acid decarboxylase (GAD) are found in the blood of approximately 70% of individuals diagnosed with T1DM. Thus, the presence of these antibodies may serve as an immunologic predictor of the future development of the disease.

1.4.2 TYPE-II: Genetic factor, a β -cell defect and peripheral site defects have been implicated.

a) Genetics: There is greater than a 90% concordance rate in identical twins if one has T2DM, suggesting that the development of T2DM is predominately dependent on genetics. The risk of offspring development of T2DM is at least 15%.

b) β -cell defect: A primary β -cell dysfunction has been postulated in the development of T2DM because at diagnosis, typically only about 50% of β -cells are functioning. The number of functioning β -cells continues to decline with duration of T2DM at least 15%.

c) Peripheral site defect: It may also contribute to the expression of T2DM. Defects in post-receptor binding or a decreased number of insulin receptors can lead to hyperglycemia.

1.4.3 SECONDARY DIABETES: Genetic defect of β -cell function due to mutations in various enzymes (e.g., hepatocyte nuclear transcription factor-HNF, glucokinase), genetic defect in insulin action (e.g., type A insulin resistance), exocrine pancreatic diseases (e.g., chronic pancreatitis, pancreatic tumors, post-pancreatectomy), endocrinopathies (e.g., Acromegaly, Cushing's syndrome, pheochromocytoma), drug or chemical induced (e.g., steroids, thyroid hormones, thiazides, β -blockers), infections (e.g., congenital rubella, cyto-megalo virus), uncommon forms of immune-mediated DM (stiff man syndrome, anti-insulin receptor antibodies), other genetic syndromes (e.g., Down's syndrome, Klinefelter's syndrome, Turner's syndrome).

GESTATIONAL DIABETES: Due to metabolic changes during pregnancy [Harsh Mohan, 2010]^[22].

1.5 CLINICAL PRESENTATION:

It can be appreciated that hyperglycemia in Diabetes Mellitus doesn't cause a single disease but is associated with numerous diseases and symptoms, especially due to complications. Overlapping of clinical features occurs as a regard the age of onset, duration of symptoms and family history.

1.5.1 TYPE-I DIABETES: Onset of symptoms is abrupt. Symptoms include- polyuria, polydipsia, polyphagia, weight loss. High risk for developing metabolic complications like Ketoacidosis, Hypoglycemia.

1.5.2 TYPE-II DIABETES: Onset of symptoms is slow and insidious. Symptoms include- glucosuria, hyperglycemia, polyuria, polydipsia, unexplained weakness and weight loss but generally obesity will be present. Metabolic complications like Ketoacidosis are infrequent.

1.6 PATHOPHYSIOLOGY:

Depending upon etiology of DM, hyperglycemia may result from the following- reduced insulin secretion, decreased glucose use by the body, increased glucose production.

Pathogenesis of two main types of DM and its complications is distinct. They are as follows-

1.6.1 TYPE-I DM: The basic phenomenon in T1DM is destruction of β -cell mass, usually leading to absolute insulin deficiency. While T1DM remains idiopathic, pathogenesis of T1DM is immune-mediated and has been extensively studied. Currently, pathogenesis of T1DM is explained on the basis of 3 mutually-interlinked mechanisms: Genetic susceptibility, autoimmune factors and certain environmental factors.

a) Genetic susceptibility: T1DM involves inheritance of multiple genes to confer susceptibility to the disorder.

ii. It has been observed in identical twins that if one twin has T1DM, there is about 50% chance of the second twin developing it, but not all. This means that some additional modifying factors are involved in development of DM in these cases.

iii. About half the cases with genetic predisposition to T1DM have the susceptibility gene located in the HLA region of chromosome 6 (MHC class II region), particularly HLA DR3, HLA DR4 and HLA DQ locus.

b) Autoimmune factors: Studies on humans and animal models on T1DM have shown several immunological abnormalities:

- i. Presence of islet cell antibodies against glutamic acid decarboxylase (GAD), insulin etc, though their assay largely remains a research tool due to tedious method.
- ii. Occurrence of lymphocytic infiltrate in and around the pancreatic islets termed insulinitis. It chiefly consists of CD8⁺ T lymphocytes with variable number of CD4⁺ T lymphocytes and macrophages.
- iii. Selective destruction of β -cells while other islet cell types (glucagon-producing alpha-cells, somatostatin-producing delta cells or polypeptide-forming PP cells) remain unaffected. This is mediated by T-cell mediated cytotoxicity or by apoptosis.
- iv. Role of T cell-mediated autoimmunity is further supported by transfer of T1DM from diseased animal by infusing T lymphocytes to a healthy animal.
- v. Association of T1DM with other autoimmune diseases in about 10-20% cases such as Grave's disease, Addison's disease, Hashimoto's thyroiditis, pernicious anemia. Remission of T1DM in response to immuno-suppressive therapy such as administration of Cyclosporin A.

c) Environmental factors: Epidemiological studies in T1DM suggest the involvement of certain environmental factors in its pathogenesis, though role of none of them has been conclusively proved. In fact, the trigger may precede the occurrence of the disease by several years. It appears that certain viral and dietary proteins share antigenic properties with human cell surface proteins and trigger the immune attack on β -cells by a process of molecular mimicry. These factors include-

- i. Certain viral infections preceding the onset of disease- e.g., mumps, measles, coxsackie B virus, cytomegalovirus and infectious mononucleosis.
- ii. Experimental induction of T1DM with certain chemicals has been possible-e.g., alloxan, streptozotocin and Pentamidine.
- iii. Geographic and seasonal variations in its incidence suggest some common environmental factors.
- iv. Possible relationship of early exposure to bovine milk proteins and occurrence of autoimmune process in T1DM is being studied.

1.6.2 TYPE-II DM: The basic metabolic defect in T2DM is either a delayed insulin secretion relative to glucose load (impaired insulin secretion), or the peripheral tissues are unable to respond to insulin (insulin resistance). T2DM is a heterogeneous disorder with a more complex etiology and is far more common than T1DM, but

much less is known about its pathogenesis. A number of factors have been implicated though, but HLA association and auto-immune phenomena are not implicated. These factors are as follows:

a) Genetic factors: Genetic component has a stronger basis for T2DM than T1DM. Although no definite and consistent genes have been identified, multifactorial inheritance is the most important factor in development of T2DM:

- i. There is approximately 80% chance of developing diabetes in the other identical twin if one has the disease.
- ii. A person with one parent having T2DM is at an increased risk of getting diabetes, but if both parents have T2DM, the risk in the offspring rises to 40%.

b) Constitutional factors: Certain environmental factors such as obesity, hypertension and level of physical activity play contributory role and modulate the phenotyping of the disease.

c) Insulin resistance: One of the most prominent metabolic features of T2DM is the lack of responsiveness of peripheral tissues to insulin, especially of the skeletal muscle and liver.

- i. Obesity, in particular, is strongly associated with insulin resistance and hence T2DM. Mechanism of hyperglycemia in these cases is explained as under:
- ii. Resistance to action of insulin impairs glucose utilization and hence hyperglycemia.
- iii. There is increased hepatic synthesis of glucose.
- iv. Hyperglycemia in obesity is related to high levels of free fatty acids and cytokines (e.g., TNF- α and adiponectin) affect peripheral tissue sensitivity to respond to insulin.

The precise underlying molecular defect responsible for insulin resistance in T2DM has yet not been fully identified. Currently, it is proposed that insulin resistance may be possibly due to one of the following defects:

- I. Polymorphism in various post-receptor intracellular signal pathway molecules.
- II. Elevated free fatty acids seen in obesity may contribute- e.g., by impaired glucose utilization in the skeletal muscle, by increased hepatic synthesis of glucose and by impaired β -cell function.
- III. Insulin resistance syndrome is a complex of clinical features occurring from insulin resistance and its resultant metabolic derangements that includes hyperglycemia and compensatory hyper-insulinaemia. The clinical features are in the

form of accelerated cardiovascular disease and may occur in both obese as well as non-obese T2DM patients. The features include: mild hypertension (related to endothelial dysfunction) and dyslipidaemia (characterized by reduced HDL level, increased TGL and LDL levels).

d) Impaired insulin secretion: In T2DM, insulin resistance and insulin secretion are interlinked-

- i. Early in the course of disease, in response to insulin resistance there is compensatory increased secretion of insulin (hyper-insulinaemia) in an attempt to maintain normal blood glucose levels.
- ii. Eventually, however, there is failure of β -cell function to secrete adequate insulin, although there is some secretion of insulin i.e. cases of T2DM have mild to moderate deficiency of insulin (which is much less severe than that in T1DM) but not its totally absent.

The exact genetic mechanism why there is a fall in insulin secretion in these cases is unclear. However, following possibilities are proposed-

- i. Islet Amyloid polypeptide (amylin) which forms fibrillar protein deposits in pancreatic islets in longstanding cases of T2DM may be responsible for impaired function of β -cells of islet cells.
- ii. Metabolic environment of chronic hyperglycemia surrounding the islets (glucose toxicity) may paradoxically impair islet cell function.
- iii. Elevated free fatty acid levels (lipotoxicity) in these cases may worsen islet cell function.

e) Increased hepatic glucose synthesis: One of the normal roles played by insulin is to promote hepatic storage of glucose as glycogen and suppress gluconeogenesis. In T2DM, as a part of insulin resistance by peripheral tissues, the liver also shows insulin resistance i.e. in spite of hyper-insulinaemia in the early stage of disease, gluconeogenesis in the liver is not suppressed. This results in increased hepatic synthesis of glucose which contributes to hyperglycemia in these cases [Harsh Mohan, 2010] ^[22].

1.7 DIAGNOSIS:

In June 2000, the UK formally adopted the World Health Organization criteria for diagnosing Diabetes Mellitus was initially published in 1999. It has since been

updated and the diagnostic criteria have been reiterated (WHO, 2006) [Roger Walker et al., 2012]^[17].

1.7.1 PHYSICAL FINDINGS: Include the “polys” (e.g., polyuria, polydipsia & polyphagia), weight loss, blurred vision, fatigue, headache, frequent vaginal infections and poor wound healing. Because hyperglycemia typically exists for extended periods prior to the diagnosis of T2DM, these persons may also present with signs and symptoms of chronic complications from diabetes [Leon Shargel et al., 2013]^[33].

1.7.2 DIAGNOSTIC TESTING: It should be performed from venipuncture testing. Home blood glucose monitors and point-of-care (POC) A1c monitors are not sufficiently accurate for diagnostic purposes. A1c tests reflect the average blood glucose level over the preceding 2-3 months and correlate with an estimated average glucose ($EAG = 28.7 \times A1c - 46.7$). **A1c testing should not be done in individuals with abnormal Red cell turnover** (e.g., pregnancy, recent blood loss or transfusion, some anemias). These individuals should only be diagnosed with glucose criteria. Repeat testing, preferably with the same method, must be performed to confirm diagnosis, unless there is unequivocal hyperglycemia (e.g., random blood glucose sample >200 in a symptomatic individual, hyperglycemia crisis). Fasting is defined as no caloric intake for at least 8hrs [Leon Shargel et al., 2013]^[33].

Diabetes in non-pregnant adults & children:

- a) Fasting blood glucose (FBS): $\geq 126\text{mg/dl}$
- b) Random (casual) blood glucose (RBS) & symptoms of hyperglycemia: $\geq 180\text{mg/dl}$
- c. Oral glucose tolerant test (OGTT) using oral glucose load equivalent to 75g anhydrous glycerin dissolved in water: $>200\text{mg/dl}$
- d. A1c $\geq 6.5\%$

Gestational diabetes: Screening should occur between weeks 24-28 gestation if not previously diagnosed with overt diabetes. A fasting 75g OGTT should be performed in the morning. Venipuncture should be measured at fasting & 1hr & 2hr post-oral glucose solution ingestion.

- a. Diagnosis of GDM based on OGTT: Fasting $\geq 92\text{mg/dl}$; 1hr $\geq 180\text{mg/dl}$; 2hrs $\geq 153\text{mg/dl}$
- b. If diagnosed with GDM, screening for persistent diabetes should occur between 6-12 weeks postpartum and, if negative, at least every 3 years thereafter.

Prediabetes: Relatively high risk for the future development of diabetes

- a. Impaired fasting glucose (IFG): FBS 100-125mg/dl
- b. Impaired glucose tolerance (IGT): OGTT results of 140-199mg/dl
- c. A1c 5.7-6.4%

Testing in asymptomatic individuals:

- a. Adults who are overweight (BMI $\geq 25\text{kg/m}^2$) or who have one or more risk factors for diabetes should be tested immediately and at least 3 years thereafter if tests are negative.
- b. Asymptomatic adults without risk factors should have screening beginning at the age of 45 years.
- c. Testing for T2DM in the asymptomatic pediatric population should occur at the age of 10 years or the onset of puberty (whichever comes first) in children who are overweight (BMI $> 85^{\text{th}}$ percentile; weight $> 120\%$ for weight) and have at least two risk factors. If negative, repeat testing should occur for every 3 years [Leon Shargel et al., 2013].

1.8. COMPLICATIONS:

1.8.1 ACUTE COMPLICATIONS:

1.8.1.1 DIABETIC KETOACIDOSIS: It is caused by profound insulin deficiency, typically occurs in persons with T1DM, but can also occur in those with T2DM. It is characterized by hyperglycemia, ketosis, dehydration and electrolyte imbalance.

a) Pathophysiology:

i. Insulin deficiency leads to the following actions:

- Impairs glucose uptake in the peripheral tissues, resulting in hyperglycemia.
- Impairs protein synthesis and promotes breakdown of protein, thus leading to a loss of lean body mass.
- Increases hydrolysis of triglycerides, which leads to increased hepatic glucose production (further hyperglycemia) and formation of Ketone bodies.

ii. Hyperglycemia causes osmotic diuresis, which leads to hypotonic fluid losses, dehydration and electrolyte depletion.

b) Precipitating factors: illness or infection, inadequate dosing of insulin or discontinuation of insulin.

c) Signs and symptoms: often include those typical of hyperglycemia (e.g., polyuria, polydipsia, weight loss and blurred vision), Kussmaul respirations (deep, rapid breathing), dehydration and mental status changes. Persons may appear lethargic, have a fruity odor to the breath, or have gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain).

d) Laboratory findings: typically include plasma glucose level $>250\text{mg/dl}$, but $<600\text{mg/dl}$; positive urine and serum ketones; arterial pH <7.3 ; sodium bicarbonate $<15\text{mEq/l}$.

e) Treatment: focused on correction of dehydration, hyperglycemia and electrolyte imbalance. Treatment may include any of the following as necessary: IV fluids, insulin, potassium, and/or sodium bicarbonate.

1.8.1.2 HYPEROSMOLAR HYPERGLYCEMIC STATE: predominantly affects elderly individuals and is an extreme manifestation of impaired glucose regulation. HHS is associated with a higher mortality than DKA, likely due to severe metabolic changes, delay in diagnosis, or other medical complications that can affect the elderly individuals.

a) Pathophysiology: it is not clear as DKA. However, HHS does differ from DKA in that insulin deficiency is not as profound, thus increased lipolysis does not occur. Individuals with HHS do have osmotic diuresis that produces dehydration, electrolyte depletion and hypotonic fluid loss to a greater extent than seen in DKA.

b) Precipitating factors: illness or infections, hypertonic feedings, excessive fluid loss secondary to hyperglycemia, severe burns, severe diarrhea, dialysis or the use of diuretics.

c) Signs and symptoms: may include hyperglycemic symptoms (e.g., polyuria, polydipsia, polyphagia, blurred vision, decreased wound healing), decreased mentation (e.g., lethargy and mild confusion) or focal neurological signs that mimic a cerebrovascular accident.

d) Laboratory findings: typically include plasma glucose levels $>600\text{mg/dl}$, normal sodium bicarbonate levels, minimal to no ketones, normal arterial pH and high serum osmolality (measure of dehydration).

e) Treatment: goals are similar to DKA, in HHS, caution should be used with aggressive fluid replacement to avoid fluid overload in elderly individuals.

1.8.1.3 HYPOGLYCEMIA: It is the limiting factor for providing aggressive insulin therapy in individuals with T1DM & T2DM.

a) Definition: Hypoglycemia is difficult to define, but typically is represented by plasma glucose levels <70mg/dl. However, symptoms are the driving determinant rather than an absolute glycaemic value since the threshold for the onset of symptoms varies among individuals.

b) Symptoms: For mild hypoglycemia include sweating, shaking, vision changes, immediate hunger, confusion and lack of co-ordination. Severe hypoglycemia occurs when an individual is unable to self-treat due to mental confusion, lethargy or unconsciousness. Some individuals may have neuroglycopenia and present with symptoms of crying, argumentativeness, inappropriate giddiness or euphoria.

c) Causes: can include advanced age, poor nutrition, renal diseases, excess of glucose-lowering agents (insulin or insulin secretagogues) or strenuous activity.

d) Treatment:

Mild: individuals should check their blood glucose level prior to treating, if possible. If the blood glucose level is low, the person should eat or drink 10-15g of a fast-acting glucose source to raise the plasma glucose level to 30-45mg/dl. If plasma glucose levels are <50mg/dl, treatment with 20-30g of carbohydrate may be necessary. The blood glucose level should be rechecked 15-20mins after treatment. If blood glucose levels are low, then hypoglycemia treatment can be repeated.

Severe: individuals able to swallow may be treated with glucose gel, syrup or jelly placed inside the individual's cheek. If this is not possible, glucagon, which stimulates hepatic glucose production, may be given by SC or IM injection. Nausea and vomiting are the primary adverse effects of a glucagon injection, so the treated person may not immediately feel like consuming further carbohydrates.

1.8.2 CHRONIC COMPLICATIONS:

Diabetic complications are frequently divided into Macro vascular and Micro vascular complications. Macro vascular complications arise from damage to large blood vessels and micro vascular complications occur from damage to smaller vessels. The general etiology of macro and micro vascular complications is the same and they results from atherosclerosis of the vessels, which may lead to occlusion.

1.8.2.1 MACRO VASCULAR COMPLICATIONS: The risk of these complications, including cardiovascular diseases (coronary artery disease and stroke) and peripheral vascular disease, is 2-4 times higher for people with diabetes.

a) Cardiovascular disease: The most common cause of death in patients with T2DM is cardiovascular disease, which accounts for an estimated 80% of deaths in this patient group. The risk of a patient with Diabetes having a Myocardial infarction (MI) is the same as someone having a second MI. If Nephropathy is present, the risk of cardiovascular disease is increased further. Other cardiovascular disease risk factors are the same as in the non-diabetic population and include smoking, hypertension and dyslipidemia. Cerebrovascular disease is also most commonly associated with diabetes and patients have greater mortality and morbidity when compared to the general population.

b) Hypertension: it is twice as common amongst the diabetic population compared to normal population. It affects over 80% of those with T2DM. For people with T2DM, HTN is a feature of metabolic syndrome and is associated with insulin resistance. For those with T1DM, it is closely associated with renal disease.

c) Peripheral vascular disease: PVD affects the blood vessels that are present outside the heart. In diabetic patients, it often affects the arteries of the legs and may give rise to intermittent claudication, a cramping pain experienced on walking, due to reversible muscle ischemia secondary to atherosclerosis. The iliac vessels can be affected, causing buttock pain and erectile dysfunction also. PVD increases the risk of cardiovascular disease. About 20% of patients with PVD die from MI within 2 years of symptom onset. PVD is also responsible for much of the morbidity associated with diabetic foot problems.

1.8.2.2 MICRO VASCULAR COMPLICATIONS: They include retinopathy, nephropathy and neuropathy.

a) Retinopathy: Diabetic retinopathy is the leading cause of blindness in people under the age of 60 in industrialized countries. 20 years from the onset of diabetes, over 90% of people with T1DM and over 60% of people with T2DM, will have Diabetic retinopathy. The main problem with diagnosing retinopathy is that it is symptomless until the disease is far advanced. Therefore, regular screening is not undertaken; diagnosis may not be made early enough for successful treatment

intervention. Tight glycemic control has been shown to prevent and delay the progression of retinopathy in patients with T1DM. Likewise, for patients with T2DM, both tight glycemic control and tight blood pressure control reduce the risk of developing retinopathy. When retinopathy is detected early, sight may be saved by laser photocoagulation. In advanced cases, surgery may be required. Pregnancy may worsen moderate-to-severe retinopathy, particularly if there is poor or sudden improvement in glycemic control. However, tight glycemic control reduces the long-term risk of retinopathy during pregnancy.

b) Nephropathy: In diabetic renal diseases, the kidneys become enlarged and the glomerular filtration rate (GFR) initially increases. However, if the nephropathy progresses, the GFR starts declining. Serum creatinine used alone to estimate renal function has limitations. The GFR can be estimated (eGFR). Micro albuminuria (small amount of albumin in urine) indicates the presence of nephropathy. If higher amounts of albumin are detected, it is termed as Proteinuria (or macro albuminuria) and signifies more severe renal damage. Micro albuminuria is defined as an albumin: creatinine ratio (ACR) $\geq 2.5\text{mg}/\text{mmol}$ (men) and $3.5\text{mg}/\text{mmol}$ (women) or albumin concentration $>200\text{mg}/\text{L}$. Proteinuria may progress to end-stage renal disease and require dialysis. Albumin in the urine increases the risk of cardiovascular disease, with micro albuminuria associated with 2-4 times the risk, Proteinuria with 9 times the risk and end-stage renal disease increasing risk by 50 times. Tight control of both glycemic levels and blood pressure reduces the risk of developing nephropathy.

c) Peripheral neuropathy: It is defined as the progressive loss of peripheral nerve fibers resulting in nerve dysfunction. Diabetic neuropathies can lead to a wide variety of sensory, motor and autonomic symptoms. Most common is the symmetrical distal sensory type, which is particularly evident in the feet and may slowly progress to a complete loss of feeling. It is most prevalent in elderly patients with T2DM but may be found with any type of diabetes, at any age beyond childhood. Painful diabetic neuropathy is another manifestation of sensory neuropathy; it can be extremely disabling and may cause considerable morbidity. Diabetic proximal motor neuropathy is rapid in onset and involves weakness and wasting, principally of the thigh muscles. Muscle pain is common and distal motor neuropathy can lead to symptoms of impaired fine co-ordination of the hands and/or foot slapping.

Autonomic neuropathy may affect any part of the sympathetic or parasympathetic nervous systems; may cause dry skin and lack of sweating, both of which may

contribute to diabetic foot problems. Diabetic impotence is the most common manifestation; diabetic diarrhea is uncommon but can be troublesome as it tends to occur at night. Gastro-paresis may cause vomiting and delayed GI transit and variable food absorption. Disorders of the efferent and afferent nerves controlling cardiac and respiratory function are more common, but rarely asymptomatic.

1.8.3 MACRO AND MICRO VASCULAR DISEASE COMBINED:

a) Diabetic foot problems: Infected diabetic foot ulcers account for the largest number of diabetes-related hospital bed-days and are the most common non-trauma cause of amputations. Diabetic foot ulcers are a costly problem and are associated with considerable morbidity. Sensory and autonomic neuropathy, PVD, hyperglycemia, poor foot care and poorly controlled diabetes are the contributory factors for developing diabetic foot problems. Diabetic foot ulcers are prone to infections.

b) Charcot arthropathy: It is an uncommon foot complication caused by severe neuropathy which results in progressive destruction of joints with marked inflammation, reduced bone density leading to bone fractures, altered foot shape and gross deformity. Owing to the deformity that occurs, excess pressure over protruding bone frequently leads to ulceration unless footwear is extensively modified [Leon Shargel et al., 2013].

1.9. ORAL HYPOGLYCEMIC DRUGS

These are the drugs which lower blood glucose levels and are effective orally. The chief drawback of insulin is it must be given by injection; orally active drugs have always been sought

1.9.1. CLASSIFICATION

A. ENHANCE INSULIN SECRETION

1. Sulfonylureas (K_{ATP} channel blockers):

First generation: Tolbutamide, Chlorpropamide, Tolazamide

Second generation: Glibenclamide (Glyburide), Glipizide, Gliclazide, Glimepiride

2. Meglitinide/Phenylalanine analogues

Repaglinide, Nateglinide

3. Glucagon-like peptide-1(glp-1) receptor agonist (injectable drugs)

Exenatide, Liraglutide

4. Dipeptidyl peptidase-4 (DPP-4) inhibitors

Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, Linagliptin

B. OVERCOME INSULIN RESISTANCE

1. Biguanides (AMP_K activator)

Metformin

2. Thiazolidinediones (PPAR γ ACTIVATOR)

Pioglitazone

C.MISCELLANEOUS ANTIDIABETIC DRUGS

1. α -Glucosidase inhibitors

Acarbose, Miglitol, Voglibose

2. Amylin analogue

Pramlintide

3. Dopamine –D2 receptor agonist

Bromocriptine

4. Sodium –glucose cotransport-2 (SGLT-2) inhibitors

Dapagliflozin

1.9.2. INSULIN SECRETION ENHANCERS

Sulfonylureas exert their hypoglycemic effects by stimulating insulin secretion from pancreatic beta cell. The primary mechanism of action is to close ATP- sensitive K-channels in beta cell plasma membrane and initiate a chain of events resulting in

insulin release and additionally the two mechanisms include reduction of serum glucagon levels and closure of potassium channels in extra pancreatic tissue.

A. Insulin release from pancreatic beta cells

Sulfonylureas bind to high affinity sulfonylurea receptor that is associated with a beta cell inward rectifier ATP sensitive potassium channel. Binding of Sulfonylureas inhibits the efflux of potassium ions through the channel and results in depolarization which opens a voltage gated calcium channels and results in influx of calcium and the release of preformed insulin.

B. REDUCTION OF SERUM GLUCAGON CONCENTRATIONS

Long term administration of Sulfonylureas in type 2 diabetics reduces serum glucagon levels, which may contribute to the hypoglycemic effects of drugs. the mechanism of this suppressive effect of Sulfonylureas on glucagon levels is unclear but appears to involve indirect inhibition due to enhanced release of both insulin and somatostatin, which inhibit alpha- cell secretion.

1.9.2.1 FIRST GENERATION SULFONYL UREAS

Tolbutamide

It is well absorbed but rapidly metabolized in the liver. Its duration of effect is relatively short, with an elimination half-life of 4-5 hours, and it is best administered in divided doses. It is safest sulfonylurea for elderly diabetic patients because of its short half life prolonged hypoglycemia has reported rarely, mostly in patients receiving certain drugs like Dicumarol, Phenylbutazone, sulfonamides that inhibits the metabolism of Tolbutamide.

Chlorpropamide

Chlorpropamide also interacts with drugs like Dicumarol, Phenylbutazone, sulfonamides that depends on hepatic oxidative catabolism, and it is contraindicated in patients with hepatic and renal insufficiency. Dose higher than 500 mg/day increase the risk of jaundice. the average maintenance dose is 250mg/day. Other adverse effects include hyperemic flush after alcohol ingestion in genetically predisposed patients and dilutional hyponatremia. Hematologic toxicity occurs in less than 1% patients.

Tolazamide

It is comparable to Chlorpropamide in potency but has a shorter duration of action. It is slowly absorbed than other Sulfonylureas, and its effect on glucose does not appear

for several hours. Its half life is about 7 hours. It is metabolized in several compounds that retain hypoglycemic effects. If more than 500 mg/day are required, the dose should be divided and given twice daily.

1.9.2.2. SECOND GENERATION SULFONYLUREAS

The second-generation Sulfonylureas are more frequently than the first-generation agents because of their adverse effects and drug interactions these should be used with caution in patients with cardiovascular disease or in elderly patients in whom hypoglycemia would be especially dangerous.

Glyburide

It is metabolized in liver into products with very low hypoglycemic activity. The usual starting dose is 2.5mg/day or less and the average maintenance dose is 5-10mg/day given as a single morning dose; maintenance dose higher than 20mg/day are not recommended. It has fewer adverse effects other than its potential for causing hypoglycemia. Flushing has rarely been reported after ethanol ingestion, and the compound slightly enhances free water clearance. It is contraindicated in patients with hepatic and renal impairment [Bertram G Katzung et al., 2012, Pg-754] ^[24].

Glipizide

It has shortest half life 2-4 hours of the more potent agents. For maximum effect in reducing postprandial hyperglycemia, this should be ingested 30 minutes before breakfast because absorption is delayed when the drug is taken with food. The recommended starting dose is 5-15 mg/day when higher daily doses are required, they should be divided and given before meals. This therapy is contraindicated in patients with hepatic and renal impairment [Bertram G Katzung et al., 2012, Pg-755] ^[24].

Glimepiride

It is approved for once daily use as monotherapy or in combination with insulin. It achieves blood glucose lowering with the lowest dose of any sulfonylurea compound. A single daily dose of 1 mg has been shown to be effective, and the recommended maximal daily dose is 8mg. It has long duration of effect with half life of 5 hours, allowing once daily dosing and thereby improving compliance. It is completely metabolized in liver [Bertram G Katzung et al., 2012, Pg-756] ^[24].

1.9.3 PHENYL ALANINE ANALOUGES

Repaglinide

It is the member of the Meglitinide group of insulin secretagogues. These drugs modulate beta cell insulin release by regulating potassium efflux through the potassium channels. This drug should be taken just before each meal in doses of 0.25-4mg; hypoglycemia is a risk if the meal is delayed or skipped or contains inadequate carbohydrate. Repaglinide is approved as monotherapy or in combination with Biguanides. There is no sulfur in its structure, so Repaglinide may be used in type 2 diabetics with sulfur or Sulfonylurea allergy.

Nateglinide

It is a D-phenylalanine derivative, is the latest insulin secretagogues to become clinically available. Nateglinide stimulates very rapid and transient release of insulin from beta cells through closure of the ATP-sensitive K⁺ channel. It is ingested just before meals. The incidence of hypoglycemia with Nateglinide may be the lowest of all the secretagogues and it has the advantage of being safe in those with much reduced renal function [Bertram G Katzung et al., 2012, Pg-756] ^[24].

1.9.4 BIGUANIDES:

Metformin

The full explanation of the mechanism of action of the Biguanides remains elusive, but their primary effect is to reduce hepatic glucose production through activation of the enzyme AMP-activated protein kinase (AMPK). Possible minor mechanism of action includes impairment of renal gluconeogenesis, slowing of glucose absorption from the gastrointestinal tract, with increased glucose to lactate conversion by enterocytes, direct stimulation of glycolysis in tissues, increased glucose removal from blood, and reduction of plasma glucagon levels.

Metabolism and excretion

Metformin has a half life of 1.5-3 hours, it is not bound to plasma proteins, it is not metabolized and is excreted by the kidneys as the active compound. As a consequence of Metformin's blockade of gluconeogenesis, the drug may impair the hepatic metabolism of lactic acid in patients with renal insufficiency; Biguanides accumulate and thereby increase the risk of lactic acidosis, which appears to be dose related complication.

Clinical use

Biguanides are recommended as first line therapy, because Metformin is an insulin sparing agent and does not increase bodyweight or provoke hypoglycemia, it offers

obvious advantage over insulin or Sulfonylureas in treating hyperglycemia in such persons. The dosage of Metformin is 500mg to a maximum of 2.55g daily, with the lowest effective dose being recommended. Depending on whether the primary abnormality is fasting hyperglycemia or postprandial hyperglycemia, Metformin therapy can be initiated as a once- daily dose at bedtime or before meal. The speculative mechanism of action is a decrease in insulin levels as well as direct cellular effects mediated by AMPK.

Toxicities

The most common toxic effects of Metformin are anorexia, nausea, vomiting, abdominal discomfort and diarrhea which occur in 20% of patients. Absorption of vitamin B12 appears to be reduced during long term Metformin therapy and annual screening of serum vitamin B12 levels and red blood cell parameters need for vitamin B12 injections. In the absence of hypoxia or renal or hepatic insufficiency, lactic acidosis is less common with Metformin therapy.[Bertram G Katzung et al., 2012, Pg-756]^[24]

1.9.5 THIAZOLIDINEDIONES

Thiazolidinediones acts to decrease insulin resistance. These are ligands of Peroxisome proliferator- activated receptor gamma (PPAR- γ) part of steroid and thyroid super family of nuclear receptors. These PPAR receptors are found in muscle, fat and liver. PPAR receptors modulate the expression of genes involved in lipid and glucose metabolism, insulin signal transduction, adipocyte and other tissue differentiation. In addition of targeting adipocytes, myocytes and hepatocytes, Thiazolidinediones also have significant effects on vascular endothelium, the immune system, the ovaries, and tumor cells. In persons with diabetes, a major site of Thiazolidinediones action is adipose tissue, where the drug promotes glucose uptake and utilization and modulates the synthesis of lipid hormones or cytokines and other proteins involved in energy regulation.

Pioglitazone

It has PPAR activity .it is absorbed within 2 hours of ingestion; although food may delay uptake, total bioavailability is not affected. Absorption is decreased with concomitant use of bile acid sequestrants. It is metabolized by CYP2C8 and CYP3A4 to active metabolites. The bioavailability of numerous other drugs also degraded by these enzymes which may be affected by the Pioglitazone therapy, including estrogen containing oral contraceptives; additional method of contraception are advised.

Pioglitazone may be taken once daily the usual starting dose is 15-30mg/day and the maximum dose is 45mg/day. A triglyceride- lowering effect is observed with Pioglitazone and is more significant than that of Rosiglitazone, presumably because of its PPAR activity. [Bertram G Katzung et al., 2012, Pg-757-758] ^[24].

Rosiglitazone

It is rapidly absorbed and highly protein –bound. It is metabolized in liver to minimally active metabolites, predominantly by CYP2C8 and lesser extent by CYP2C9. It is administered once or twice daily; 2-8mg is the usual total dose. Rosiglitazone shares the common Thiazolidinediones adverse effects but has more cardiovascular risk than pioglitazone. An adverse effect common to both Thiazolidinediones is fluid retention, which presents as mild anemia and peripheral edema, especially when the drugs are used in combination with insulin or insulin secretagogues.

1.9.6 ALPHA –GLUCOSIDASE INHIBITORS

Acarbose and Miglitol

Acarbose and Miglitol are competitive inhibitors of the intestinal- glucosidases and reduce post meal glucose excursion by delaying the digestion and absorption of starch and disaccharides. Acarbose and Miglitol both target the glucosidases: sucrose, maltase, glucoamylase, and dextranase. Miglitol alone has effects on isomaltose and on glucosidases which split linked sugars such as lactose. Acarbose alone has a small effect on amylase. Both Acarbose and Miglitol are taken in doses of 25-100 mg just before ingesting the first portion of each meal. Prominent adverse effects include flatulence; diarrhea, abdominal pain and result in appearance of undigested carbohydrate in the colon that is then fermented into short chain fatty acids, releasing gas. [Bertram G Katzung et al., 2012, Pg-759] ^[24].

1.9.7 AMYLIN ANALOG

Pramlintide

Pramlintide, a synthetic analog of Amylin, it is an injectable anti-hyperglycemic agent that modulates postprandial glucose levels and is approved for Pre-prandial use in persons with diabetes. It is administered in addition to insulin in those who are unable to achieve their target postprandial blood sugar levels. Pramlintide suppresses glucagon release via undetermined mechanisms, delays gastric emptying and has central nervous system mediated anorectic effects. The major adverse effect of

Pramlintide is hypoglycemia, gastrointestinal symptoms, including nausea, vomiting and anorexia.

1.9.8 GLUCAGON-LIKE POLYPEPTIDE-1 RECEPTOR AGONISTS

In type 2 diabetes, the release of glucagon like polypeptide is diminished postprandial, which leads to inadequate glucagon suppression and excessive hepatic glucose output. Two synthetic analogs of glucagon like polypeptide, Exenatide and Liraglutide help to restore GLP—1 activity. These therapies have multiple actions such as potentiation of glucose mediated insulin secretion, suppression of postprandial glucagon release. The increase in insulin secretion is speculated due to an increase in beta cell mass.

Exenatide

It is a derivative of exendin-4 peptide. It has homology with native GLP-1 and a glycine substitution to reduce degradation by Dipeptidyl peptidase-4. It should be administered subcutaneously within 60 minutes before a meal; therapy is initiated at 5 mcg twice daily, with a maximum dose of 10 mcg twice daily. The major adverse effects are nausea, vomiting and diarrhea. Exenatide mono and combination therapy results in HbA1c reduction.

Liraglutide

It is a long acting synthetic GLP-1 analog; it has prolonged half life that permits once daily dosing. It interacts with the GLP-1 receptor and acts to increase insulin and decrease glucagon levels. Treatment is initiated at 0.6mg and is titrated in weekly increments of 0.6 mg as needed and as tolerated, to achieve glycemic goals. Peak levels are obtained in 8-12 hours, and the elimination half life is about 13 hours. Liraglutide therapy results in a reduction of HbA1c from 0.8-1.5%; weight loss ranges from nominal to 3.2 kg. Common side effects are headache, nausea, diarrhea, antibody formation, urticaria and other immune reactions were observed. [Bertram G Katzung et al., 2012, Pg-760] ^[24].

1.9.9 DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

Sitagliptin, Saxagliptin and Linagliptin are inhibitors of DPP-4, the enzyme that degrades incretin hormones. These drugs increase circulating levels of native GLP-1 and glucose dependent insulinotropic polypeptide (GLP), which ultimately decreases post prandial glucose excursions by increasing glucose- mediated insulin secretion and decreasing glucagon levels. They are approved as adjuvant therapy to diet and exercise in the treatment of individuals with diabetes who have failed to achieve glycemic goals.

Sitagliptin

The usual dose is 100 mg/day orally. Therapy with Sitagliptin has resulted in HbA1c reduction between 0.5-1%. Common adverse effects include nasopharyngitis, upper respiratory infections, headaches, and hypoglycemia when drug is combined with insulin secretagogues or insulin.

Saxagliptin

It is given orally as 2.5-5mg daily. This drug reaches maximal concentrations within 2 hours (4 hours for its active metabolite). It is minimally protein bound, and undergoes hepatic metabolism by CYP3A4/5. The major metabolite is active, and excretion is by both renal and hepatic pathways. The terminal plasma half life is 2.5 hours and 3.1 hours for its active metabolite. The dose of concurrently administered insulin secretagogues or insulin may need to be lowered to prevent hypoglycemia.

Linagliptin

It is the most commonly introduced drug in this class and appears to have similar properties to Sitagliptin and Saxagliptin. It is approved for the use as monotherapy and in combination with Metformin, Glimepiride, and Pioglitazone.

1.10. COMBINATION THERAPY-**1.10.1 ORAL ANTIDIABETIC AGENTS AND INJECTABLE MEDICATIONS****Combination therapy in Type 2 Diabetes mellitus**

Failure to maintain a good response to therapy over the long term owing to a progressive decrease in beta cell mass, reduction in physical activity, decline in lean body mass, or increase in ectopic fat deposition remains a disconcerting problem in the management of type-2 diabetic patients. Multiple medications may be required to achieve glycemic control. Unless there is a contraindication, medical therapy should be initiated with a Biguanides. If clinical failure occurs with Metformin monotherapy, a second agent or insulin is added. The second line drug can be insulin secretagogues, Thiazolidinediones, incretin-based therapy, Amylin analog, or a glucosidase inhibitor; preference is given to Sulfonylureas or insulin because of cost, adverse effects and safety concerns. Third line therapy can include Metformin, multiple other oral medications, or a non insulin injectable and Metformin and intensified insulin therapy. Recommended fourth –line therapy is intensified insulin management with or without Metformin or Thiazolidinediones.

A. COMBINATION THERAPY WITH GLP-1 RECEPTOR AGONISTS

Exenatide and Liraglutide are approved for use in individuals who fail to achieve desired glycemic control on Metformin, Sulfonylureas, Metformin plus Sulfonylureas, or Metformin plus Sulfonylureas and Thiazolidinediones. Hypoglycemia is the risk GLP-1 receptor agonists are used with insulin secretagogues or with insulin. The doses for the latter drugs should be reduced at the initiation therapy and subsequently titrated [Bertram G Katzung et al., 2012, Pg-761] ^[24].

B. COMBINATION THERAPY WITH DPP-4 INHIBITORS

Sitagliptin, Saxagliptin, Linagliptin are approved for use in individuals who fail to achieve desired glycemic control on Metformin, Sulfonylureas or Thiazolidinediones. Hypoglycemia is a risk when the DPP-4 inhibitors are used with insulin secretagogues or with insulin, and a dosage adjustment of the latter drugs may be required to prevent hypoglycemia.

C. COMBINATION THERAPY WITH PRAMLINTIDE

Pramlintide is approved for concurrent mealtime administration in individuals with type-2 diabetes treated with insulin, Metformin, or Sulfonylureas that are unable to achieve their postprandial glucose targets. Combination therapy results in a significant reduction in early postprandial glucose excursions; mealtime insulin or Sulfonylureas doses usually have to be reduced to prevent hypoglycemia.

D. COMBINATION THERAPY WITH INSULIN

Bedtime insulin has been suggested as an adjunct to oral antidiabetic therapy in patients with type-2 diabetes who have not responded to maximal oral therapy. Although not formally FDA approved, clinical practice has evolved to include Sulfonylureas, Metformin, D-phenylalanine derivatives, Biguanides, Thiazolidinediones, glycosidase inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and bile acid sequestrants given in conjunction with insulin. Person unable to achieve glycemic control with bedtime insulin as described generally require full insulin replacement and multiple daily injections of insulin. Insulin secretagogues are redundant when a person is receiving multiple daily insulin injections, but persons with severe insulin resistance may benefit from the addition of Metformin. When Metformin is added to the regimen of person already taking insulin, the blood glucose should be closely monitored and the insulin dose to be reduced as to avoid hypoglycemia [Bertram G Katzung et al., 2012, Pg-762] ^[24].

1.11. PHARMACIST INTERVENTIONS:

Pharmacist interventions (also known as pharmaceutical care plans) are the pharmacist contribution to the care of individuals in order to optimize medicines use and improve health outcomes.

In 1987, pharmaceutical care was philosophically defined as a covenantal relationship between a pharmacist and a patient in which the pharmacist performs drug use control functions governed by the awareness of and commitment of the patient's interest [Hepler et.al. 1987] ^[23].

The original and most popular definition of pharmaceutical care was developed by Charles D. Hepler and Linda M in 1990. The helper and strand definition are pharmaceutical care interventions are the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life.

These outcomes are as follows

- Controlling diabetes, prolonging morbidity and mortality.
- Therapeutic interventions delay the life span to 5-10 years.
- Eliminating or reducing a patient's symptoms.
- Arresting or slowing down a disease process or preventing a disease.

In 1992, the American society for health system (ASHP) pharmacists adopted the Hepler and strand definition with two changes. The ASHP definition is:

Pharmaceutical care interventions are direct, responsible provisions of medication related care for the purpose of achieving definite outcomes that improve patient's quality of life [American Society of Health-System Pharmacists. ASHP guidelines on a standardized method for pharmaceutical care, 1996] ^[5]. Pharmacist's interventions (also known as pharmaceutical care plans) are means of solving the drug therapy problems identified in pharmaceutical care. Outcomes are the results of pharmacist interventions activities. Patient's satisfaction refers to patients feeling of fulfillment, happiness with the services they have received. Patient satisfaction with healthcare reflects the quality of services from the patient's perspective. Its measurement can help evaluate the performance of health service delivery, identify patients who need additional attentions or targeted interventions, predict treatment adherence and outcomes. [Goode et.al, 2011] ^[21].

Implementation of pharmaceutical care involves six basic steps which includes

- a) Establishment of a professional/ therapeutic relationship.
- b) Collection of patient specific data.

- c) Evaluation of data to identify health related and drug related problems.
- d) Development and implementation of pharmaceutical care plans (pharmacist's intervention which could be patient focused intervention or drug focused intervention).
- e) Evaluation of interventions and follow up.
- f) Documentation.

To effectively implement a pharmaceutical care intervention a collaborative relationship between the pharmacist and the physician must be developed. Pharmacists must accept responsibility to educate prescribers, patients about the extent and value of pharmaceutical care services [MacDonough et.al, 1998]^[40].

1.11.1 The role of pharmacists in diabetes management

It includes patient identification, assessment, education, referral, monitoring and early detection of metabolic complications. Pharmacists can help identify patients with diabetes through screening and should target patients at high risk, people with a family history of the disease, and women with a history of gestational diabetes or who delivered a baby weighing more than nine pounds. Patient education should be provided immediately after diagnosis, at a second stage at which time a patient assessment can be performed, and at a third stage during which patients can receive continuing education to reinforce concepts and a motivational boost. One of the pharmacist's most important roles is the referral of patients to other members of the diabetes care team [Campbell RK 2002]^[12].

The pharmacist can play an important role in diabetes care by screening patients at high risk for diabetes, assessing patient health status and adherence to standards of care, educating patients to empower them to care for themselves, referring patients to other health care professionals as appropriate, and monitoring outcomes. Providing diabetes management services requires market savvy, communication skills, and a commitment of time, effort, and resources. Pharmacists who obtain training in diabetes management reap rewards in professional satisfaction and financial reimbursement [Campbell RK 2002]^[12].

1.11.2 Pharmacist Interventions include:

- Improving medication adherence.
- Life style modifications (diet, physical activity, exercise)
- Minimising drug related problems.

- To improve patient quality of life.
- Improving patient education.

a) Medication adherence:

Medication adherence is the voluntary cooperation of the patient in taking drugs or medicine as prescribed, including timing, dosage, and frequency. For patients with chronic diseases and multiple medications adherence is essential for effective treatment. By employing comprehensive pharmacist interventions that include patient education and follow up, patients could become more adherent and feel empowered to take their health into their own hands. Also, by simplifying the drug regimen, patients may be better able to understand their treatment and the importance of remembering to take their medications. It is important for patients to understand why they are using their medications and how they work, as this can increase their involvement in their own healthcare and encourage them to learn about their condition and take charge of their disease. It can also help prevent therapeutic duplications by prescribers [Al Mazroui NR et.al, 2009] ^[3].

One of the barriers to the ideal management of diabetes is the patient's adherence to a diabetes regimen. In one study, only 7% of patients were found to be fully adherent to all aspects of their antidiabetic regimen, which included adherence to medication, diet, exercise, and self-monitoring. Medications play an important role in the control of type 2 diabetes mellitus and its complications, and regular medication review, ongoing diabetes self-management education, coaching and monitoring by pharmacists can empower the patient and assist in the early identification and resolution of drug-related problems and improve overall disease control [Krass I and Taylor SJ, 2005] ^[26].

Reasons for Non adherence:

The Diabetes management still in new evolving stages. Some reasons for not taking medication are involuntary, such as forgetfulness. Some are voluntary, such as fear of adverse events or a negative attitude toward medications in general. Other reasons include high cost, complex regimen, lack of education, multiplication of drugs and regimens, frequent changes in the prescriptions from physician to physician, costly prescriptions by endocrinologists, lack of self monitoring of glucose, poor quality of life, busy schedule, poor patient–physician relationship, perceptions of

disease severity and drug effectiveness, asymptomatic disease (e.g., hypertension, diabetes, hyperlipidemia) and low literacy.

Low compliance to prescribed medical interventions is an ever present and complex problem, especially for patients with a chronic illness. With increasing numbers of medications and other medical interventions shown to do better than harm when taken or implemented as prescribed, low compliance is a major problem in health care [Lindenmeyer A et.al, 2005] ^[39].

Measuring adherence:

Patient self-report is probably the easiest way to determine adherence. Medication adherence was assessed using the morisky-green test. This test consists of 4 questions.

1. Do you ever forgotten to take your medications?
2. Are you careless at times about taking your medication?
3. When you feel better do you stop taking your medications?
4. When you feel worse do you stop taking your medications?

Patients were considered adherent if they answered “no” to all questions. If a patient answered “yes” to any question, the patient was considered as non adherent [Morisky DE and Green LW, 1986] ^[31].

b) Cost effectiveness:

An assessment or determination of the most efficient and least expensive approaches to providing health care and preventive medicine services. To control costs, health care providers and health care customers must also understand the comparative value of procedures and medicines. Cost of medical aid and medical advice differs from hospital to hospital this will affect the patients adherence, patient self-care and quality of life.

c) Quality of life:

The pharmaceutical care interventions are defined as the responsible provision of drug therapy to achieve definite outcomes that improves patient’s Quality of life (QoL). Quality of life is notably core of this definition. Pharmacists with their knowledge and skills are in the best position to work together with physicians and other health care providers to manage patient drug therapy and improve QoL [Leal S and Glover JJ, 2002] ^[27].

Assessing the quality of life:

There are many methods of assessing the QoL. The one made use of in this research is Short Form 36 (SF 36).

Short form 36:

The short form 36 is a health survey which used to measure the health-related quality of life in patients with disorders. It is useful in evaluating individual patient's health status, monitoring and comparing the disease burden on quality of life [Ware Jr JE, 1992]^[37].

The short form 36 consists of nine scaled scores which are weighted sums of the questions in their section. Each scale is directly transformed into 0-100 scale. The lower the score higher disability. The higher the score the lesser disability.

The nine sections are

1. Physical functioning
2. Social functioning
3. General health
4. Emotional well being
5. Physical role functioning
6. Emotional role functioning
7. Energy/fatigue
8. Pain
9. Health change

d) Life style modifications:

The life style modification strategies that are most commonly recommended within treatment guidelines include proper nutrition, physical activity, weight control, tobacco cessation, alcohol moderation and health behavior change strategies [Thomas L et.al, 2008]^[34]. Pharmacists have frequent contact with patients who could potentially benefit from life style modification education. Pharmacists are in ideal position to offer patients information, guidance and counseling regarding life style changes that can help manage their medical condition [Lenz TL et.al, 2008]^[28]. Behavioral modification aspects for patients were physical exercise this involved initiation of an exercise plan that could be incorporated into the patient's daily schedule after taking into consideration of their physical fitness, e.g. 1-hour walk daily; diet include dietary plan that influences the good blood glucose control;

medication adherence i.e., patients were offered education and practical help to encourage them to take medicines prescribed for them by the physician; and smoking cessation patients were encouraged to stop smoking [Korcegez EI et.al, 2017] ^[25].

e) Self-care activities:

The ability of individuals and communities to promote health, prevent disease, maintain health and to cope with illness with or without support of health care provider is called self-care[Manjula Narasimhan et.al, 2019] ^[35]. This self-care of the patients can be improved by patient counseling and patient education by the pharmacist. This self-care activities can be measured by Summary of Diabetic Self Care Activities form (SDSCA form) in diabetic patients. [Korcegez EI et.al, 2017] ^[25].

SDSCA Questionnaire:

The SDSCA questionnaire is a well-documented, validated tool that measures the self-care behavior of the patients. It has 5 sections each section is answered and scored separately by recalling their self-care behaviors during the previous 7 days [da Silva GR, 2014].

1. Diet (4 questions), for example “How many of the last 7 days have you followed a healthy eating plan?
2. Exercise (2 questions), for example “During how many of the last 7 days did you participate in at least 30 minutes of physical activity?
3. Foot care (2 questions), for example “During how many of the last 7 days did you check your feet?
4. Smoking (2 questions), for example “Have you smoked a cigarette during past 7 days?
5. Medication (1 question) “Have you forget the administration of medication in past 7 days?

REVIEW OF LITERATURE

- **Sohyunjeong, Minhee Lee., (2018)** conducted a study on **“Effect of pharmaceutical care interventions on glycemic control in patients with diabetes”** the study showed that an adequate duration of pharmaceutical care was effective in patients with diabetes in LMIC and HIC.
- **Mohamed A Mohamed*, (2016)** conducted a study on **“Impact of pharmaceutical care interventions on health-related quality of life outcomes”** and concluded that Pharmaceutical care interventions can significantly improve the health-related quality of life on the type 2 diabetes mellitus patients.
- **Sarah pousinhoet.al (2016)** conducted a study on **“Pharmacist interventions in management of type2 diabetes mellitus”** and concluded that pharmacist interventions can have a positive influence on metabolic control, medication adherence and HRQoL of patients with type2 diabetes. This promising finding support the involvement of pharmacist as members of a health care team in the management of type2 diabetes.
- **Liang Chen et al., (2015)** conducted the study on **“Effect of lifestyle intervention in patients with type 2 diabetes”** and concluded that life style intervention showed significant benefit in risk factors that are known to be associated with development of cardiovascular diseases in patients with type 2 diabetes.
- **Maxwell O. Adibe, N. Aguvaetal., (2013)** conducted a study on **“The impact of pharmaceutical care interventions on the quality of life of Nigerian patients receiving treatment with type 2 diabetes”** and concluded that the overall health related quality of life of the patients was significantly improved in the intervention group when compared with control group.
- **[M. Ali et al., \(2012\)](#)** conducted a study on **Impact of community pharmacy diabetes monitoring and education programme on diabetes management: a randomized controlled study** and concluded that Education and counselling by community pharmacists can result in favorable improvements to the cardiovascular risk profile of patients with Type II diabetes mellitus.
- **Paulo Roque Obrelineto, et al., (2011),** conducted the study on **“Effect of 36month pharmaceutical care programme in pharmacotherapy adherence in elderly diabetic and hypertensive patients”** and concluded that the effectiveness of

pharmaceutical care in improving pharmacotherapy adherence with positive effects in clinical outcomes of the patients studied.

➤ **ShadiFarsaei, (2011)** conducted the study on **“Effect of pharmacist led patient education on glycemic control of type 2 diabetes patients”** and concluded that an improvement in diabetes management of type 2 diabetics by involving a pharmacist in the multidisciplinary teams in outpatient clinics.

➤ **Courtney Collins et.al (2011)** conducted a study on **“Effect of pharmacist interventions on glycemic control in diabetic patients”** and concluded that pharmacist interventions improve A1C and FBG in patients with type1 or type2 diabetes, pharmacist may play integral role in management of diabetes care.

➤ **Shanmugam Sriram, Lini Elizabeth chack (2011)** Conducted study on **“Impact of pharmaceutical care on quality of life in patients with type 2 diabetes mellitus”** and conclusion of the study that the pharmaceutical care program was effective in improving the clinical outcome and the patients QOL with type 2 diabetes mellitus.

➤ **Anna Paula de saborges, (2010)** conducted a study on **“The pharmaceutical care of patients with type 2 diabetes mellitus”** and the concluded that a significant reduction in the levels of glycosylated hemoglobin was detected in patients in the pharmaceutical care group and an average increase was observed in control group.

➤ **N. Rashid Al Mazroui, Mostafa Mohamed Kamal., et al., (2009)** conducted a study on **“the influence of pharmaceutical care programme on health outcomes in patients with type 2 diabetes mellitus”** found that the pharmaceutical care programme resulted in better glycaemic control and reduced cardiovascular risk scores in type 2 diabetes patients over a 12-month period.

➤ **Ruba A. Wishah , M.Albsoul (2008)** conducted a study on **“Impact of pharmaceutical care interventions on glycemic control and other health related clinical outcomes in patients with type 2 DM: randomized clinical trial”** and concluded that an improvement in Hb1ac,FBS and lipid profile in addition to self-reported medication adherence in patients with type 2 diabetes mellitus who received pharmaceutical care interventions. The results suggest that the benefits of integrating clinical pharmacist services in multidisciplinary healthcare team.

➤ **Deborah P Wubben (2008).**, conducted the study on **“Effects of pharmacist outpatient interventions on adults with diabetes mellitus: a systematic review”**

and concluded that overall improvement in intervention group of A1c levels and the pharmacist interventions can reduce long term costs by improving glycemic control and thus diminishing the future diabetes complications.

➤ **A. Lindenmeyer et.al (2005)** conducted a study on **“Interventions to improve adherence to medication in people with type 2 diabetes mellitus”** and found that potential benefit of pharmacist interventions to improve medication adherence in type2 diabetes, especially in providing patient education.

➤ **Joel Wermeielle*(2004)** conducted a study on **“pharmaceutical care model for patients with type 2 diabetes: integration of community pharmacist in to diabetes team”** in conclusion a feasible pharmaceutical care model for diabetes patients. The results have been shown the pharmacist to be effective by his interventions for better glycemic control and well accepted by the physicians.

➤ **Carole W. Cranor, (2003)** conducted the study on **“The short-term outcomes of a community pharmacy diabetes care program”** and concluded that improved A1c improved patient satisfaction with pharmacy services, and decreased all diagnosis costs. Findings from this study demonstrate that pharmacists provided effective cognitive services and refute the idea that pharmacists must be certified diabetes educators to help patients with diabetes improve clinical outcomes.

AIM AND OBJECTIVES

➤ **AIM:**

- To study the impact of pharmacist interventions on therapeutic outcomes of 150 Type 2 diabetes mellitus patients in a tertiary care hospital.

➤ **OBJECTIVES:**

- To study the impact of pharmacist interventions on the relevant clinical parameters i.e., Glycosylated haemoglobin (HbA1c), Blood pressure, fasting blood sugar(FBS), Post prandial blood sugar(PPBS) in type II diabetes mellitus patients.
- To study the impact of pharmacist interventions on quality of life by using Short Form 36 scale in type II diabetes mellitus patients.
- To study the impact of pharmacist interventions on self-care activities by using summary of diabetes self-care activities form (SDSCA form) in type II diabetes mellitus patients.
- To study the impact of pharmacist interventions on pharmacotherapy adherence by using Morisky green Levine test in type II diabetes mellitus patients.
- To create awareness about glycaemic control in diabetes mellitus patients.

PLAN OF WORK

Title selection and literature review



Ethical committee approval



Designing of patient data collection form



Patient informed consent form



Screening and identification of Type 2 diabetes patients



Categorising the patients into intervention group and control group



Collection of data



Follow up



Statistical analysis of the data



Interpretation and results

MATERIALS AND METHODS

5.1 MATERIALS:

1. Institutional ethics committee approval (**Annexure – I**).
2. Patient informed consent form in English (**Annexure-II**).
3. Patient informed consent form in Telugu (**Annexure-III**).
4. Patient data collection form (**Annexure-IV**).
5. Patient information leaflet (**Annexure-V**).

METHODS:

5.2 Ethical consideration: The protocol of the study was approved by the institutional ethics committee of Santhiram medical college and general hospital, Nandyal. The study was conducted in compliance with good clinical practice guidelines.

5.3 Study design: It is a prospective observational study which includes patients with type II diabetes mellitus from general medicine department of Santhiram medical college and general hospital to assess the impact of pharmacist interventions on therapeutic outcomes in type 2 diabetes mellitus patients in tertiary care hospital.

5.4 Study site: Santhiram general hospital and medical college, Nandyal, which is tertiary care teaching hospital.

5.5 Study duration: 6 months (July 2019-December 2019)

5.6 Sample size: 150 patients

5.7 STUDY CRITERIA: Patients are included in the study by taking prior permission from the patient by using patient informed consent form

➤ **INCLUSION CRITERIA:**

- The patients who are diagnosed with Type II Diabetes mellitus
- Patients with informed consent form
- Patients with no other co-morbid conditions.
- Patients able to attend regular visits.
- Patient above the age of 35 years.

➤ **EXCLUSION CRITERIA:**

- Participants unwilling to join the study.
- Pregnant women

5.8 STUDY PROCEDURE:

1) Development of patient data collection proforma:

The patient data collection proforma contains the patient details includes patient name, age, sex, height, weight, occupation, life style, social history, past medical and medication history, laboratory investigations and treatment including SDSCA form, Short Form 36, Morisky green levine test form.

2) Patient consent:

The type II Diabetes mellitus patients were identified Study details were explained to the patients and the written informed consent forms were obtained, and interviewing them for different parameters which was mentioned in the patient data profile form.

3) Source of data:

- Prescriptions
- Case sheets
- Discharge medication chart

4) Data collection:

The IP/OP.NO, age and gender of each individual were recorded in the patient profile form, all the relevant information was collected by interacting with the patient and also by direct measurement of physical parameters.

5) Baseline measures and assessments:

After recruitment each patient was interviewed face to face for approximately 15 minutes by the research pharmacist and a chart review undertaken to obtain details on demographics, family history of diabetes, medications being used, diabetes symptoms, frequency of daily blood glucose monitoring, diabetes and medication knowledge, adherence to medication and life style advise and to record the HbA1c, fasting blood glucose, post prandial blood glucose, systolic and diastolic blood pressure. Patients were also asked to self-complete the questionnaires on health-related quality of life [short form 36], adherence scale [morisky green levine test] and

self-care activities [SDSCA]. If they are unable to fill themselves the research pharmacist ask the questionnaire and filled it in front of patients.

6) Description of pharmacist interventions:

Patients who are randomized to the intervention group were educated by the research pharmacist on their illness and their medication including the risk of diabetes complications, proper dosage, time and route of administration, side effects and storage of medications, importance of self-monitoring of glucose, a healthy diet, physical exercise and smoking cessation, healthy life style and management of type 2 diabetes signs and symptoms through self-monitoring.

A printed leaflet to assist with the education program was developed and the patient was given a copy to take home. The educational advice reinforced when patients came for follow up or by a telephone follow up. This pamphlet contains the information about type 2 diabetes, complications, treatment goals and self-care.

In addition to this behavioral modification aspects for patients were physical exercise this involved initiation of an exercise plan that could be incorporated into the patient's daily schedule after taking into consideration of their physical fitness, e.g. 1-hour walk daily; diet include dietary plan that influences the good blood glucose control; medication adherence i.e., patients were offered education and practical help to encourage them to take medicines prescribed for them by the physician; and smoking cessation patients were encouraged to stop smoking.

The patients randomized to the control group received their normal care but did not receive the clinical pharmacy service, i.e. did not receive pharmacist input into treatment plans or patient education. However, they receive advice in self-monitoring of blood glucose levels by medical staff.

5.9 PARAMETERS OF THE STUDY

5.9.1 Age:

Age in years is the primary parameter to evaluate the occurrence of disease, severity of the disease and treatment outcomes of the disease in patients diagnosed with type 2 diabetes.

5.9.2 Gender:

By evaluating gender, we can analyze the occurrence of disease, severity of disease, treatment outcomes of the disease.

5.9.3 Literacy status:

The literacy status of the patients influences the important health outcomes, including the acquisition of diabetes specific knowledge, improving self-efficacy, adherence with medication regimens and self-care behaviors. Low literacy of the patients has been consistently associated with worse diabetes knowledge and they may not improve their knowledge as recipients of pharmacist interventions as much as those patients with adequate literacy.

5.9.4 Occupational status:

The occupational status of the patients plays a major role in management of diabetes. Reduction in physical activity and an increase in sedentary behavior have impact on the glycemic levels in the blood. Reduced physical activity can increase the chances of developing insulin resistance.

5.9.5 DM duration in years:

The longer the duration of diabetes in the patients resulted in poorer glycemic control, lower adherence and decreased self-care activities due to diabetes-related stress. Diabetes education has more favorable clinical outcomes in newly or recently diagnosed patients as compared with the longer duration of diabetic patients. Hence diabetic patients with a longer duration need special attention from the pharmacists in providing the pharmacist interventions. It is important to consider the psychological and emotional support for type 2 diabetic patients especially those with longer duration of diabetes to maximize the effectiveness of pharmacist interventions.

5.9.6 Social history:

The social history of the patients is the important parameter in the management of diabetes. Drinking the moderate amounts of alcohol may actually doesn't affect the risk of diabetic complications. But higher amounts of alcohol consumption may cause the inflammation of pancreas, which leads to impair its ability to secrete insulin and influences the blood glucose levels.

Diabetes patients who smoke have the trouble with controlling their disease and they may require higher dosing of insulin than the non smoker diabetic patients. Smokers with diabetes have higher risk of complications including heart and kidney disease, DVT, retinopathy and peripheral neuropathy.

5.9.7 Prescribed drugs (OHA's, insulin and combination therapy):

The number of prescribed drugs to the patients will also affect the adherence towards the prescribed drugs. The newly diagnosed patients may be advised with life style modifications along with metformin monotherapy. If glycemic targets not achieved then switch to combination therapy or insulin therapy. This will help the pharmacist in explaining the proper dosage, time and route of administration, side effects and storage of medications.

5.9.8 Glycosylated hemoglobin (HbA1c):

This is a blood test that measures the form of hemoglobin that is bound to glucose. The blood test for HbA1c level is routinely performed in people with type 1 and type 2 diabetes mellitus. This level is reflective of how well diabetes is controlled.

5.9.9 Fasting blood sugar (FBS):

This is a blood test that measures the amount of glucose in a blood sample after an overnight fast which is measured in mg/dl. This test is commonly used to detect diabetes and how well diabetes is controlled.

5.9.10 Post prandial blood sugar (PPBS):

This is a blood test that measures the amount of glucose in a blood sample after a certain meal past 2 hours which is measured in mg/dl. This test is commonly used to detect diabetes and how well diabetes is controlled.

5.9.11 Blood pressure:

It is the pressure of the blood in the circulatory system, often measured for diagnosis since it is closely related to the force and rate of the heart beat which is measured in mmHg. Monitoring and controlling of blood pressure is useful in early detection of various cardiovascular problems.

5.9.12 Short form 36:

The short form 36 is a health survey which used to measure the health-related quality of life in patients with disorders. It is useful in evaluating individual patient's health status, monitoring and comparing the disease burden on quality of life.

The short form 36 consists of nine scaled scores which are weighted sums of the questions in their section. Each scale is directly transformed into 0-100 scale. The lower the score more disability. The higher the score the less disability.

The nine sections are

1. Physical functioning
2. Social functioning
3. General health
4. Emotional well being
5. Physical role functioning
6. Emotional role functioning
7. Energy/fatigue
8. Pain
9. Health change

5.9.13 SDSCA Questionnaire:

The SDSCA questionnaire is a well-documented, validated tool that measures the self-care behavior of the patients. It has 5 sections each section is answered and scored separately by recalling their self-care behaviors during the previous 7 days.

1. Diet (4 questions), for example "How many of the last 7 days have you followed a healthy eating plan?"
2. Exercise (2 questions), for example "During how many of the last 7 days did you participate in at least 30 minutes of physical activity?"
3. Foot care (2 questions), for example "During how many of the last 7 days did you check your feet?"
4. Smoking (2 questions), for example "Have you smoked a cigarette during past 7 days?"
5. Medication (1 question) "Have you forget the administration of medication in past 7 days?"

5.9.14 Morisky Green Levine test:

Medication adherence was assessed using the morisky-green test. This test consists of 4 questions.

1. Do you ever forgotten to take your medications?
2. Are you careless at times about taking your medication?
3. When you feel better do you stop taking your medications?
4. When you feel worse do you stop taking your medications?

Patients were considered adherent if they answered “no” to all questions. If a patient answered “yes” to any question, the patient was considered as non adherent.

5.10 TIME LINE:

I.Phase I (1month)

- Selection of topic- 1 week
- Collection and review of literature- 1 week
- Preparation of protocol- 1 week
- Institutional Ethical committee approval-1 week

II.Phase II (4months) – Data collection

- Selection of patient by reviewing case reports.
- Selection of patient by reviewing prescriptions.

III.Phase III (1month) – Data Analysis and Final submission.

- Result calculation based on statistical analysis- 1 week
- Thesis preparation- 1 week
- Manuscript correction- 1 week
- Planning for submission of final project work- 1 week

5.11 STATISTICAL ANALYSIS

The data was analyzed using Graph Pad Prism statistical software version 6.04 and SPSS (statistical package for social science) software version 22.0. fishers test is used to compare the analyzed data and a value of $p \leq 0.05$ is taken as statistical significance.

RESULTS& OBSERVATION

6.1 Age wise distribution

Age wise distribution is the primary parameter to evaluate occurrence, severity and treatment outcomes of the disease in patients diagnosed with type 2 diabetes mellitus.

Table No 6.1Age wise distribution

Age (in years)	Intervention group(n)	(%)	Control group(n)	(%)	P value
35-45	15	18.6	7	9.33	0.393
46-55	28	37.3	16	22.66	
56-65	23	30.6	36	48	
66-75	9	13.3	11	14.66	
76-85	0	0	5	5.33	
Total	75	100	75	100	

*NS=No significant differences in variables according to fishers exact test

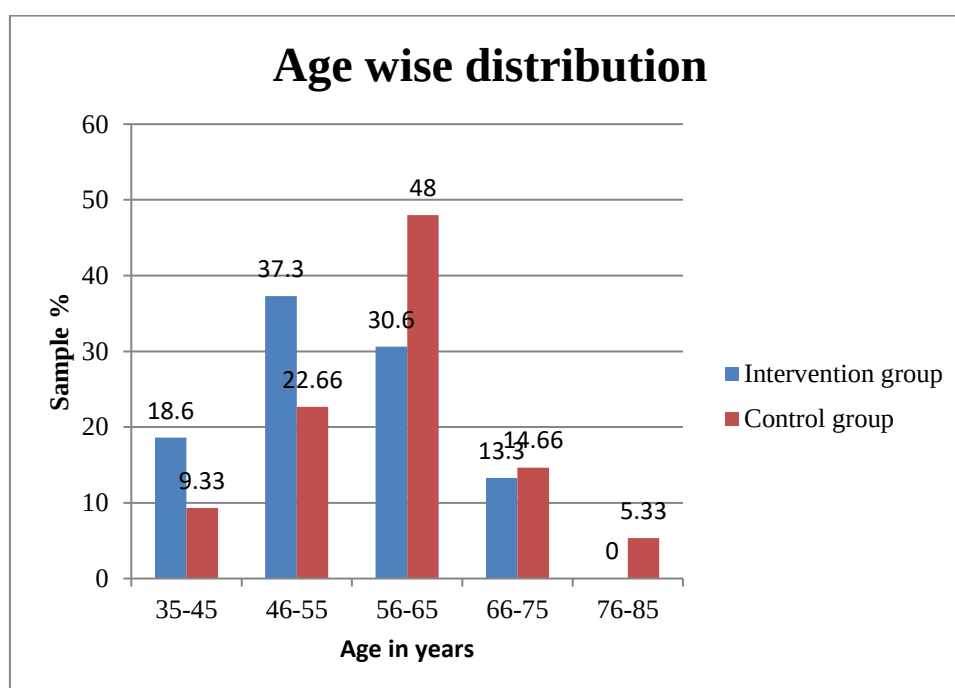


Fig no 6.1 Age wise distribution of type 2 diabetic patients

6.2 Gender wise distribution

By evaluating the gender we can analyse the occurrence, severity and treatment outcomes of the disease in patients diagnosed with type 2 diabetes mellitus.

Table no 6.2 Gender wise distribution

Education	Intervention group(n)	%	Control group(n)	%	P value
Males	40	53.3	48	64	0.14
Females	35	46.6	27	36	
Total	75	100	75	100	NS

*NS=No significant differences in variables according to fishers exact test

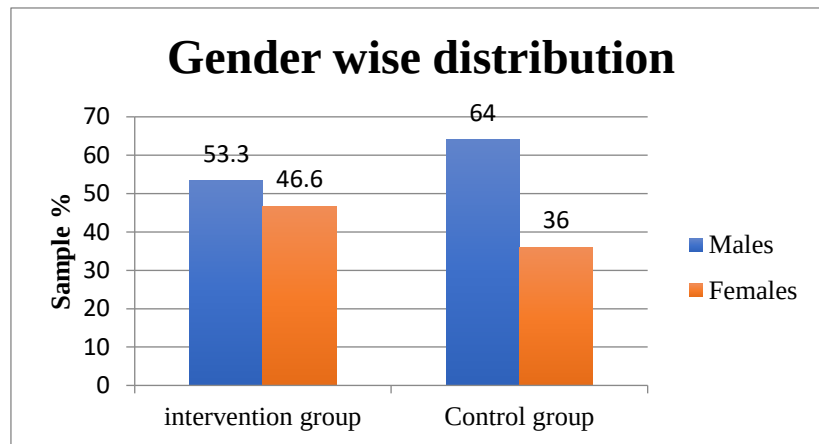


Fig no 6.2 Gender wise distribution of type 2 diabetic patients

6.3 Educational status of Type 2 diabetes patients

Among the 150 patients of both intervention and control groups percentage of Type 2 diabetes mellitus occurrence is more in the illiterate patients.

Table No 6.3: Educational status of Type 2 diabetes patients

Education	Intervention group(n)	%	Control group(n)	%	P value
Illiterate	42	56	47	62	0.28
literate	33	44	28	38	
Total	75	100	75	100	NS

*NS=No significant differences in variables according to fisher's exact test

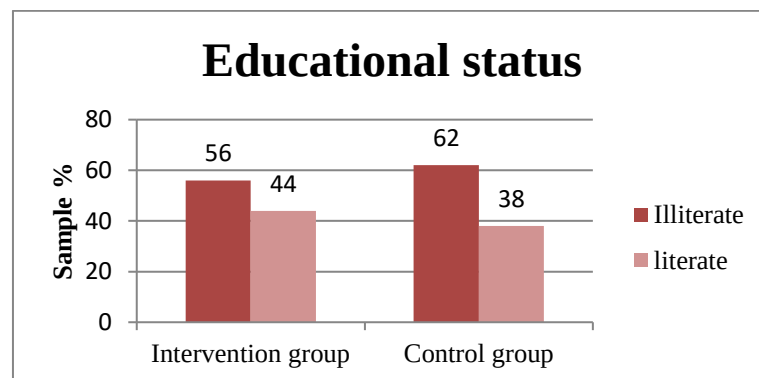


Fig no 6.3 Educational status of Type 2 diabetes patients

6.4 Occupational wise distribution

Table No 6.4: Occupation wise distribution of Type 2 diabetes patients

Working status	Intervention group(n)	%	Control group(n)	%	P value
Domestic	4	5.3	1	1.3	0.31
Employee	6	8	1	1.3	
Agriculture	40	53.3	49	65.3	
Sedentary	25	33.3	24	32	
Total	75	100	75	100	NS

*NS=No significant differences in variables according to fishers' exact test

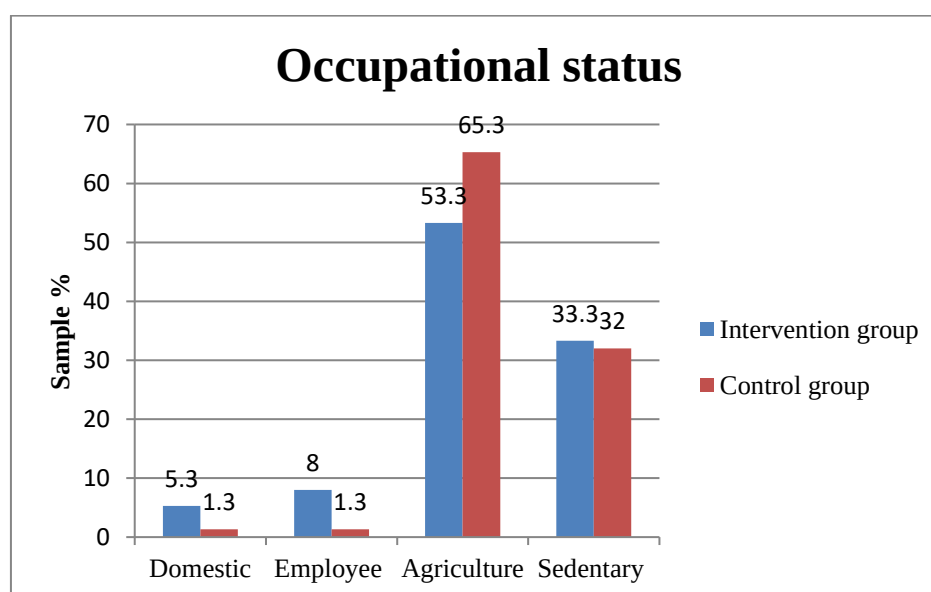


Fig no 6.4 Occupation wise distribution of Type 2 diabetes patients

6.5 Duration of Type II DM in patients

Table no 6.5 Duration of Type II DM in patients

Duration of diabetes in years:	Intervention group(n)	%	Control group (n)	%	P value
De novo	11	14.6	5	6.6	0.35
1-10	47	62.6	55	73.3	
11-20	15	20	15	20	
21-30	2	2.6	0	0	
Total	75	100	75	100	NS

*NS=No significant differences in variables according to fisher's exact test

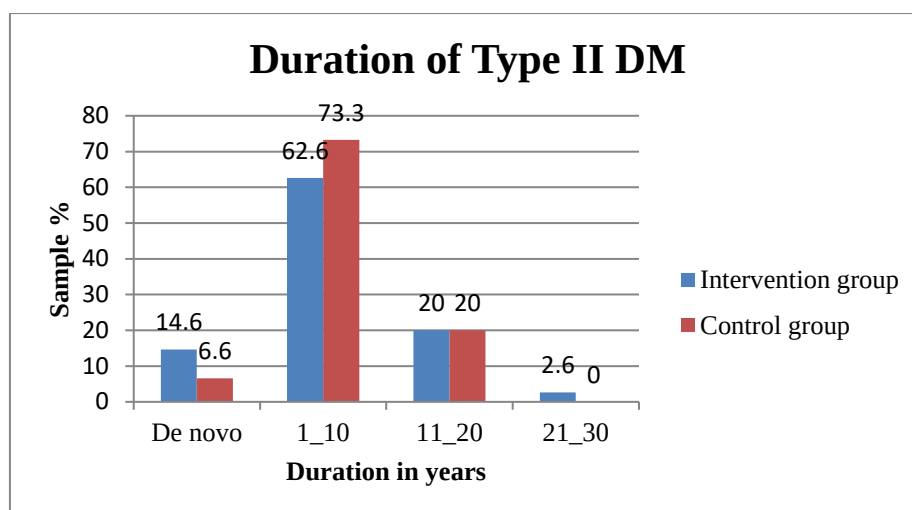


Fig no 6.5 Duration of Type II DM in Patients

6.6 Drug wise distribution

Among 150 patients of both intervention and control groups were prescribed with the anti-diabetic drugs equally.

Table no 6.6 Drug wise distribution of Type 2 diabetes patients

Anti-diabetic medications	Intervention group	Control group	P value
Metformin	60	62	0.44
Sulphonyl urea's	48	48	
Insulin	30	30	
Other hypoglycemic's	5	4	
Anti-hypertensives	18	14	NS

*NS=No significant differences in variables according to fisher's exact test

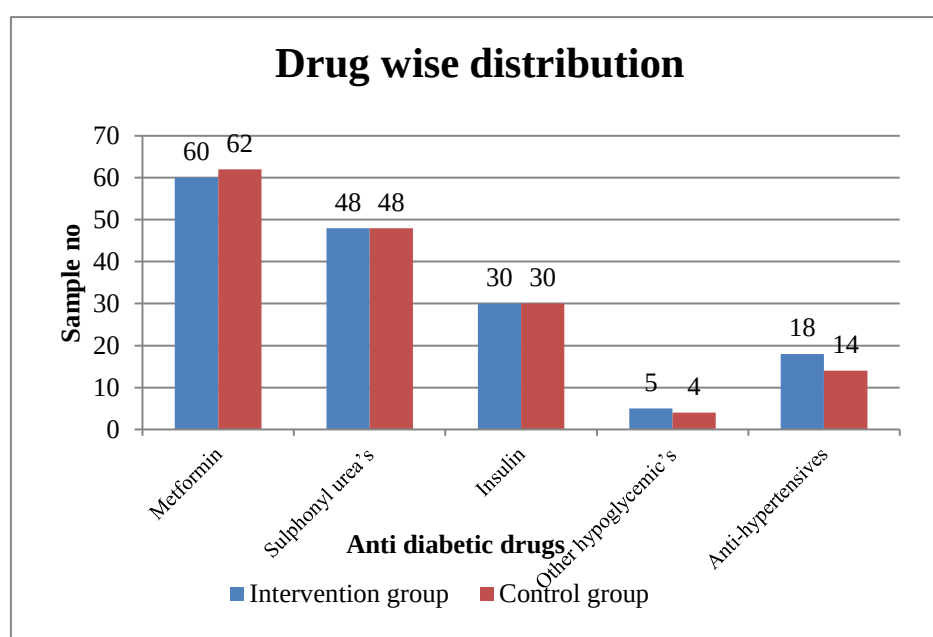


Fig no 6.7 Drug wise distribution of Type 2 diabetes patients

6.7 Social history

The social histories of the intervention group and control group patients at the baseline are as follows

Table no 6.7 Social history of Type 2 diabetes patients

Social history	Intervention group				Control group			
	Alcoholics	%	Smokers	%	Alcoholics	%	Smokers	%
Yes	14	18.3	12	16	20	26.6	21	28
No	61	81.6	63	84	55	73.3	54	72
Total	75	100	75	100	75	100	75	100

6.10 Changes in therapeutic outcomes between Groups

The changes in the therapeutic outcomes from baseline to end of the study of the patients in both intervention group and control group are as follows

Table No 6.8 Changes in therapeutic outcomes between Groups

Clinical parameter	Intervention group				Control group			
	Baseline mean	1 st month mean	2 nd month mean	4 th month mean	Baseline mean	1 st month mean	2 nd month mean	4 th month mean
HbA1c%	8.34			7.16	7.18			7.12
Fasting blood glucose (mg/dl)	191.4	135.8	116.3	110.4	178.9	163.8	144	134.1
Post prandial blood glucose (mg/dl)	279.9	201.9	170.3	152.6	274.5	235.9	210.4	193.1
Systolic blood pressure (mmHg)	133.1	125.7	124.5	121.2	129.6	128.6	127.6	123.6
Diastolic blood pressure (mmHg)	84.9	82	80.8	80	83.2	80.2	81.4	81.2

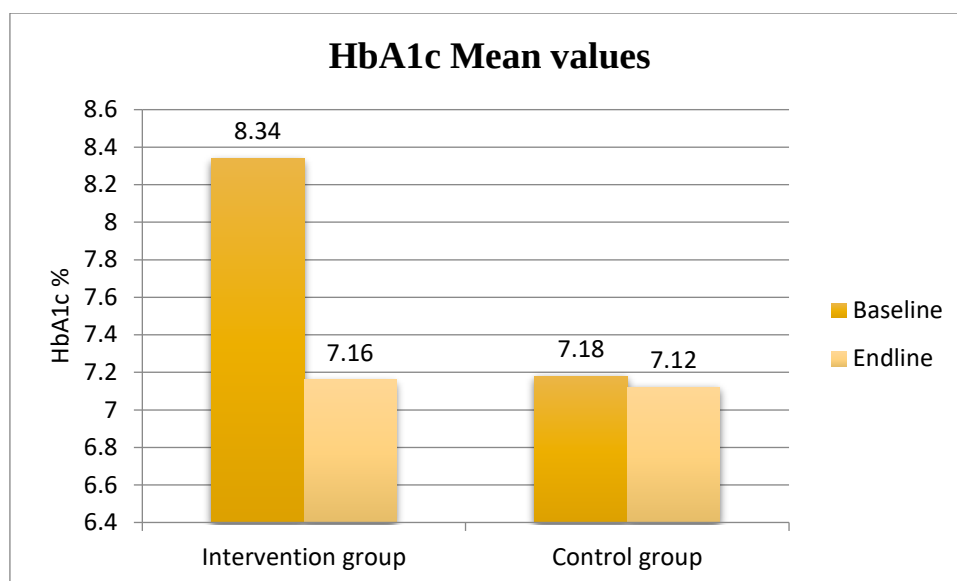


Fig no 6.7 Changes in HbA1c Mean values

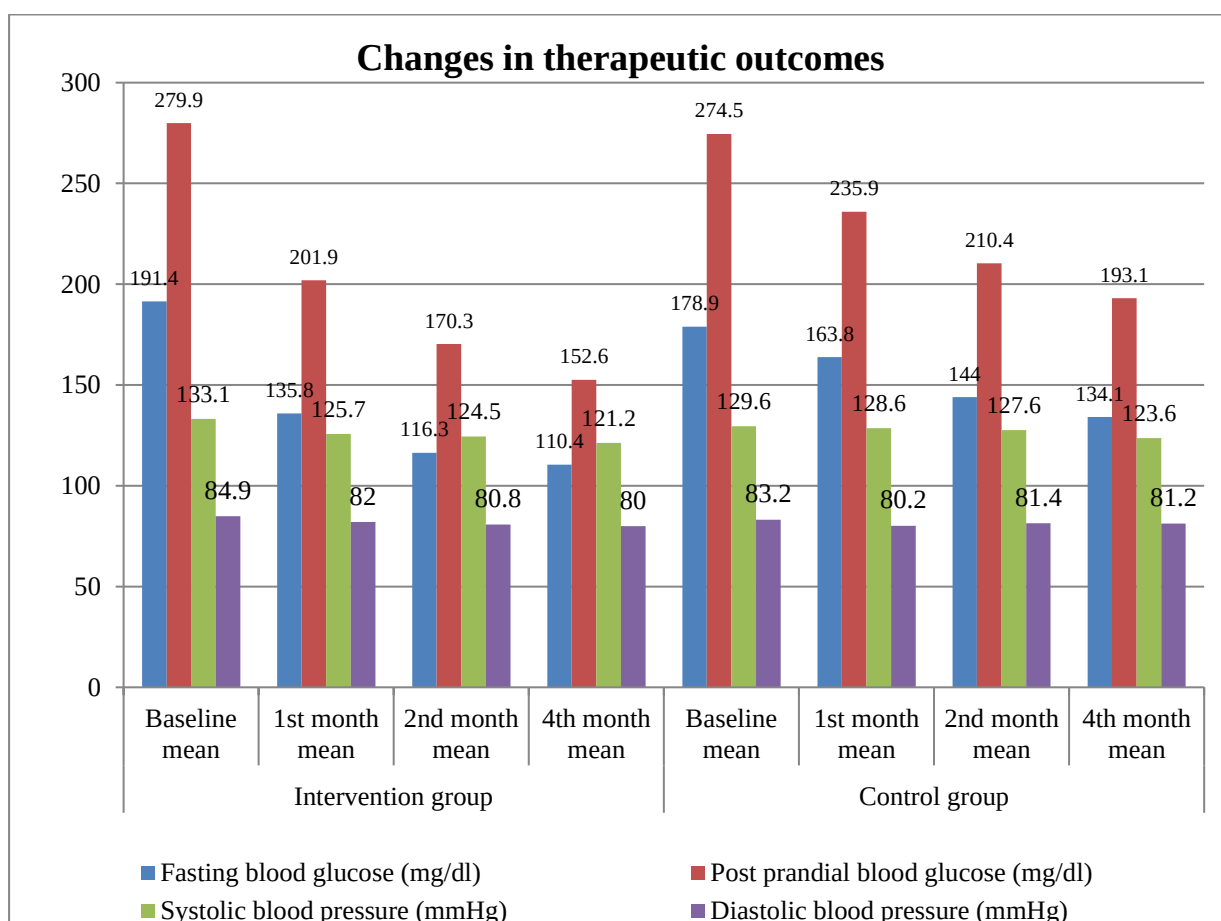


Fig no 6.8 Changes in therapeutic outcomes

Table no 6.9 Changes in therapeutic outcomes between Groups from baseline to end line

Clinical parameter	Intervention group				Control group			
	Baseline mean	End line mean	Mean difference	P value	Baseline mean	End line mean	Mean difference	P value
HbA1c%	8.34	7.16	-1.18	0.1	7.18	7.12	-0.51	0.3
Fasting blood glucose (mg/dl)	191.4	110.4	-81	0.001	178.9	134.1	-44	0.1
Post prandial blood glucose (mg/dl)	279.9	152.6	-127	0.001	274.5	193.1	-81	0.01
Systolic blood pressure (mmHg)	133.1	121.2	-12	0.001	129.6	123.6	-6	0.5
Diastolic blood pressure (mmHg)	84.9	80	-2	0.001	83.2	81.2	-0.2	0.02

*p value<0.01 indicates significant according to student independent t test

HbA1c, FBS and PPBS:

- The intervention group patients achieved a significant reduction in HbA1c values than the usual care patients (mean difference-1.18% vs. -0.51%) at the end of the four-month study period.
- The intervention group patients show a greater reduction of FBS and PPBS values ($P<0.001$) than the control group patients (-81mg/dl vs -44mg/dl) and (-127mg/dl vs -81mg/dl).

Blood pressure:

- Comparing the intervention group with control group there were significant decreases in systolic blood pressure($p<0.001$) of intervention group than the control group systolic blood pressure($P=0.80$) and the diastolic blood pressure of both groups have a similar reduction ($p<0.01$).

6.10 Health related Quality of life

Table No 6.10 Summary of Short Form 36 data

Domain	Intervention group			Control group		
	Baseline	End of study	P value	Baseline	End of study	P value
Physical functioning	66.8	77	0.08	59	62.2	0.9
Social functioning	76.5	81.09	0.6	73.1	75.3	0.92
General health	77	86.1	0.08	72	75.1	0.46
Emotional well being	73	82	0.46	67.05	69.9	0.68
Role-physical	55.4	64.8	0.21	44	50.0	0.6
Role-emotional	87.02	93.7	0.0001	89.3	91.1	0.7
Energy/Fatigue	74.8	81.5	0.02	69.5	73.4	0.88
Pain	61.2	74.2	0.08	55.6	60.9	0.42
Health change	45.3	59.6	0.0001	42.2	51.3	0.06

*p value<0.01 indicates significant according to student independent t test

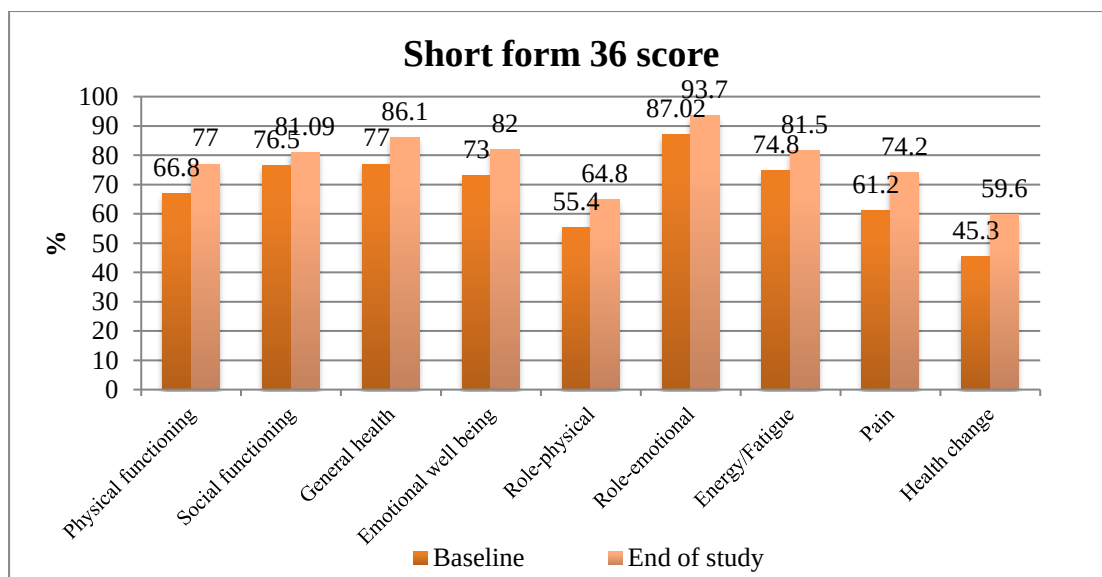


Fig no 6.9 Short form 36 score of intervention group

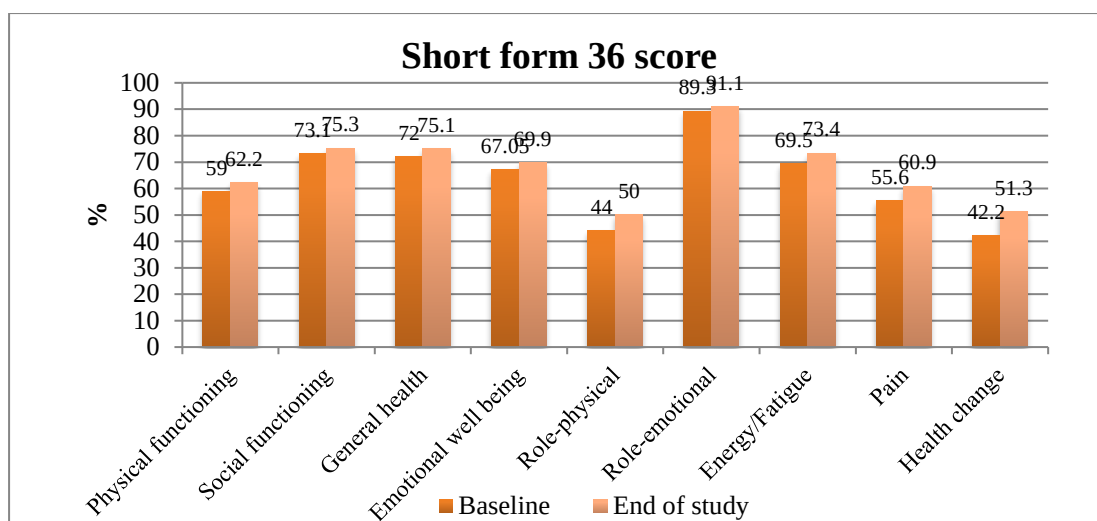


Fig no 6.10 Short form 36 score of control group

Health related Quality of life (SF36 questionnaire):

- In the SF36 some domains almost have the same score at baseline but after 4-month study period the intervention group patients have the higher domain scores. This shows intervention group patients quality of life were improved better than the control group.

6.11 Adherence Rate of patients according to Morisky green test

Table no 6.11 Adherence Rate of patients according to Morisky green test

Adherence assessment	Intervention group					Control group				
	Baseline	%	End of study	%	P value	Baseline	%	End of study	%	P value
Adherent	30	46.6	65	86.6	0.001	26	34.6	37	49.3	0.13
Non-Adherent	45	66.4	10	13.3		49	65.3	38	50.6	
Total	75	100	75	100		75	100	75	100	

*p value<0.01 indicates significant according to student independent t test

Adherence:

- According to the morisky green levine test at baseline 66% of intervention group and 65% of control group patients were non adherent (Table 11). During the study period intervention group showed a significant increase ($p<0.001$) in pharmacotherapy adherence whereas the control group showed slighter changes compared with baseline values ($p=0.13$).

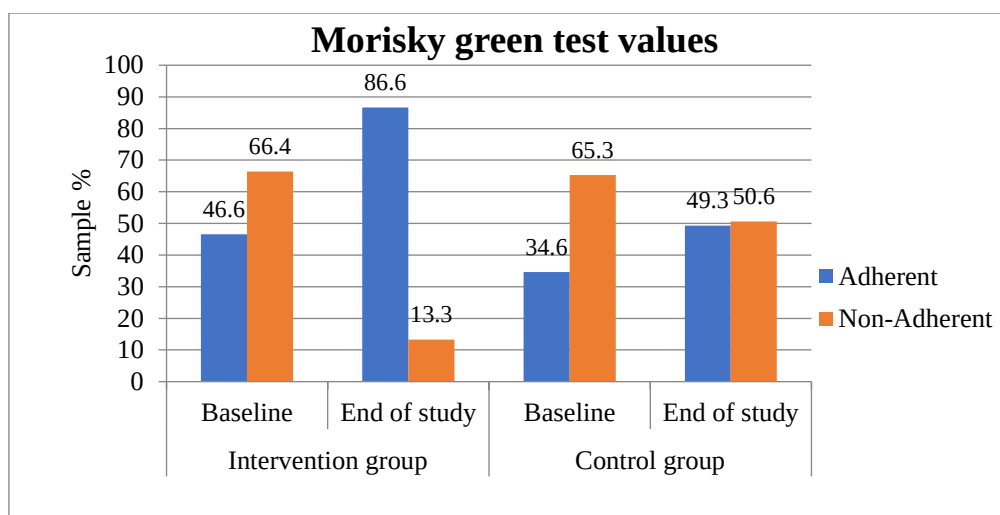


Fig no 6.11 Adherence Rate of patients

6.12 Self-care activities score

Table no 6.12 Change in self-Care activity scores

Self-care Activities	Intervention group			Control group		
	Baseline	End of study	P value	Baseline	End of study	P value
Total diet score	3.32	4.40	0.006	3.12	3.39	0.16
Total exercise score	1.99	3.64	0.52	1.43	2.08	0.82
Total foot care score	1.44	2.92	0.005	1	1.9	0.08
Smokers (n)	12	8	0.88	21	19	0.58
Total medication score	5.4	6.88	0.001	5.32	5.88	0.04

*p value<0.01 indicates significant according to student independent t test

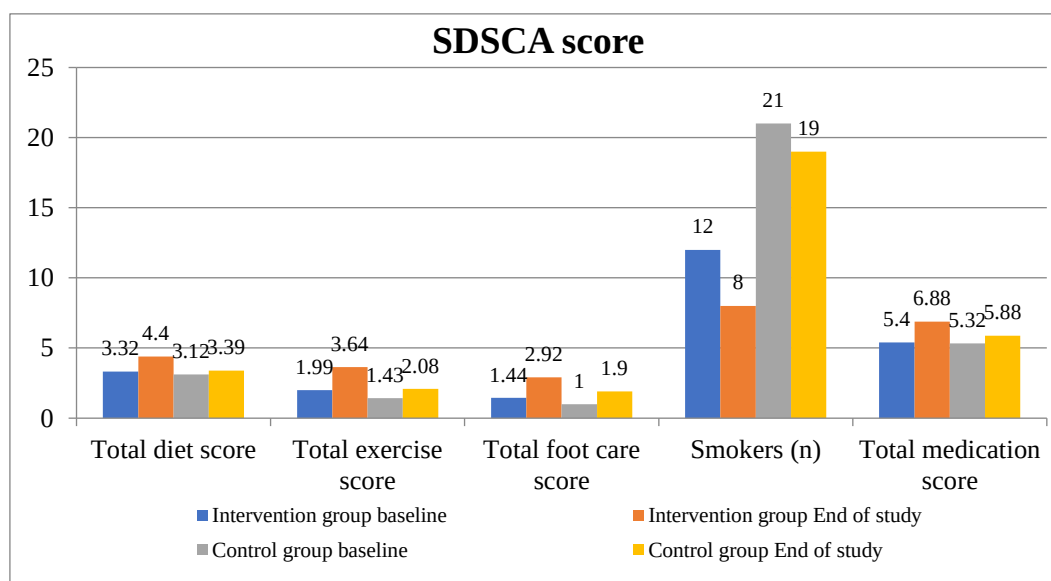


Fig no 6.12 SDSCA score of type 2 diabetic patients

Self-care activities (SDSCA score)

- Patients in intervention group achieved significant improvements in their total diet score ($p < 0.01$), total foot care score ($p < 0.01$), total medication score ($p < 0.01$) versus usual care patients (Table 12). Patients in the control group did not achieve any significant improvements in the any of above domains except for the total exercise score of both the groups were same.

DISCUSSION

The present study was designed to measure the impact of pharmacist interventions on the clinical outcomes in the patients with type 2 diabetes mellitus. During the study period 150 eligible patients were identified and the clinical data was collected from them by getting consent form in bilingual languages (Telugu and English).

In the 150 patients 75 patients were in intervention group and 75 patients were in control group. The baseline clinical parameters of the patients were collected from the first visit of the patients to the hospital. Patients of intervention group received the pharmacist interventions, Patients who are randomized to the intervention group were educated by the research pharmacist on their illness and their medication including the risk of diabetes complications, proper dosage, time and route of administration, side effects and storage of medications, importance of self-monitoring of glucose, a healthy diet, physical exercise and smoking cessation, healthy life style and management of type 2 diabetes signs and symptoms through self-monitoring.

A printed leaflet to assist with the education program was developed and the patient was given a copy to take home. The educational advice reinforced when patients came for follow up or by a telephone follow up. This pamphlet contains information about type 2 diabetes, complications, treatment goals, diet chart, and self-care.

In addition to this behavioral modification aspects for patients were physical exercise this involved initiation of an exercise plan that could be incorporated into the patient's daily schedule after taking into consideration of their physical fitness, e.g. 1-hour walk daily, diet include dietary plan that influences the good blood glucose control, medication adherence i.e., patients were offered education and practical help to encourage them to take medicines prescribed for them by the physician and smoking cessation patients were encouraged to stop smoking.

The patients randomized to the control group received their normal care but did not receive the clinical pharmacy service, i.e. did not receive pharmacist input into treatment plans or patient education. However, they receive advice in self-monitoring of blood glucose levels by medical staff.

All the patients in the intervention group and control group were advised to attend for the Follow up - I and Follow up- II Follow up-III, the clinical parameters of the patients was collected at every follow up through phone or direct contact.

The observations revealed that from the table No.6.1 and Fig No.6.1 all 150 patients (intervention group 75 and control group 75) were divided based upon their age. All the patients were within 35-85 years of age. In that 51(67.9%) of intervention group and 52(70.6%) of control group with maximum occurrence of DM was noticed between 46-65 years of age group.

From the table No 6.2 and Fig No 6.2 it was revealed that maximum distribution of DM patients were noticed in the males of both intervention group 40(53.3%) and control group 48(64%). Whereas the female patients distributed to 35(46.6%) of intervention group and 27(36%) of control group in this study.

From the table No 6.3 and figure No 6.3 it was revealed that 42(56%) of intervention group patients and 47(62%) of control group patients were illiterates. The 33(44%) of intervention group and 25(38%) of control group patients were literates.

The observations revealed that from the table No.6.4 and Fig No.6.4 the maximum of DM patients having the occupation of agriculture were found in the intervention group 40(53.3%) and control group 49(65.3%), then the 25(33.3%) of intervention group patients and 24(32%) of control group patients were sedentary.

From the table No.6.5 and Fig No.6.5 the results revealed the time (in years) since the patients were diagnosed with type 2 DM in both intervention and control group. 11(14.6%) of the patients from intervention group and 5(6.6%) of patients from control group were newly diagnosed with type 2 diabetes, 47(62.6%) of patients from intervention group and 55(73.3%) of patients from control group are affected with type 2 diabetes mellitus since in between 1-10 years.

The observations revealed from the table No.6.6 and Fig.No.6.6 shows the Drug wise distribution of the patients from the intervention group and control group. The both group of patients were mostly prescribed with the metformin and Glimipiride (68.3%) and insulin (18.8%). The anti hypertensive's prescribed to the intervention and control group are 10.3% of the total drug distribution.

The observations revealed from the table No.6.7 explains the social history of type 2 diabetic patients. In the intervention group 14(18.3%) of the patients were alcoholics and 12(16%) were smokers. In the control group 20(26.6%) were alcoholics and 21(28%) were smokers. The patients in the intervention group were advised to quit smoking and restrict the alcohol intake.

From the table No.6.8, table No.6.9 and Fig no.6.8 the results denotes the changes in therapeutic outcomes between the patients of intervention group and control group from baseline to follow up-I, follow up-II and end line. The intervention group patients achieved a significant reduction in HbA1c values than the usual care patients (mean difference -1.18% vs. -0.51%) at the end of the four-month study period. The intervention group patients show a greater reduction of FBS and PPBS values ($P<0.001$) than the control group patients (mean difference -81mg/dl vs. -44mg/dl) and (mean difference -127mg/dl vs. -81mg/dl). Comparing the intervention group with control group there were significant decreases in systolic blood pressure ($p<0.001$) of intervention group than the control group systolic blood pressure ($P=0.80$) and the diastolic blood pressure of both groups have a similar reduction ($p<0.01$).

From the table No.6.10 and Fig. No.6.9, 6.10 the results show the summary of SF 36 data between the intervention group and control group from baseline to end of study. In the SF36 some domains almost have the same score at baseline but after 4-month study period the intervention group patients have the higher domain scores than the control group scores. This indicates intervention group patient's quality of life was improved better than the control group.

From the table No 6.11 and Fig No 6.11 it was revealed that according to the morisky green levine test at baseline 46.6% of intervention group and 34.6% of control group patients were adherent. At the end of the study 86.6% of intervention group patients and 49.3% of control group patients were adherent. During the study period intervention group showed a significant increase ($p<.001$) in pharmacotherapy adherence at the end of study when compared to baseline. Whereas the control group showed slighter changes at the end of the study when compared with baseline values ($p=0.13$).

From the table No 6.12 and Fig No 6.12 the results revealed the changes in self-care activities of the patients according to SDSCA score from baseline to end of study for intervention group and control group patients. Patients in intervention group achieved significant improvements in their total diet score ($p<0.01$), total foot care score ($p<0.01$), total medication score ($p<0.01$) versus usual care patients (Table 12). Patients in the control group did not achieve any significant improvements in the any of above domains except for the total exercise score of both the intervention group and control group were same.

CONCLUSION

The finding of this study revealed that the pharmacist interventions have a positive effect on glycemic control as well as medication adherence. The pharmacist interventions can provide a care to the patients with type 2 diabetes by reducing HbA1c, FBS, PPBS, Blood pressure, improves the quality of life and self care activities. The pharmacist interventions can reduce the DM mortality, morbidity and increase the life span of patients. In this study a pharmacist who was a qualified educator used his expertise to help the patients by providing the knowledge about disease management, encouraging them to reach their therapeutic outcomes and supporting them in adherence of the medications. The results of this study shown the therapeutic beneficiary of the many people with type 2 diabetes mellitus.

Recommendations:

This study recommends that this type of studies needed in wast sample under “Diabetes Health Care” banner with highly motivated, cost-effective medicines and health education measures.

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