EVALUATION OF INCRETIN BASED THERAPIES IN PATIENTS WITH TYPE II DIABETES MELLITUS

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EVALUATION OF INCRETIN BASED THERAPIES IN PATIENTS WITH TYPE II DIABETES MELLITUS

ABSTRACT

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia due to impaired insulin secretion with or without insulin resistance. It is a condition in which the body either does not produce enough insulin or cannot use insulin properly..It is the fourth leading cause of death globally by disease, and the evidence suggests that by 2025 the largest increase will be in developing countries. The main aim & objectives of the study were to record utilization pattern of incretins which includes DPP-4 inhibitors and GLP-1agonist in type II DM patient from out-patients(O.P) and in-patients(I.P)during follow-up visits and how much it confirms to standard treatment guidelines(STG). In the study, 200 patients enrolled for the study during the study period, out of which 100 patients were followed-up with a mean duration of 6 months including patients who were receiving incretins ie 70 patients (35%).The FBG and PPG levels at follow-up and drug usage were recorded and analyzed using Microsoft excel. Variables were analyzed using Fisher's exact test. The results showed that in the study population males were found to be more (60.50%) compared to female (39.50%). Among 200 patients the most common risk factor was found to be HTN(84%). In the study population ,among the classes prescribed ,we found that class biguanides was mostly used contributing to majority (87.5%),followed by sulfonylureas (79.50%),incretins(35%),insulin(19%),TZD (8.5%) and α-GI(6.0%).As our study is mainly focused on the utilization pattern of incretins including DPP-4 inhibitors and GLP-1 agonist .Among 200 patients 70(35%) patients included incretins in their prescription. Within the class of incretin the mostly prescribed DPP-4 inhibitors were saxagliptin (40%), followed by sitagliptin(31.4%) and vildagliptin(17.1%) and the least use was of linagliptin (11.4%). Whereas mostly prescribed GLP-1 agonist was found to be liraglutide with the percentage use of 4.2% among all the incretins.. Majority of the patients achieved desired glycemic control after including incretins in their treatment along with lifestyle changes.

Key words: Diabetes mellitus, incretin, hypoglycemia, HTN, TZD

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex and progressive disease with complication affecting multiple organ systems. Diabetes is a global epidemic, with a prevalence estimated to reach 380 million by 2025. It is the fourth leading cause of death globally by disease, and the evidence suggests that by 2025 the largest increase will be in developing countries. Approximately 90% of patients with diabetes have the type 2 form of

disease. The treatment of T2DM is complicated by disease progression; the need to balance target blood glucose levels against an increased risk of adverse treatment effects, including hypoglycaemia and weight gain; treatment adherence that is compromised by the fear of hypoglycaemia and weight gain, and by complex regimens. An optimal diabetes therapy would provide improved glycaemic control with minimal rise of hypoglycaemia, improve beta-cell function and target other associated pathological defects of T2DM such as obesity, hypertension and dyslipidaemia. Existing therapies fall short of providing this combination of clinical benefits. A new class of diabetes treatment incretins offers an attractive alternative to existing treatments. We do not have data regarding the exact prevalence and incidence of diabetes mellitus. There is a need for the study which will help us and provide us the detailed information related to diabetes mellitus incidence, prevalence, aetiology and thus guiding us for adopting management strategies which increases the use of evidence based therapy in patients with Type II diabetes mellitus. There is a need to determine the evolution of latest anti-hyperglycemic class ie incretins in today's continuum of care. [1-10]

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia due to impaired insulin secretion with or without insulin resistance. It is associated with abnormalities in carbohydrate, fat and protein metabolism. It results from defects in insulin secretion, insulin sensitivity or both. [11-13]

It is a condition in which the body either does not produce enough insulin or cannot use insulin properly. Insulin is a naturally occurring hormone in the blood that is necessary for providing our cells with energy to function. Insulin helps sugar (glucose) to move from the bloodstream into the cells. When glucose cannot enter our cells, it builds up in the blood (hyperglycemia), leading to damage of organs including the eyes and kidneys, or damage of blood vessels and nerves .Most people with diabetes have "Type II diabetes" (adult-onset diabetes) which means that the body does not produce enough insulin or the insulin is not able to transfer glucose into cell. [14-17]

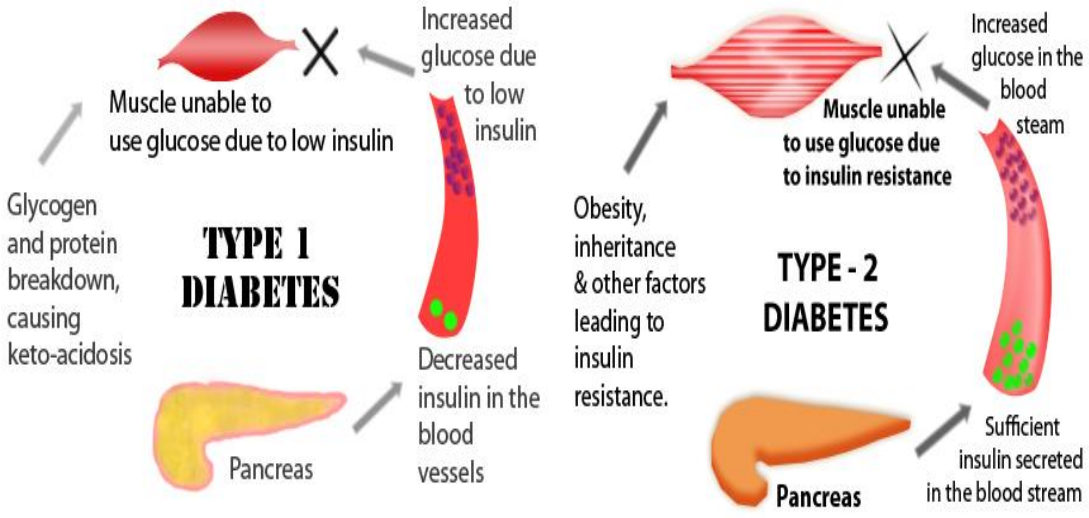


Figure1- Types of diabetes

Symptoms

Figure2:Symptoms of diabetes mellitus

Diabetes can cause a variety of symptoms-urinating frequently, particularly at night, feeling very thirsty ,feeling very tired ,unexplained weight loss and loss of muscle bulk ,itching of the genitals or frequent episodes of thrush, cuts and wounds that heal slowly, blurred vision. The symptoms of type 2 diabetes may not be so obvious, because the condition usually develops slowly over a number of years. It may only be picked up during a routine medical check-up. [18-21]

Classification-

Diabetes can be classified into four clinical categories:

1) Type 1 diabetes (due to b-cell destruction, usually leading to absolute insulin deficiency)
2) Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance)
3) Other specific types of diabetes due to other causes, e.g., genetic defects in b-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation)
4) Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes. [22-25]

Epidemiology

India is facing an epidemic of diabetes. At present confirmed diabetic patients in India are 67 million, with another 30 million in pre-diabetic group. Over the past 30 years the prevalence of diabetes has increased to 12-18% in urban India and 3-6% in rural India. Indians develop diabetes at a younger age and those younger than 45 years accounts for 36% of all diabetics in India and 60-69 years accounts for all diabetes. Diabetes is a global epidemic, with a prevalence estimated to reach 380 million by 2025.It is the fourth leading cause of death globally by disease, and the evidence suggests that by 2025 the largest increase will be in developing countries As the overall prevalence of diabetes is expected to rise to 380 million by 2025,342 million people worldwide are expected to haveT2DM by this time. Approximately 90% of patients with diabetes have the type 2 form of the disease. [26-29]

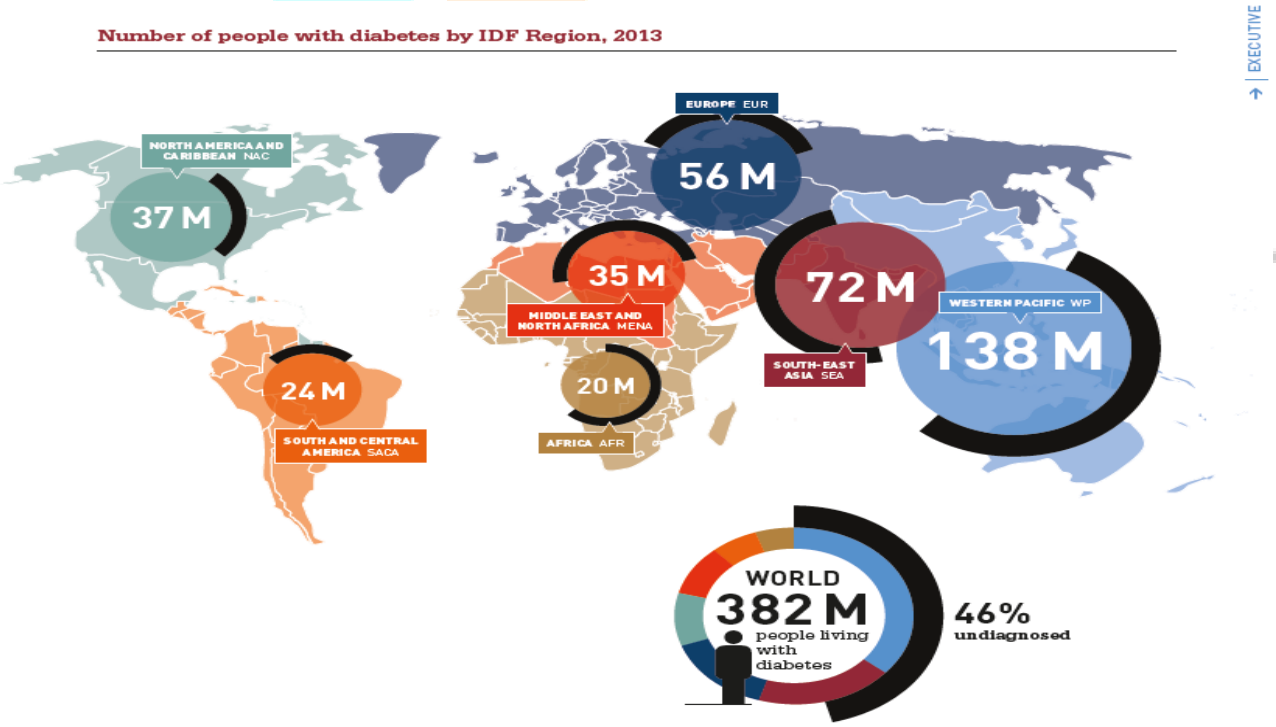


Figure 3: Diabetes a Global burden

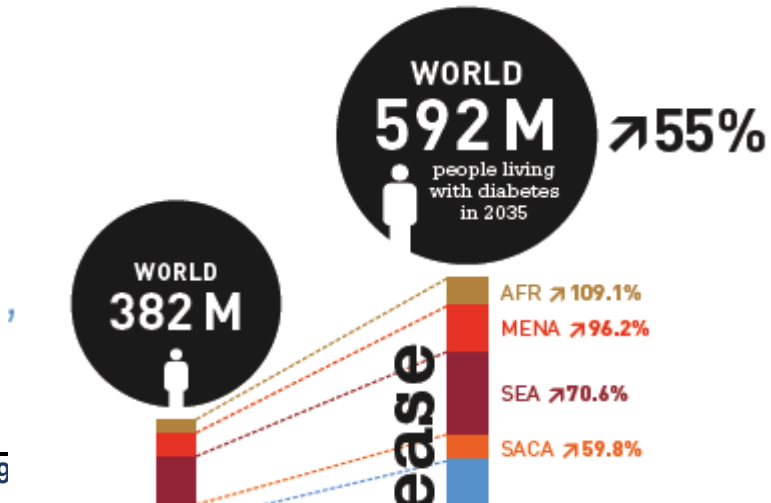


Figure 4- Diabetes: World burden of disease

Diabetes is more common in men than women reflecting the greater incidence of diabetes in men. In the first half of the last century the prevalence of type 2 diabetes was higher among women than among men, but this trend has shifted, so more men than women are now diagnosed with type 2 diabetes. This change in the gender distribution of type 2 diabetes is mainly caused by a more sedentary lifestyle particularly among men, resulting in increased obesity. However, recent data have also shown that men develop diabetes at a lower degree of obesity than women - a finding which adds support to the view that the pathogenesis of type 2 diabetes differs between men and women. [30-33]

Etiology

Diabetes causes vary depending on your genetic makeup, family history, ethnicity, health and environmental factors. There is no common diabetes cause that fits every type of diabetes .The reason there is no defined diabetes cause is because the causes of diabetes vary depending on the individual and the type .For instance; the causes of type 1 diabetes vary considerably from the causes of gestational diabetes. Similarly, the causes of type 2 diabetes are distinct from the causes of type 1 diabetes. [34-37]

Figure 5:There is no one common cause of diabetes

AIM AND OBJECTIVES

1) To record utilization pattern of incretins which includes DPP-4 inhibitors and GLP-1agonist in type II DM patient from out-patients(O.P) and in-patients(I.P)during follow-up visits and how much it confirms to standard treatment guidelines.
2) To study the prescription pattern of incretin class in type II diabetes mellitus patients.
3) To provide information to the patient or its representatives about diabetes and educating them about it.

METHODOLOGY [38-47]

Study Design:

A Prospective Observational study was carried out for studying the Prescribing Pattern of incretin class of anti-diabetic drugs in patients with Type II DM.

Study Site:

The study was conducted in Department of Endocrinology, Krishna Institute of Medical Sciences (KIMS) Hospital, (1-8-31/1, Minister Road, secunderabad-500003, Telangana, India), which is a 1000 bedded multispecialty teaching hospital.

Study Period:

This study was conducted for six months from August 2014 to January 2015.

Sample Size:

The sample size of the study was 200.

Selection Criteria:

Inclusion Criteria:

1) All Type II diabetes mellitus patients.

2) Patients from age group of 18 to 85 years of either sex.

Exclusion Criteria:

1) Pediatric age group.
2) Pregnant/ lactating women.
3) Patient not willing for consent for enrollment in the study
4) Patients brought to emergency care department.

Tools used:

Microsoft Excel 2007.

Graphpad Software - Quick Calcs.

Source of data:

Patient data was collected prospectively from the case sheets in Out-patient(O.P) and In-patient(I.P) departments after taking consent from the patient to be included in the study.

Study Procedure:

1) A Prospective Observational study was carried out for studying the Prescribing Pattern of incretin class of anti-diabetic drugs in patients with Type II diabetes mellitus.
2) Patient data collection form, consent forms were designed to obtain the extent of usage of incretins in common clinical practice and to know the skills, ability and attitude of patients with Type II diabetes mellitus
3) All patients dealing with the condition in Type II diabetes mellitus Inpatient wards & Outpatient department at KIMS hospital were identified and data including patient's demographic data, medical history, laboratory data & medication chart was collected in patient data collection form, after taking the consent from the patients.
4) Patient counseling was provided to the enrolled patients.
5) Patients were checked out for the class of incretins most frequently prescribed drug and their doses .
6) Finally the effect of presence of co-morbid conditions and related aspects which play an important role

in prescribing a incretin class of Type II diabetes mellitus patients were analysed using statistical analysis.[49-57]

Statistical analysis: [58-68]

The Fisher's exact test, a statistical test was done to examine differences with categorical variables and compare the observed and expected values using MicrosoftExcel 2007 and p values were calculated using Graph pad software - Quick Calcs.

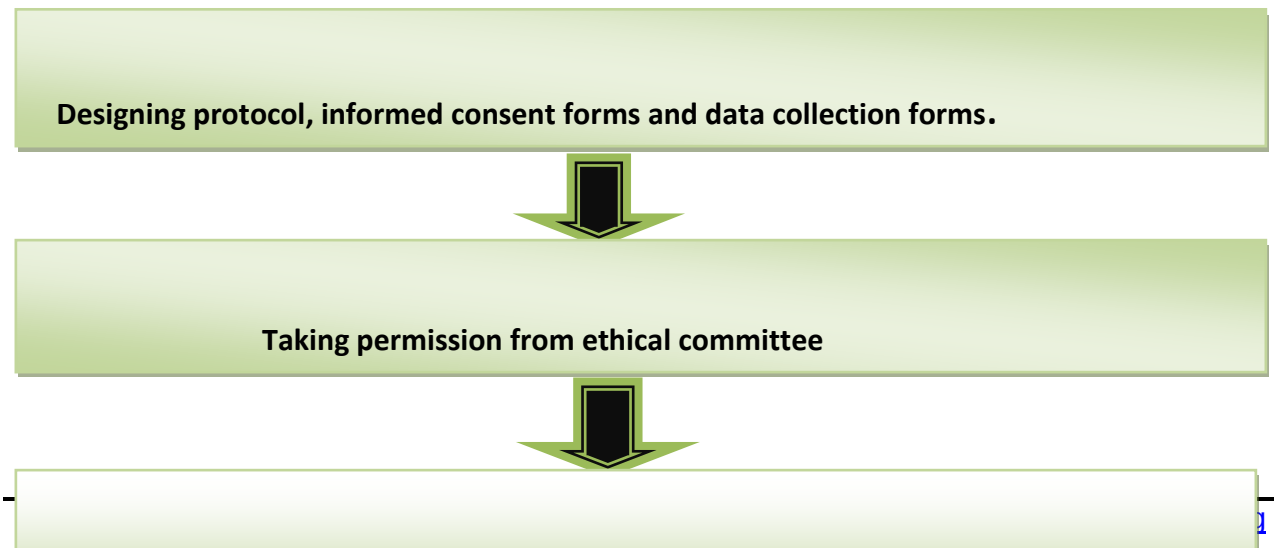
The following parameters were analysed statistically using **Fisher's exact test.**

Comparison of Alcohol & Smoking Status of the patients before and after counselling.

Comparison of Lifestyle (Diet, Exercise, Stress avoidance etc.) of patients before and after counselling.

P value less than 0.05 was considered statistically significant.

Plan of Work:



RESULTS AND DISCUSSION

A prospective study of evaluation of incretin based therapies in patients with type II diabetes mellitus was conducted during the study period of 6 months from August 2014 to January 2015.A total of 200 cases of diabetes mellitus type II patients were identified during the study period.

The rate of usage of various drugs of incretin class in diabetes mellitus type II patients were analyzed according to the data collected in the patient data collection forms in KIMS hospital during the study period & a relative study with respect to age gender was determined. The effect of presence of co-morbid conditions & related aspects which play an important role in prescribing incretins in diabetes mellitus type II patients was analyzed.

Profile of the patients:

Gender Wise Categorization of The Patients:

Total 200 patients were enrolled for the study, 121 were male patients &79 were female patients. The distribution of patients as per the gender is indicated in table 5

Table 5: Gender Wise Distribution of the Patients

Gender	Number of patients(n)	Percentage of patients
Male	121	60.50
Female	79	39.50
Total	**200**	**100**

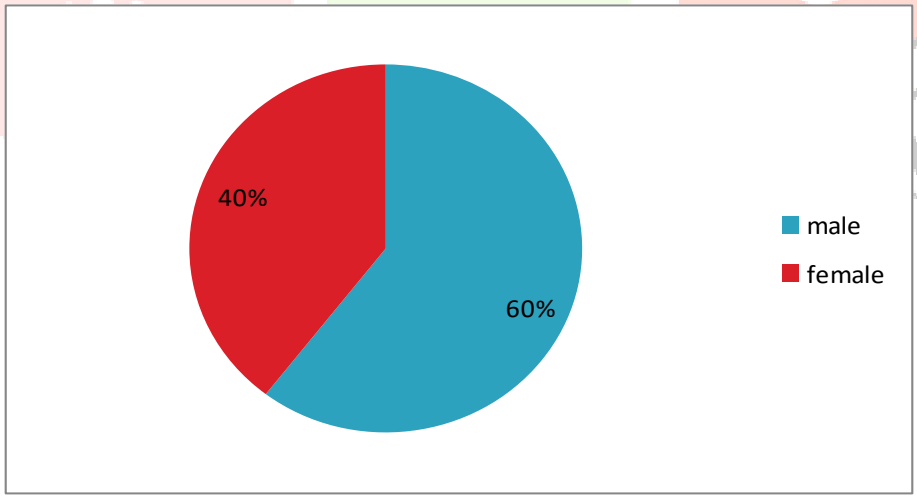


Figure 18- Gender Wise Distribution of the Patients

Among the total population of 200 patients, 121 males and 79 females were observed. This showed that the prevalence of men (60%) was found to be higher than females (40%) indicating that men develop type II

diabetes than females. This fact is supported by other studies which say that the risk of developing diabetes in males is slightly greater than in females.

Age and Gender Wise Categorization of the Patients:

The gender wise distribution of patients as per age group along with the gender differentiation was analyzed and represented in the following table and figure.

Table 6: Age and Gender Wise Distribution of the Patients

Age(Years)	Male		Female		Total Patients	Overall Percentage
	N	%	N	%		
18-29	0	0	2	2.53	2	1.00
30-59	79	65.28	41	51.89	120	60.00
60-85	42	34.72	36	45.58	78	39.00
Total	**121**	**100**	**79**	**100**	**200**	**100**

Prevalence of diabetes increases with the higher age. The above table shows the age distribution2 patient (1.00%) was between 18-29 years, 120 patients (60.0%) were between 30-59 years and 78 Patients (39%) were between 60-85 years.

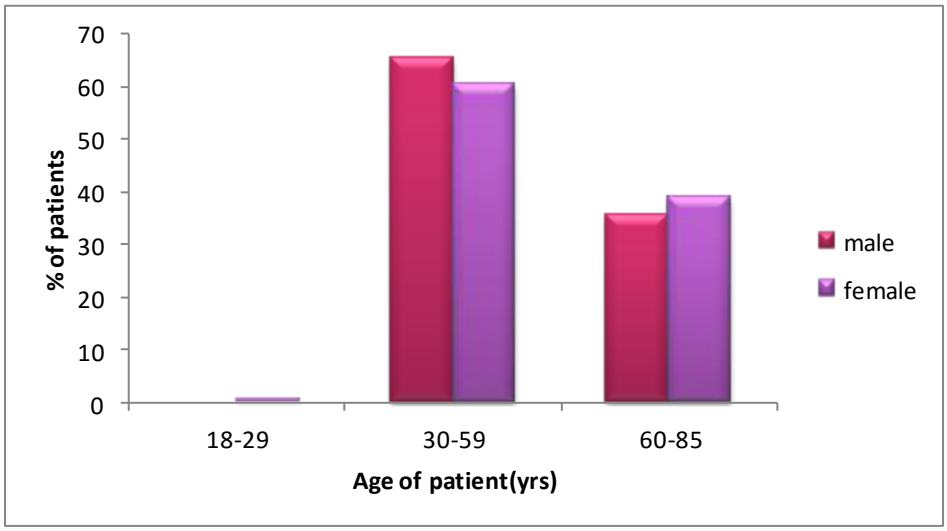


Figure19: Age and Gender Differentiation Wise Distribution of the Patients

The above figure shows that incidence of DM II is higher in females (2.53%) than males (0%) in the age group 18-29 years. The incidence of DM II is higher in males (65.28%) than females (51.89%) in the age group 30-59 years .Similarly the incidence of DM II is higher in females (45.5%) than males (34.72%) in age group 60-85 years.

Risk factors:

Patients at a high risk for development of diabetes mellitus type II includes-

1) **Weight.** Being overweight is a primary risk factor for type 2 diabetes. Men and women with a male abdominal type of obesity are more susceptible to the effect of excess body fat on lipid and carbohydrate metabolism
2) **Fat distribution.** If your body stores fat primarily in your abdomen, your risk of type II diabetes is greater. Not only the degree of obesity but also the localization of fat is a risk factor for diabetes.
3) **Inactivity.** The less active you are, the greater your risk of type 2 diabetes. Physical activity helps you control your weight, uses up glucose as energy and makes your cells more sensitive to insulin.
4) **Family history.** The risk of type 2 diabetes increases if your parent or sibling has type 2 diabetes.
5) **Race.** Although it's unclear why, people of certain races — including blacks, Hispanics, American Indians and Asian-Americans — are more likely to develop type 2 diabetes than whites are.

6) **Age.** The risk of type 2 diabetes increases as you get older, especially after age 45. That's probably because people tend to exercise less, lose muscle mass and gain weight as they age. But type 2 diabetes is also increasing dramatically among children, adolescents and younger adults.

7) **Prediabetes.** Prediabetes is a condition in which your blood sugar level is higher than normal, but not high enough to be classified as diabetes. Left untreated, prediabetes can progress to type 2 diabetes.

8) **Gestational diabetes.** If you developed gestational diabetes when you were pregnant, your risk of developing type 2 diabetes increases. If you gave birth to a baby weighing more than 9 pounds (4 kilograms), you're also at risk of type 2 diabetes.

9) **Polycystic ovary syndrome.** For women, having polycystic ovary syndrome — a common condition characterized by irregular menstrual periods, excess hair growth and obesity — increases the risk of diabetes.

10) **Hypertension.** Hypertension has been identified as a major risk factor for the development of diabetes. Patients with hypertension are at a 2–3 times higher risk of developing diabetes than patients with normal blood pressure

Our study indicated that four different types of risk factors were responsible for the development of diabetes mellitus II in different patients. The distribution of risk factors is shown in the following table and figure.

Table 7 :Distribution of Associated Risk Factors:

S.no	Risk factors	Males	Females	Total Patients	Overall Percentage
1	Weight(WT)	14	29	21	**7.00**
2	Inactive lifestyle(IL)	48	52	100	**50.00**
3	Family history(FH)	36	30	66	**33.00**
4	Hypertension(HTN)	101	67	168	**84.00**

Note: No of patients calculated for each individual risk factor from 200 patients .Some patients may show more than one risk factor.

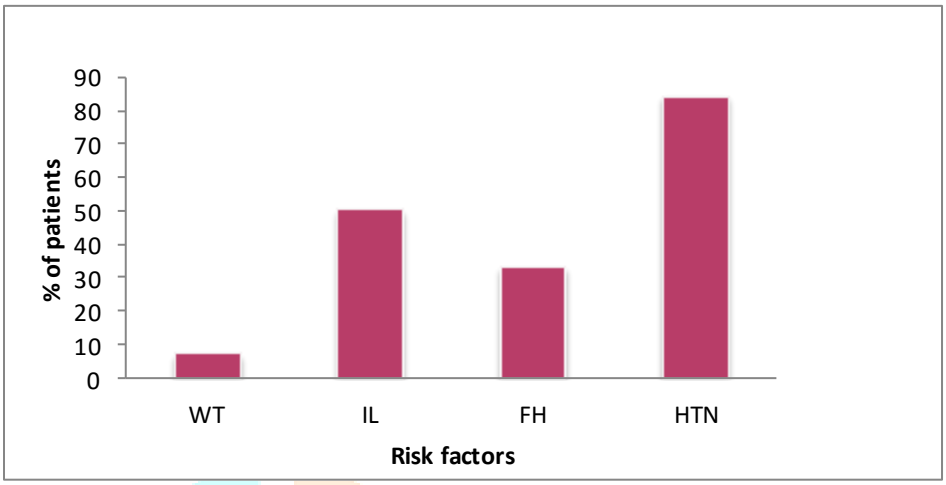


Figure 20 : Distribution of Associated Risk Factors

In the table of associated risk factors, the patients with HTN contributed to majority(84%) among patients who developed into diabetes mellitus, followed by IL(50%), FH(33%),WT(7%).

Confounding factors-

These are those factors which may aggravate the metabolic disorder. It includes alcohol, smoking, dietary lifestyle etc. Our study indicated these three con-founding factors were responsible for aggravating the disorder.

Table 8: Distribution of Confounding Factors

S.no	Con-founding factor	Males	females	Total patients	Overall percentage
1	**Smoking**	23	0	23	**11.5**
2	**Alcohol**	30	0	30	**15.0**

Note: No of patients calculated for each individual con-founding factor from 200 patients .Some patients may show more than one con-founding factor

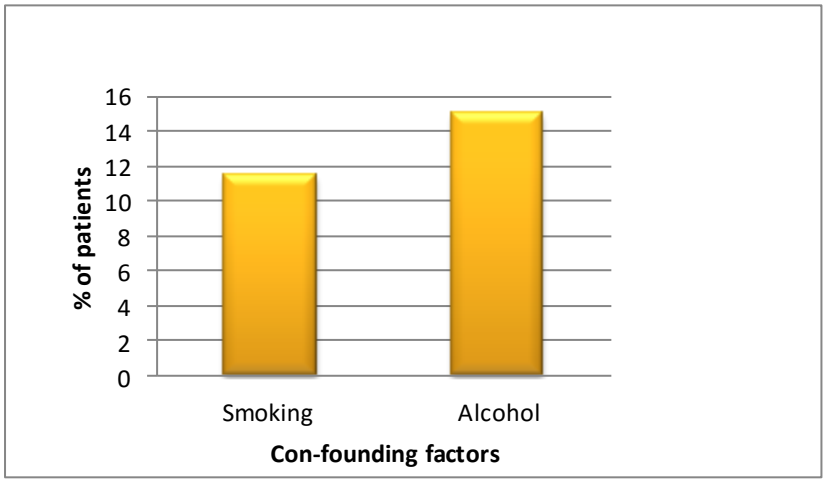


Figure 21 : Distribution of Con-Founding Factors

In the table of associated con-founding factors, the alcoholics (15.0%) contributed to majority (22.5%) followed by smokers(11.5%).

Distribution of Co-Morbidities In Patients with Type II Diabetes Mellitus:

Glycemic control among adults with T2DM is often poor. Adult patients with T2DM, especially those with poor glycemic control, hypertension, and dyslipidemia, are at increased risk for vascular complications.

Table 9: Distribution of Co-Morbidities Found in Patients with Type II Diabetes Mellitus:

S.no	Co-morbidities	Male	Female	Total Patients	Overall Percentage
1	Hypertension (HTN)	101	67	168	84.00
2	Dyslipidemia(DYS)	34	43	77	38.50
3	Hypothyroidism(HT-H)	2	27	29	14.5
4	Knee transplant(TKR)	3	0	3	1.50
5	Chronic kidney disease(CKD)	9	5	14	7.00
6	Gastric cancer(GC)	1	0	1	0.50
7	Varicella zoster infection(VZV)	1	0	1	0.50
8	Cushing's syndrome(CS)	0	1	1	0.50
9	Coronary artery disease(CAD)	19	9	28	14.00
10	Seizures(SZ)	3	1	4	2.00

11	Acute kidney disease(AKD)	15	10	25	12.50
12	Retinopathy(DR)	12	9	21	7.00
13	Coronary artery bypass grafting surgery(CABG)	1	0	1	0.50
14	Portal hypertension(PT)	2	1	3	1.50
15	Cellulitis (CL)	2	1	3	1.50
16	Cerebrovascular accident(CVA)	3	1	4	2.00
17	Stroke(S)	1	0	1	0.50
18	Decompensated Liver Disease(DLD)	1	0	1	0.50
19	Systolic bacterial peritonitis(SBP)	1	0	1	0.50
20	JAUNDICE(J)	1	0	1	0.50
21	Addison's disease(AD)	1	0	1	0.50

Note: No of patients calculated for each individual co-morbidities factor from 200 patients .Some patients may show more than one co-morbid condition.

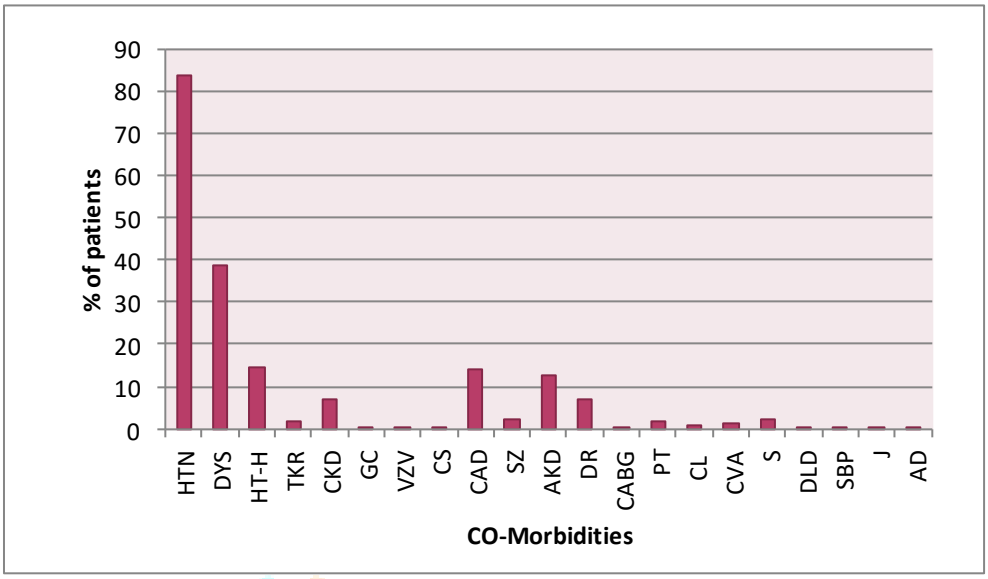


Figure 22- Distribution of Co-Morbidities Found in Patients with Type II Diabetes Mellitus.

In the table of Distribution of co-morbidities found in patients with type II diabetes mellitus most of the patients were found to be hypertensive (84%) followed by other co-morbidities like dyslipidemia(38.5%), hypothyroidism(14.5%), coronary artery disease (14.00%) retinopathy(.7%), acute kidney disease(12.5%) chronic kidney disease(7.0%).others ie knee transplant (0.5%), gastric cancer (0.5%),varicella zoster infection(0.5%),Cushing's syndrome(0.5%) and seizures(0.50%) and so on.

Our study also indicated the combination of disease found in patients with type 2 diabetes mellitus. It was analyzed and represented in the following table and figure.

Table 10: Combination of Disease Found In Patients with Type 2 Diabetes Mellitus:

S.no	Combination of diseases	male	female	Total patients	Overall percentage
1	HTN+CKD	5	3	8	4.00
2	HTN+CKD+HT-H	0	1	1	0.50
3	HT-H+SZ	0	1	1	0.50
4	HTN+AKD	7	3	10	5.00
5	HTN+DR	14	7	21	10.50
6	HTN+VZV	1	0	1	0.50
7	HTN+DYS	23	33	56	28.00
8	DLD+SBP	1	0	0	0.50

9	PH+CL	2	1	3	1.50
10	CVA+S	1	0	1	0.50
11	HTN+HT-H	0	14	14	7.00

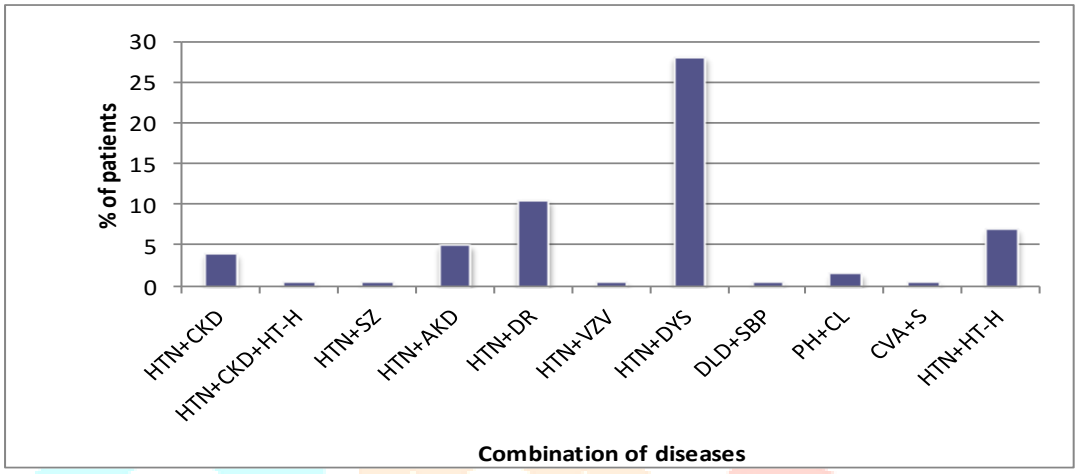


Figure 23: Combination of Disease Found in Patients with Type 2 Diabetes Mellitus.

The results showed that majority of patients had a combination of HTN+DYS(28%), followed by HTN+DR(10.5%) then HTN+HT-H that accounted for (7%), other combination seen was HTN+CKD, HTN+CKD+HT-H, HTN+SZ and HTN+VZV. This indicates that combinations affected the patients and the condition was progressed more in this group of patients.

Table11: Distribution of Co-Morbidities in Patients with Treatment Including Incretin Drugs-

S.no	Diseases	Male	Female	Total patients	Overall percentage
1	HTN	37	26	63	31.50
2	HT-H	0	9	9	4.50
3	DYS	11	14	25	12.50
4	VZV	1	0	1	0.50
5	GC	1	0	1	0.50
6	TKR	1	0	1	0.50
7	AKD	3	1	4	2.00
8	DR	5	2	7	3.50

9	OBESITY	2	1	3	1.50

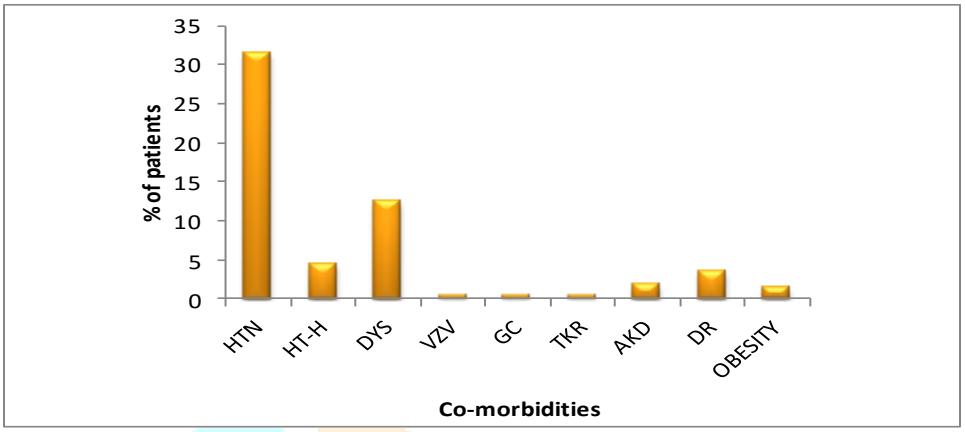
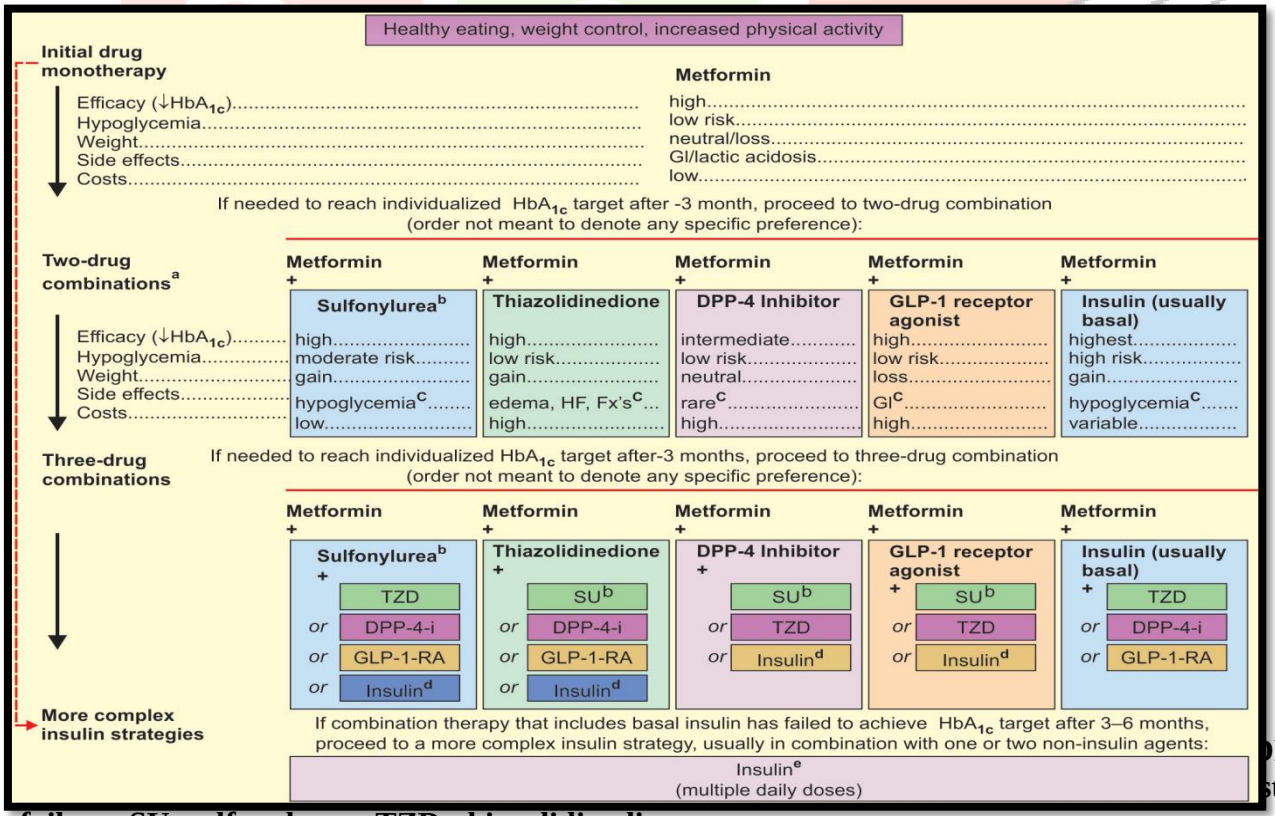


Figure 24 :Co-Morbidities Found in Patients with Treatment Including Incretins.

Drug Use Characterization:

Drug Use Characterization:

Anti-hyperglycemic therapy-



PP-4-i,DPP-4 st; HF, heart failure; SU, sulfonylurea; TZD, thiazolidinedione.

The ADA [American diabetes association] and the EASD [European Association for the Study of Diabetes] formed a joint task force to evaluate the data and develop recommendations for the use of anti hyperglycemic agents in type 2 diabetic patients.

Among the drugs prescribed for the disease it is found that Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. When metformin fails to achieve or maintain glycemic goals, another agent should be added. In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset.

If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin. A patient-centered approach should be used to guide choice of pharmacological agents.

Distribution Pattern of Overall Use of Anti- Hyperglycemic Drugs in Patients with Type II Diabetes Mellitus:

Diabetes mellitus type 2 is a disease of insulin resistance by cells. Type 2 diabetes mellitus is the most common type of diabetes. Treatments include

(1) Agents that increase the amount of insulin secreted by the pancreas,

(2) Agents that increase the sensitivity of target organs to insulin, and

(3) Agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Table-12 Distribution Pattern of Overall Use of Anti- Hyperglycemic Drugs in Patients with Type II DM

S.no	Drug class	Number of patients	Percentage of patients
1	Biguanides	175	87.50
2	Sulfonylurea's	159	79.50
3	Thiazolidinedones	17	8.50
4	Incretins	70	35.00
5	α-glucosidase inhibitor	12	6.00
6	Insulin	38	19.00
7	Other class drugs(CD)	139	69.50

Note: No of patients calculated for each individual class from 200 patients .Some patients may have been prescribed more than one class of drug.

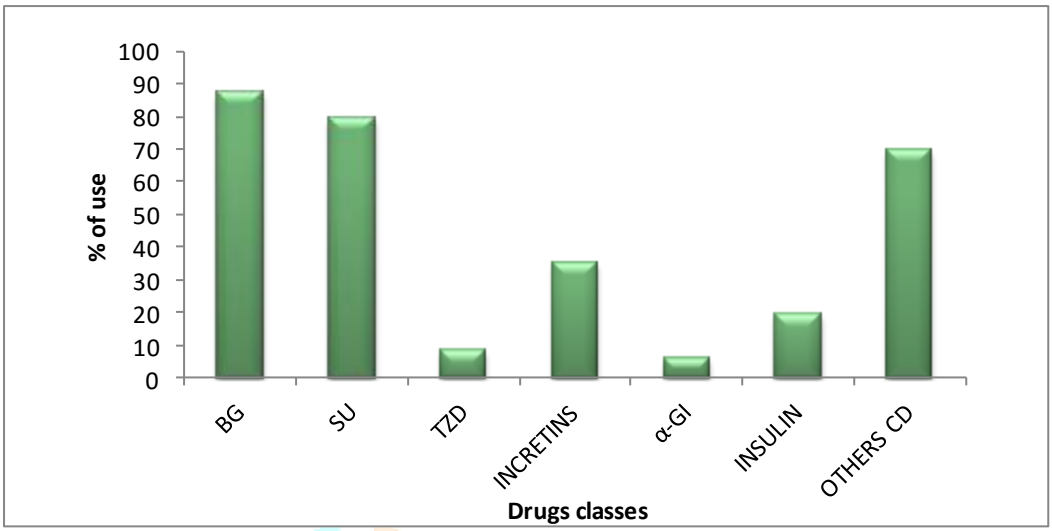


Figure 25- Distribution Pattern of Overall Use of Anti- Hyperglycemic Drugs in Patients with Type II DM.

Among the drugs prescribed according to the class, most commonly used was found to be biguanides(87%) followed by sulfonylureas(79%),incretins(35%),insulin(19%)and thiazolidinediones(8%) and α-glucosidase inhibitor(6%) and so on.

Use of Individual Drugs in Incretin Class of Anti-Hyperglycemics:

Our study indicated the prescribing pattern of incretin class in DM II .Incretin class includes two sub classes-

1. Dipeptidyl peptidase-4 inhibitor- sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin etc..
2. GLP-1 agonist (glucagon like peptide-1 agonist)- liraglutide, exenatide etc.

Incretins are gut-derived hormones, principally GLP-1 and glucose-dependent insulinotropic peptide (GIP), that are secreted at low basal levels in the fasting state. Circulating levels increase rapidly and transiently following food ingestion. As native GLP-1 displays a very short circulating half-life due to renal clearance and NH_2-terminal degradation by the enzyme DPP-4, degradation-resistant GLP-1R agonists have been developed.DPP-4 inhibitors exerts its gluco-regulatory actions through prevention of incretin degradation, leading to potentiation of GLP-1 and GIP action.

GLP-1R agonists control blood glucose through regulation of islet function, principally with the stimulation of insulin and inhibition of glucagon secretion. Notably, these GLP-1R–dependent actions are glucose dependent, thereby minimizing the risk of hypoglycemia in the absence of concomitant sulfonylurea therapy.

Table 13 - Overall Use of Incretins

Class	Sub-class	Drugs	Number of patients	Overall percentage
Incretins	DPP-4 inhibitor	Sitagliptin	22	**31.42%**
		Saxagliptin	27	**40.0%**
		Vildagliptin	11	**17.14%**
		linagliptin	7	**11.42%**
	GLP-1 agonist	liraglutide	3	**4.28%**
		Exenatide	0	**0%**

Note: No of patients calculated for each individual drug from 200 patients .Some patients may have been prescribed more than one class of drug.

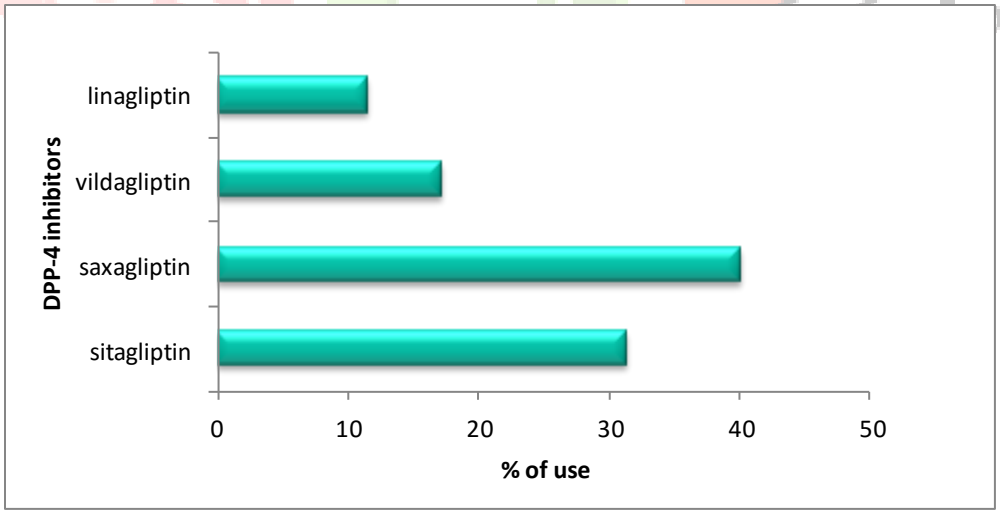


Figure 26 -Percentage Use of DPP-4 Inhibitors Belonging to Class Incretin.

Within the class of incretin the mostly prescribed DPP-4 inhibitors were saxagliptin (42%), followed by sitagliptin(33.2%) and vildagliptin(15.9%) and the least use was of linagliptin(6.9%).

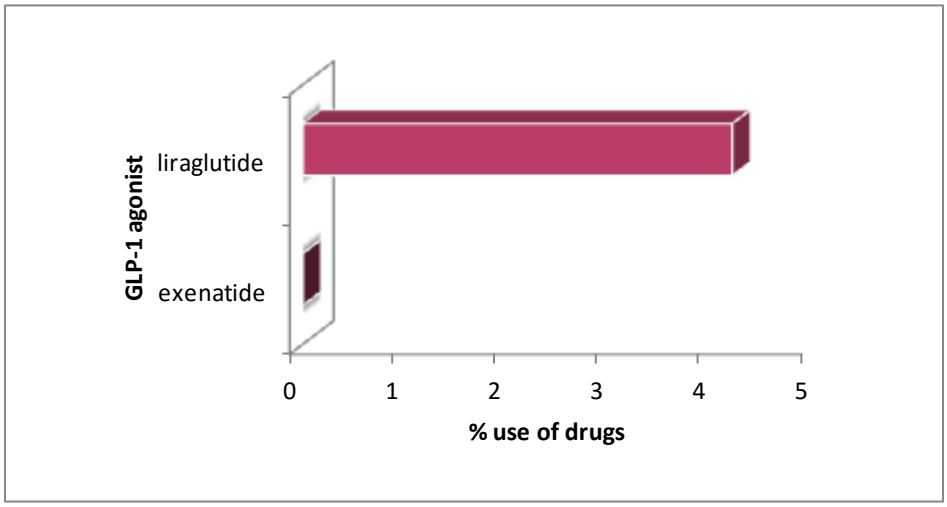


Figure 27 -Percentage Use of GLP-1 Agonist Belonging to Class Incretin.

Within the class of incretin the mostly prescribed GLP-1 agonist was found to be liraglutide with the percentage use of 4.2% among all the incretins.

Distribution Pattern of Incretin Class with Their Doses Used In DM II:

Table 14 : Use of Sitagliptin in Different Doses

Doses	Number of patients	Percentage of patients
25mg	0	0
50mg	7	31.82
100mg	15	68.18
Total	**22**	**100**

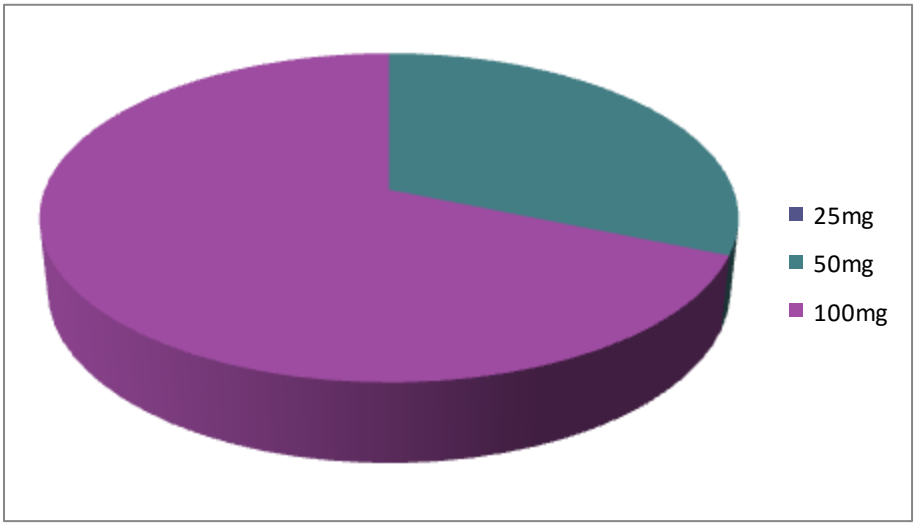


Figure 28: Use of Sitagliptin in Different Doses

The represented figure shows that among different doses of sitagliptn the only dose given for DM II was 100mg.

Table 15: Use of Saxagliptin in Different Doses

Doses	Number of patients	Percentage of patients
2.5mg	0	0
5mg	27	100
Total	**27**	**100**

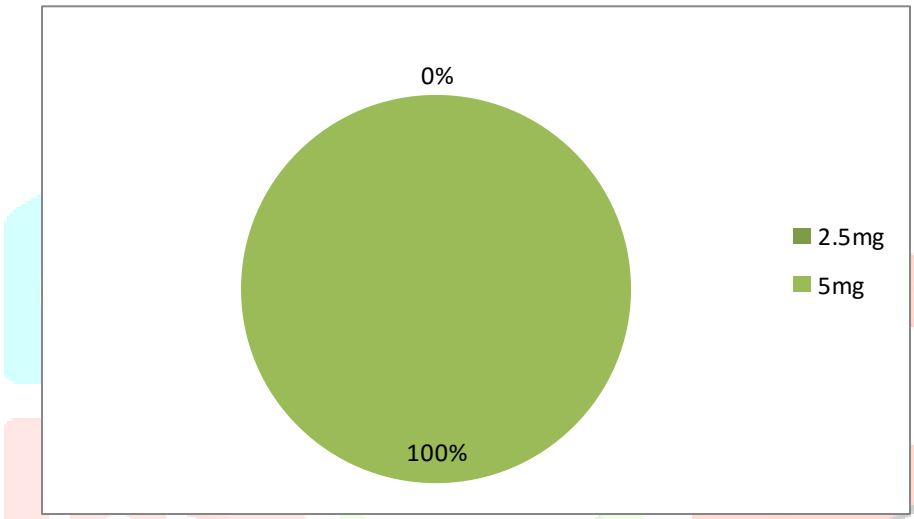


Figure 29 :Use of Saxagliptin In Different Doses

The represented figure shows that among different doses of saxagliptn the only dose given for DM II was 5mg.

Table 16 :Use of Vildagliptin in Different Doses:

Doses	Number of patients	Percentage of patients
25mg	0	0
50mg	11	100
Total	**11**	**100**

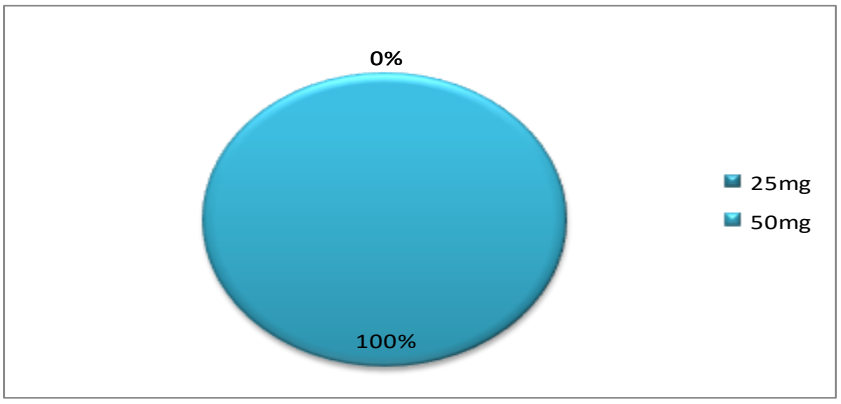


Figure 30 :Use of Vildagliptin in Different Doses

The represented figure shows that among different doses of vildagliptin the only dose given for DM II was 50mg.

Table 17 :Use of Linagliptin at Dose:

Drug	Number of patients	Percentage of patients
5mg	7	100
10mg	0	0
Total	7	100

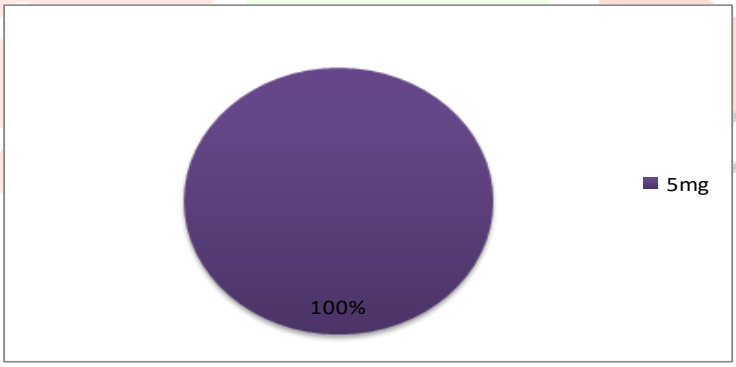


Figure 31 :Use of linagliptin in Different Doses

The represented figure shows that the only dose of linagliptin given for DM II was 5mg.

Table 18 :Use of liraglutide in Different Doses:

Drug	Number of patients	Percentage of patients
0.6mg	0	0
1.2mg	2	66.77
1.8mg	1	33.33

Total	3	100

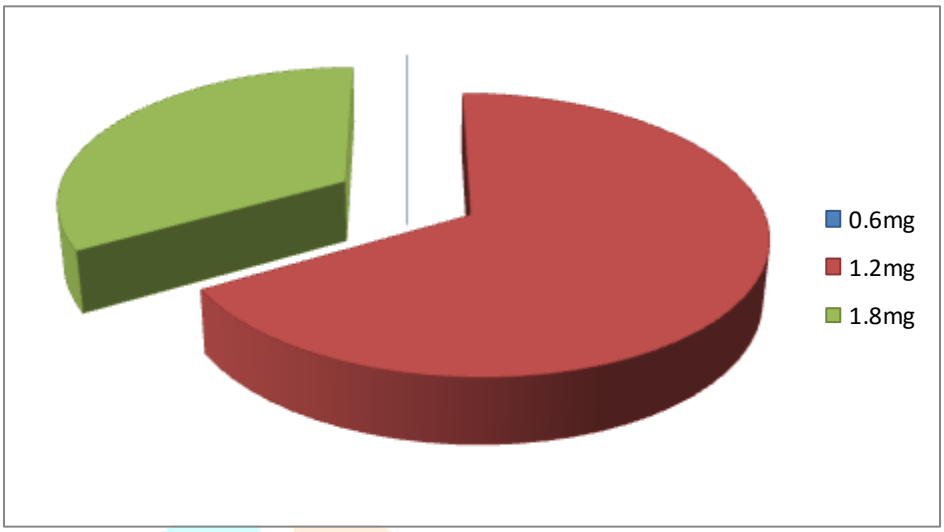


Figure 32 :Use of liraglutide in Different Doses.

The represented figure shows that among different doses of liraglutide the mostly prescribed dose was 1.8mg(66.7%) followed by 1.2 mg(33.3%).

Number of Combinations Prescribed in the Regimen:

In overall observation, incretins were also used in combination therapy ,the mostly used combination was a 2-drug therapy followed by 3-drug therapy. Our study analyzed and represented the mostly used two-drug combination in patients with type II DM.

Table 19: Distribution of Drug Combinations Including Incretins:

Drug therapy	**Number of patients**	**Percentage of patients**
2 Drug therapy	42	60
3 Drug therapy	28	40
Total	**70**	**100**

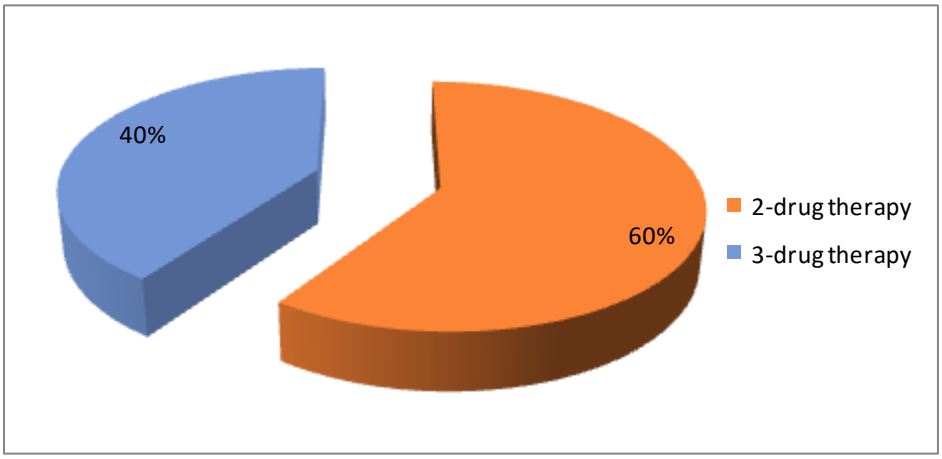


Figure 33: Distribution of Drug Combinations Including Incretins.

Table 20: Use of Two Drug Combinations Including Incretins-

Drug regimen	Number of patients	Percentage of patients
BIG+DPP-4	22	52.38
BIG+GLP-1	2	4.76
INSULIN+DPP-4	6	14.28
SU+DPP-4	12	28.58
Total	**42**	**100**

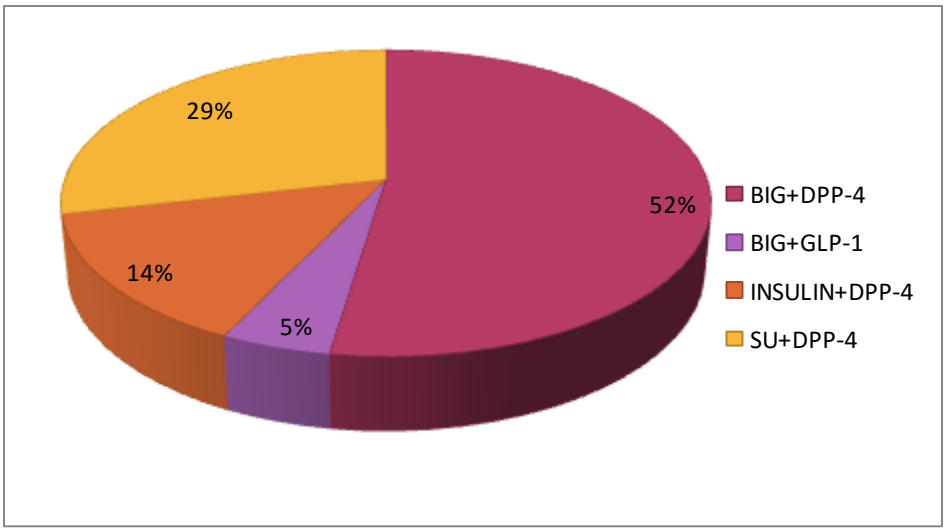


Figure 34 : Use of Two Drug Combinations Including Incretins.

In this type the most commonly prescribed drug combination is Biguanide and DPP-4 inhibitors (52.38%), followed by Sulfonylureas and DPP-4 inhibitors (28.58%), Insulin and DPP-4 inhibitors (14%) and so on. These combinations are prescribed based on the blood glucose levels and stages of diabetes.Usually prescribed in early and mild to moderate cases.

Table 21: Two Drug Combinations Given-

S.no	Two drug combinations	Combinations given	Total no of combinations	Percentage
1	**BIG+DPP-4**	Metformin+sitagliptin	7	31.82%
		Metformin+saxagliptin	7	31.82%
		Metformin+vildagliptin	4	18.18%
		Metformin+linagliptin	4	18.18%
			22	**100%**
2	**BIG+GLP-1**	Metformin+liraglutide	2	100
			2	**100%**
3	**INSULIN+DPP-4**	Insulin+saxagliptin	3	50.00%
		Insulin+sitagliptin	1	33.33%
		Insulin+vildagliptin	2	16.67%

			6	**100%**
4	**SU+DPP-4**	Gliclazide+vildagliptin	2	16.66%
		Glipizide+saxagliptin	3	25.00%
		Glimipride +sitagliptin	7	58.34%
			12	**100**

Table 22: Use of Three Drug Combinations Including Incretins:

Drug regimen	**Number of patients**	**Percentage of patients**
BIG+SU+DPP-4	19	67.86
BIG+SU+GLP-1	1	3.57
BIG+INSULIN+DPP-4	8	28.57
Total	**28**	**100**

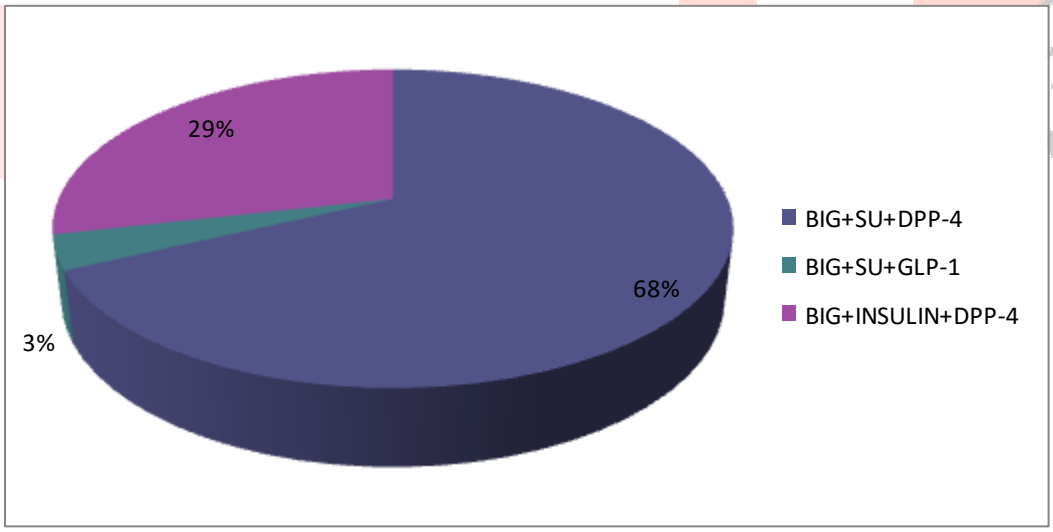


Figure 35: Use of Three Drug Combinations Including Incretins.

In this type the most commonly prescribed drug combination is Biguanide+Sulonylureas +DPP-4 inhibitors (67.8%), followed by Biguanide+Insulin+DPP-4 inhibitors(28.5%) and Biguanide+Sulonylureas+GLP-

1agonist(3.5%) and so on. These combinations are prescribed based on the blood glucose levels and stages of diabetes. Usully prescribed in moderate to severe cases.

Table 23: Three Drug Combinations Given:

S.no	Three drug combinations	Combinations given	Total no of combination	Percentage
1	**BIG+SU+DPP-4**	Metformin+glimipride+sitagliptin	7	36.85%
		Metformin+glimipride+saxagliptin	6	31.58%
		Metformin+glimipride+vildagliptin	3	15.79%
		Metformin+ glimipride+linagliptin	3	15.78%
			19	**100%**
2	**BIG+SU+GLP-1**	Metformin +glimipride+liraglutide	1	100%
			1	**100%**
3	**BIG+DPP-4+INSULIN**	Metformin +saxagliptin+Insulin	8	100%
			8	**100%**

Patient Counselling :

Patient counseling was given for 200 patients; among the study includes comparison of Alcohol & Smoking status, Lifestyle before and after counseling.

Comparison Of Alcohol & Smoking Status of the Patient Before and After Counselling

The following table represents data regarding alcohol and smoking status of the patient before and after counseling:

Table 24: Comparison of Alcohol and Smoking status of the Patient Before and After Counselling:

Risk factors	Before counselling		After counselling	
	N	%	N	%
Alcohol	30	15.00	12	6.00
Smoking	23	11.50	11	5.50
Alcohol+ Smoking	53	26.50	28	14.00
None	94	47.00	94	47.00
Total	**200**	**100**	**156**	**72.5**

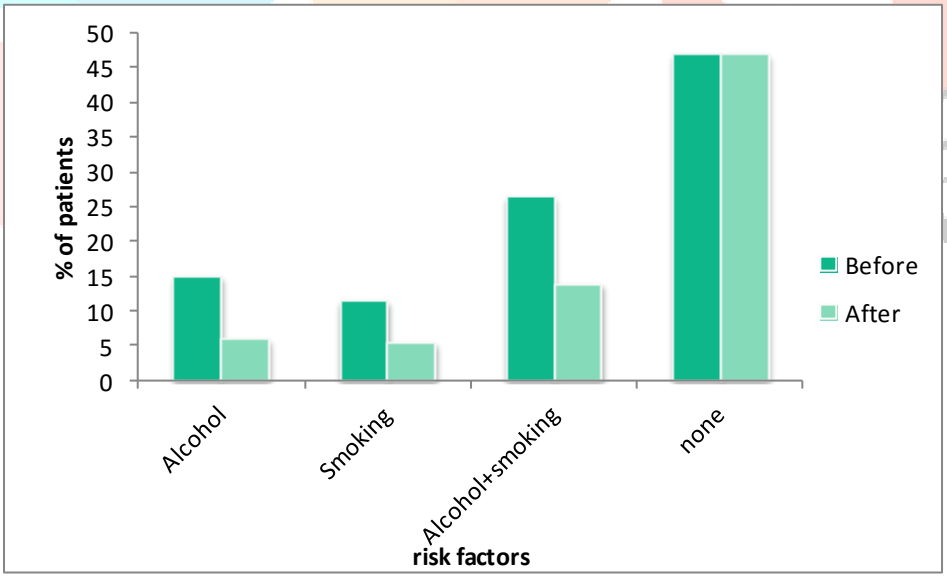


Figure 36 : Comparison of Alcohol and Smoking status of the Patient Before and After Counselling

The represented figure shows that among 200 patients, alcohol users constitute 15% and smoking users constitute 11.5% of the total population. A combination of both was seen in 26.5% of the patient population and 47% had none of the above secondary risk factors.

Smoking status of the patient:

Smoking is one of the con-founding factor but about 47% are non-smokers .This group mainly consists of males. The patient who smokes constitute 11.5%.While smoking can increase your chances of getting diabetes; it can also make managing diabetes more difficult for those who already have it. Other complications of smoking on diabetes include retinopathy (eye disease), heart disease, stroke, vascular disease, kidney disease, nerve damage, foot problems, and many others. smoking is associated with larger upper body fat distribution, a marker of insulin resistance, raised plasma glucose concentrations (after an oral glucose load), and overt diabetes

Drinking status of the patient:

Alcohol is one of the con-founding factor but about 47% are non-alcoholics .This group mainly consists of males. The patient who takes alcohol constitutes 15%. Though heavy alcohol consumption may cause transient hypoglycaemia, regular moderate drinkers are more insulin sensitive than abstainers. Among diabetic subjects alcohol taken with a meal does not substantially alter the blood glucose concentration.

Table 25 : Distribution of Alcohol Status of the Patient Before and After Counseling

Alcohol	**Before counselling**		**After counselling**	
	N	**%**	**N**	**%**
Absent	170	85.00	188	94
Present	30	15.00	12	6
Total	**200**	**100**	**200**	**100**
Fisher's Exact Test		0.0050		

P value and statistical significance:

The two-tailed P value equals 0.0050.

By conventional criteria, this difference is considered to be very statistically significant.

It indicates that most of the patients have improved their social lifestyle after counseling was given .

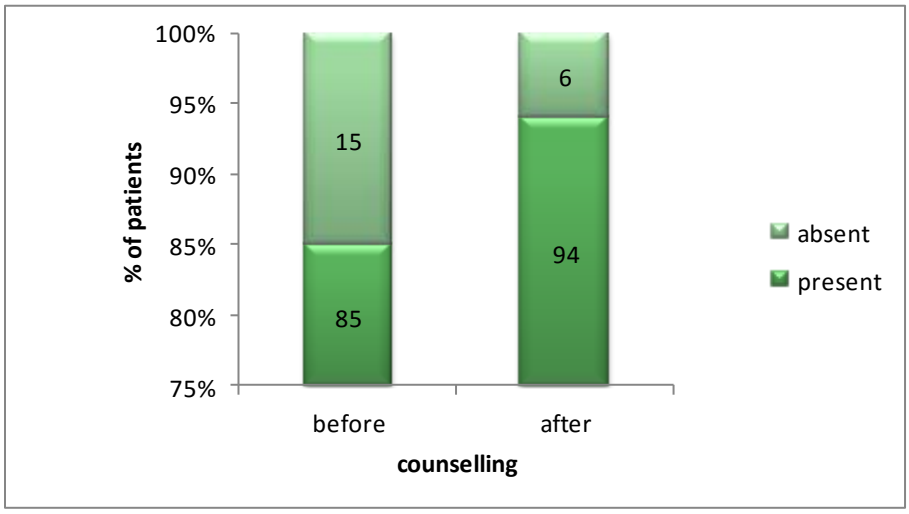


Figure 37 : Distribution of Alcohol status of the Patient Before and After Counseling

Table 26: Distribution of Smoking Status of the Patient Before and After Counseling

Smoking	**Before counselling**		**After counseling**	
	N	**%**	**N**	**%**
Absent	177	88.50	189	94.50
Present	23	11.50	11	5.50
Total	**200**	**100**	**200**	**100**
Fisher's Exact Test		0.0472		

P value and statistical significance:

The two-tailed P value equals 0.0472.

By conventional criteria, this difference is considered to be statistically significant.

It indicates that counseling given was helpful for patients in improving their social habits.

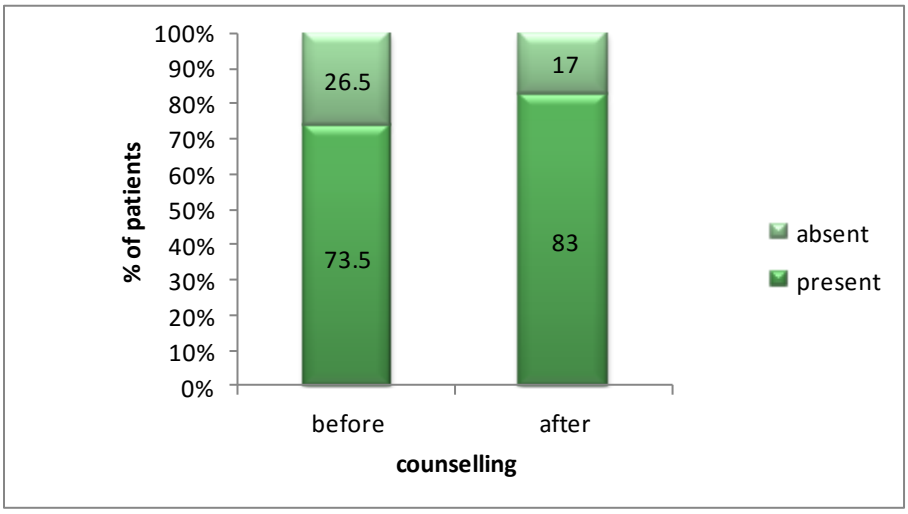


Figure 38 : Distribution of smoking status of the patient before and after counseling

Table 27 : Distribution of Alcohol and Smoking status of the patient before and after counseling:

Alcohol +Smoking	**Before counseling**		**After counseling**	
	N	**%**	**N**	**%**
Absent	147	73.5	172	86
Present	53	26.5	28	14
Total	**200**	**100**	**200**	**100**
Fisher's Exact Test		0.0027		

P value and statistical significance:

The two-tailed P value equals 0.0027.

By conventional criteria, this difference is considered to be very statistically significant.

It indicates that most of the patients have improved their social lifestyle after counseling was given.

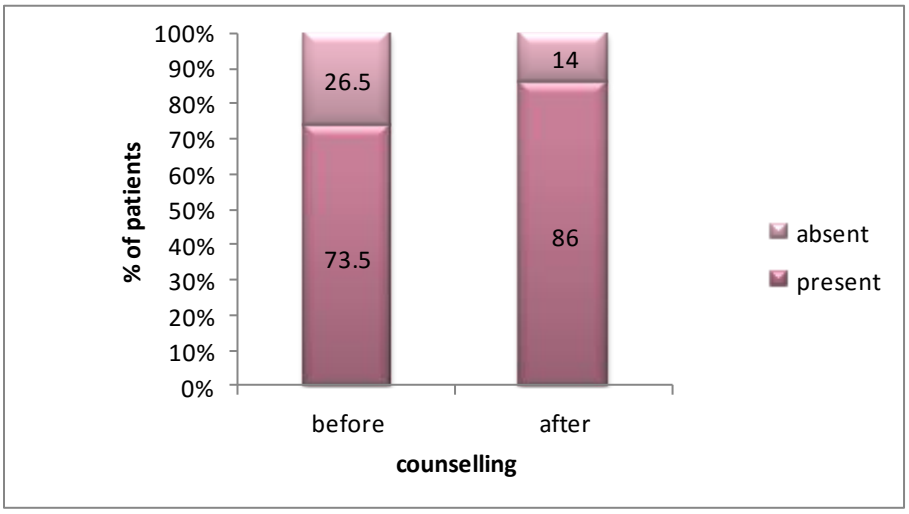


Figure 39: Distribution of Alcohol and Smoking status of the Patient Before and After Counseling

Comparison of Lifestyle of Patients Before and After Counseling:

The following table represents data regarding the lifestyle of patients before and after counseling.

Table 28 : Comparison of lifestyle of Patients Before and After Counselling

Life style	Before counselling		After counseling	
	N	%	N	%
Diet (non-veg,diary products)	50	22.5	28	14
exercise	68	34.0	45	22.5

Note: No of patients calculated for each individual lifestyle from 200 patients. Some patients may show more than one lifestyle

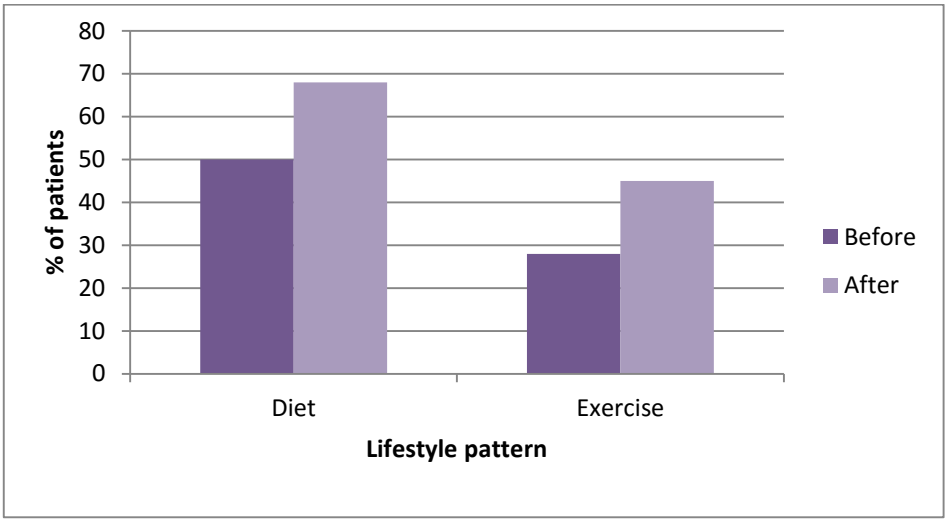


Figure 40: Comparison of Lifestyle of Patients Before and After Counseling.

The represented figure shows that among enrolled patients 77% of them followed diet correctly as their diagnosis, 66 % have good physical activity. This shows that most of the patients had an idea regarding diet and physical activity After counseling results have improved and majority have made lifestyle changes.

Table 29: Distribution of Diet of the Patients:

Diet	**Before counselling**		**After counseling**	
	N	**%**	**N**	**%**
Not-following	50	25	15	7.5
Following	150	70	185	92.5
Total	**200**	**100**	**300**	**100**
Fisher's Exact Test		0.0001		

P value and statistical significance:

The two-tailed P value equals 0.0001

By conventional criteria, this difference is considered to be extremely statistically significant.

It indicates that most of the patients have improved their lifestyle after counseling was given

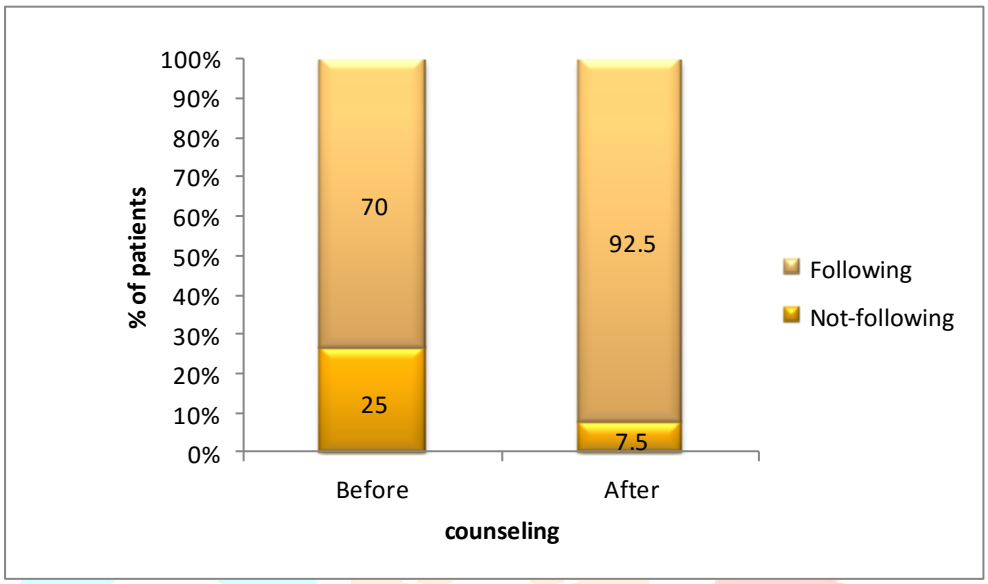


Figure 41: Distribution of Diet of the patients

Table 30: Distribution of Exercise of the Patients:

Exercise	**Before Counselling**		**After Counseling**	
	N	**%**	**N**	**%**
Not-following	78	39.0	35	17.5
Following	122	61.0	165	82.5
Total	**200**	**100**	**200**	**100**
Fisher's Exact Test		0.0001		

P value and statistical significance:

The two-tailed P value equals 0.0001.

By conventional criteria, this difference is considered to be extremely statistically significant.

It indicates that most of the patients have improved their social lifestyle after counseling was given.

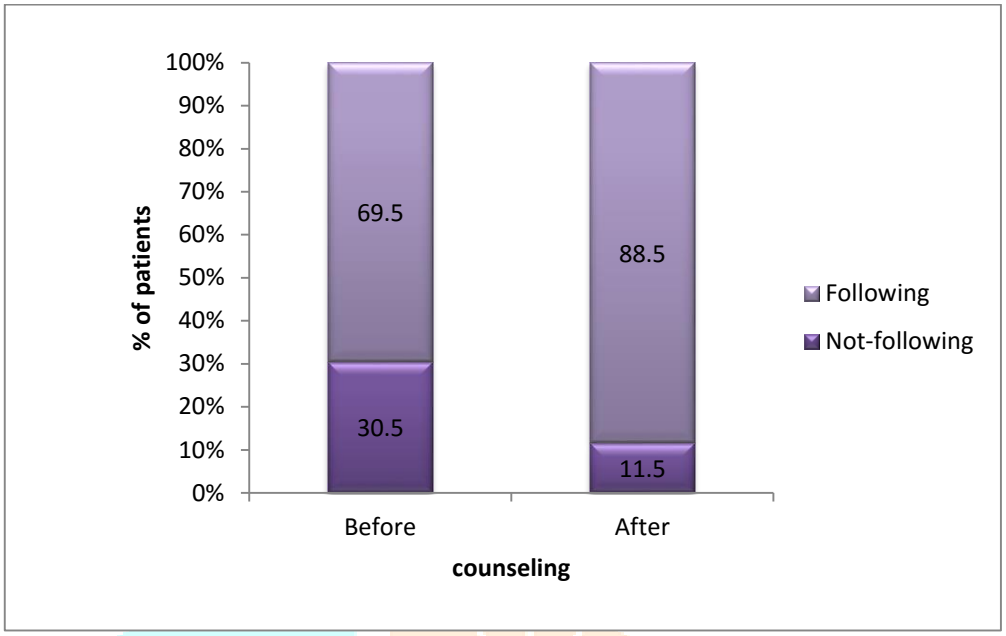


Figure 42 : Distribution of exercise of the patients

Follow-up:

Follow-up was completed for overall 100 patients (50%) ,which includes patients undergoing treatment including incretins ie 40 patients (57%)with mean duration of 6 months .

Comparision of FBG Levels Before and After Treatment Including Incretins-

Table 31: Comparision of FBG Levels before and after treatment including Incretins-

FBG	**Before**		**After**	
	N	**%**	**N**	**%**
Desired (<130)	14	35.00	28	70.00
Un-desired(>117)	26	65.00	12	30.00
Total	**40**	**100**	**40**	**100**
Fisher's Exact Test		0.0015		

P value and statistical significance:

The two-tailed P value equals 0.0015.

By conventional criteria, this difference is considered to be very statistically significant.

This difference indicates that incretins have got a good effect on FBG levels.

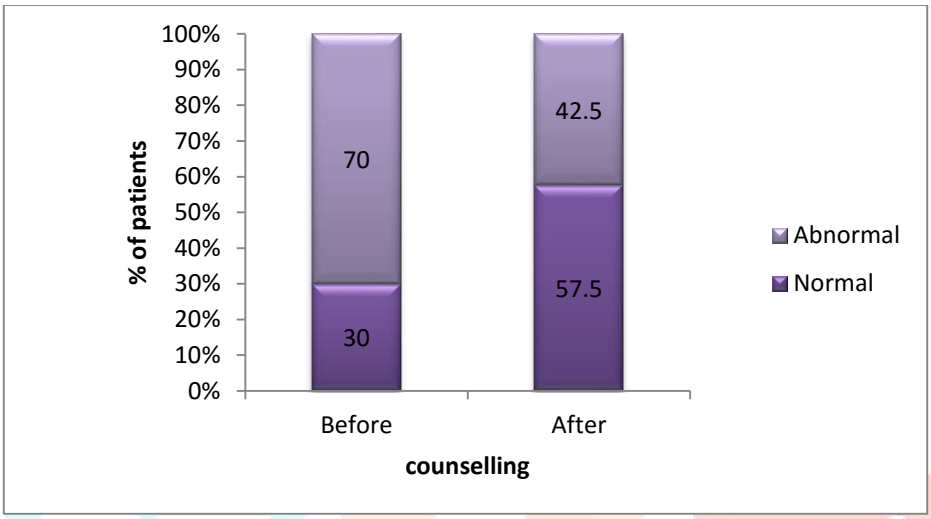


Figure43: Comparision of FBG Levels Before and After Treatment Including Incretins.

Table 32: Comparision of FBG Levels Before and After Treatment

FBG Levels	Before		After	
	N	%	N	%
90-130	14	35.00	28	70.00
131-180	20	50.00	11	27.50
181-230	6	15.00	1	2.50
TOTAL	**40**	**100**	**40**	**100**

Comparision of PPG Levels before and After Treatment Including Incretins-

Table 33: Comparision of PPG Levels Before and After Treatment Including Incretins

PPG	Before		After	
	N	%	N	%

Desired(<190)	12	30.00	27	67.50
Un-desired(>185)	28	70.00	13	32.50
Total	**40**	**100**	**40**	**100**
Fisher's Exact Test		0.0016		

P value and statistical significance:

The two-tailed P value equals 0.0016.

By conventional criteria, this difference is considered to be very statistically significant.

This difference indicates that incretins have got a good effect on PPG levels.

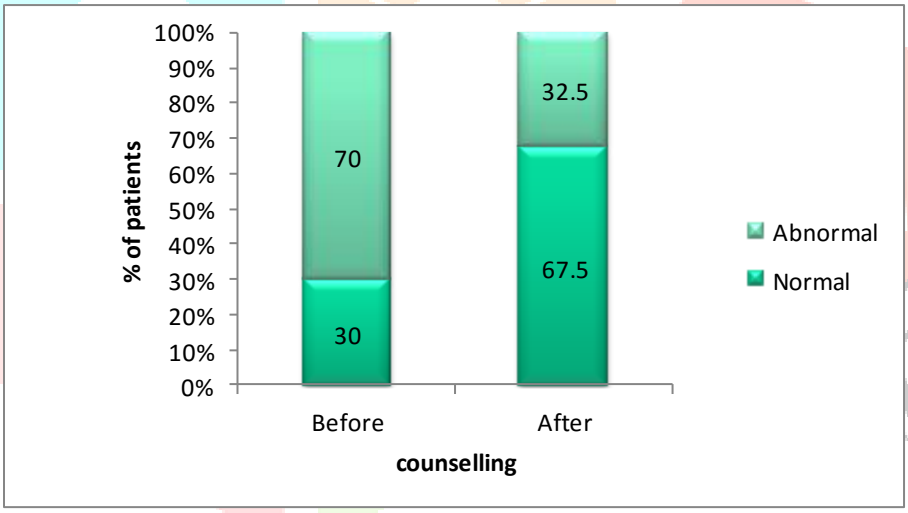


Figure44: Comparision of PPG Levels before and after treatment including Incretins

SUMMARY:

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia due to impaired insulin secretion with or without insulin resistance. It is associated with abnormalities in carbohydrate, fat and protein metabolism. It results from defects in insulin secretion, insulin sensitivity or both. It is a condition in which the body either does not produce enough insulin or cannot use insulin properly. Diabetes is a global epidemic, with a prevalence estimated to reach 380 million by 2025.It is the fourth leading cause of death

globally by disease, and the evidence suggests that by 2025 the largest increase will be in developing countries As the overall prevalence of diabetes is expected to rise to 380 million by 2025,342 million people worldwide are expected to haveT2DM by this time. Approximately 90% of patients with diabetes have the type 2 form of the disease.

The main aim & objectives of the study were to record utilization pattern of incretins which includes DPP-4 inhibitors and GLP-1agonist in type II DM patient from out-patients(O.P) and in-patients(I.P)during follow-up visits and how much it confirms to standard treatment guidelines(STG). To provide information to the patient or its representatives about diabetes and educating them about it.

In the study, 200 patients enrolled for the study during the study period, out of which 100 patients were followed-up with a mean duration of 6 months including patients who were receiving incretins ie 70 patients (35%).The FBG and PPG levels at follow-up and drug usage were recorded and analyzed using Microsoft excel. Variables were analyzed using Fisher's exact test based on requirement indicating the desired or un-desired levels of blood glucose after the treatment in the patients indicated with incretin-based therapies.

The results showed that in the study population males were found to be more (60.50%) compared to female (39.50%).Among the enrolled, patients of age group 30-59 were found to be more (60.50%).Among 200 patients the most common risk factor was found to be HTN(84%).Of all the patients HTN (84%) contributed to majority of all the co-morbidities found. When a combination of risk factors was assessed the results showed that majority (28.00%) of patients had a combination of HTN+ DYS, followed by HTN+DR(10.5%) and HTN+AKD(5%).

In the study population ,among the classes prescribed ,we found that class biguanides was mostly used contributing to majority (87.5%),followed by sulfonyureas (79.50%),incretins(35%),insulin(19%),TZD (8.5%) and α-GI(6.0%).As our study is mainly focused on the utilization pattern of incretins including DPP-4 inhibitors and GLP-1 agonist .Among 200 patients 70(35%) patients included incretins in their prescription. Within the class of incretin the mostly prescribed DPP-4 inhibitors were saxagliptin (40%), followed by sitagliptin(31.4%) and vildagliptin(17.1%) and the least use was of linagliptin(11.4%).Whereas in class of incretin the mostly prescribed GLP-1 agonist was found to be liraglutide with the percentage use of 4.2% among all the incretins. The most commonly prescribed 2-drug combination is Biguanide and DPP-4 inhibitors (52.38%), followed by Sulfonylureas and DPP-4 inhibitors (28.58%). The most commonly prescribed 3-drug combination is Biguanide+Sulonylureas +DPP-4 inhibitors (67.8%), followed by Biguanide+Insulin+DPP-4 inhibitors (28.5%).

Patient counseling was given to all patients out of which alcohol users constitute 15% and smoking users constitute 11.5% of the total population. A combination of both was seen in 26.5% of the patient population and 47% had none of the above secondary risk factors but left on advice of physician & counseling as it may worsen the present complications .Counseling was also given regarding lifestyle of patients results have improved and majority of the patients have made lifestyle changes for the better control over the disorder. Follow-up was completed for overall 100 patients (50%) ,which includes patients undergoing treatment including incretins i.e. 70 patients (35%)with mean duration of 6 months ie their before and after FBG and PPG levels. Majority of the patients achieved desired glycemic control after including incretins in their treatment along with lifestyle changes.

CONCLUSION:

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia due to impaired insulin secretion with or without insulin resistance. Other most common co-morbidities found were HTN, DYS etc. Alcohol, Smoking accounted for less percentage. A combination therapy proves to be more effective than a single drug. A combination of up to 3-drug therapy including incretins is in practice, but the most common being 2-drug therapy. Among the classes prescribed, Biguanides was mostly used contributing to majority. Among the class of incretin the mostly prescribed DPP-4 inhibitors were saxagliptin, whereas mostly prescribed GLP-1 agonist was found to be liraglutide.

In order to achieve the appropriate goal of treatment, it is necessary for discouraging complex treatment so that more people can benefit from it and ensure adherence to medicines. In the treatment of Diabetes Mellitus, lifestyle changes should also be encouraged along with the medicines prescribed. Awareness of the disorder and treatment is equally important. Majority of the prescription followed standard treatment guidelines.

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