RESEARCH ARTICLE

Rational Use of Metformin in the Management of Diabetes Mellitus Type II

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ABSTRACT

Sugar or high blood glucose level, a lay man description of a very common progressive metabolic disorder clinically referred as Diabetes Mellitus (DM), is targeting quite many people belonging to a wide spectrum of socioeconomic status and age groups. A numerical estimation revealed that sufferings and complications from DM type II has increased from 6.9 million. Metformin, the safest oral anti-diabetic and first-line drug, belongs to class of drugs called "anti-hyperglycemic agents". A study, through questionnaire based survey in Services hospital (Department of Endocrinology and Metabolism), was designed to assess the rational use of metformin in the treatment of DM Type II. Assessment forms were filled after interview of DM type II patients who were prescribed metformin. All factors contributing to rational use of metformin were considered as the right diagnosis, treatment plan, prescribing frequency, proper dose, at proper time, combination with other anti-diabetic drugs, compliance towards medication, follow up etc. It can be concluded that rational use of metformin is the safest choice for patients with early diagnosis of DM type II. The minor side effects, ranging from non-existent to significant, observed were gastrointestinal irritation, diarrhea, flatulence and indigestion. Patient compliance, food restrictions or specifications and healthy life style modifications help not only in controlling diabetes but also in improving the quality of life. Patient education, awareness campaigns and counseling either by doctor or pharmacist play remarkable role in recognition and exploration of vital aspects in combating disease.

KEYWORDS

Diabetes Mellitus Type II, Metformin, Rational Use

INTRODUCTION

Diabetes Mellitus is everlasting, chronic disease that alters the ability of body to utilize glucose, produced from food components, that is useful for cells when insulin is present. In diabetes, body either incapable of producing insulin or having cells resistant to insulin present, high levels of glucose in blood can damage small blood vessels of heart, kidneys, eyes and nerves which may result in complication.[1]

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Diabetes Mellitus (DM) was classified by WHO Expert Committee during 1979 and 1980 in to three sub types namely Insulin Dependent Diabetes Mellitus (IDDM) or type 1, Non Insulin Dependent Diabetes Mellitus (NIDDM) or Type II and gestational diabetes mainly.[2]

IDDM is characterized by inability of beta cells of pancreas to produce insulin. NIDDM being very common (about 95%) targets adults and overweight people. It has no cure but can be controlled by diet, exercise and weight control but usually progresses to be managed by medication. Hb1Ac and blood sugar level testing help to figure out condition.[1] Normal Hb1Ac level is below 5.6%, 6.7-6.4% (pre-

diabetics), above 6% (at risk) while above 6.5% are considered as diabetics.[3]

Medication therapy approaches involve use of biguanides, sulfonyl-ureas, derivatives of meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists etc.[4]

Rational use enables the patients to get medication, its dose and proper duration of therapy according to their individual requirement at economical price by rational prescribing, dispensing and administration. Irrational use may end up in failure of therapy, high frequency of side effects, economic burden, adverse effects etc.[5]

Metformin (Biguanide agent) is 1st choice drug for diabetes type II. Biguanides do not cause obesity or hypoglycemia and rarely result in lactic-acidosis. The Glucophage[R], Riomet[R], Neodipar[R], Fotamaet[R] are available brands of metformin.[4]

Metformin absorbs through intestine 50-60% bio-available, shows almost no plasma protein binding, plasma half-life almost 3.5 hours, no metabolism by liver and excretion is 90% through urine unchanged.[6] Pharmacological action is associated with inhibition of gluconeogenis in liver due to mitochondrial inhibition leading to activation of AMPK,[7] which tends to elevate the levels of cAMP to sensitize cells for insulin and increase the uptake of glucose peripherally by activating the GLUT-4.[8]

Minor side effects may be headache, myelgia, weakness, diarrhoea or other gastro-intestinal effects.[9]

LITERATURE REVIEW

Diabetes mellitus is one of the most widespread disorders with severe and serious chronic complications. An anti-diabetic drug with effective mechanism of action and minimum toxic effects is required to combat with it. Studies proved metformin as a well-tolerated and widely used oral anti-hyperglycaemic agent with no risk of hypoglycaemia and rare cases of lactic acidosis.[10]

Metformin therapy has a plus point because it tends to reduce weight, no significant hypoglycemia and glucose levels are reduced to normal. The side effects include GIT troubles, deficiency of vitamin B_{12}, folic acid deficiency, lactoacidosis rarely.[11]

Metformin, almost 50-60% bio-available, has a plasma half-life of approximately 6 hours, renal route of elimination and efficacy somewhat similar to sulfonyl-ureas. Their combination is very effective in controlling post prandial glucose levels. The reported side effects are GIT discomfort that may include nausea, diarrhoea, abdominal pain and metallic taste. The use of metformin was approved for more than 30 years in US, Canada, Europe and Great Britain.[12]

Prescribing frequency of metformin regardless of its contraindication (least chances of lactoacidosis) was found to be more than 80%.[13]

Metformin acts by reducing the gluconeogenesis in liver and helps to improve peripheral glucose uptake. All these effects are quite similar to pioglitazone, and their combination or co-formulation would be a rational approach to get maximum outcomes.[14]

Metformin alone or in combination with rosiglitazone is very much effective in controlling glucose level, improves insulin sensitivity and beta cell function.[15]

Metformin has been considered as drug of choice and 1st line drug for the management of type II DM. It has ability to combine safely with other oral hypoglycemic drugs.[16]

It has been reported that metformin can be used successfully in combination with sulfonyl-urea in the management of metabolic control in diabetic type II patients.[17]

The UK prospective diabetes studies suggested metformin to be 1st line agent for treating obese type II diabetic patients.[18] Metformin helps to reduce LDL cholesterol and triglycerides and does not change plasma lactate concentration significantly.[19]

Metformin is widely used in treating NIDDM but its metabolic effects are least understood

yet. It tends to reduce glycosylated haemoglobin and fasting blood glucose level.[20]

Metformin, discouraged only due to its risk of lactoacidosis in patients with impaired renal function, is a worldwide accepted and tolerated anti-diabetic drug with known efficacy.[21]

Some common predisposing factors for getting diabetes (also called "Metabolic syndrome") are overeating, inactivity and obesity. It has the tendency to develop cardiovascular risks which may lead to heart attack, gangrene, stroke or dementia.[22]

United Kingdom Prospective Diabetes Study (UKPDS) suggested that DM type II can initially be controlled by oral agents but eventually requires addition in oral drugs or insulin administration.[23] Some studies in China and Sweden concluded that modifications in lifestyle help in prevention of NIDDM. Almost 35% of patients with high risk of DM who failed to follow these modifications got Diabetes.[24]

Diabetes Federation estimated 194 million diabetic people worldwide. The economic burden due to diabetic patients will be beyond imagination in countries who have delayed strategies of prevention at Government and Regional level. In Asia people have strong susceptibility for getting diabetic due to genetic factors and obesity.[25] Metformin, controls blood sugar, lipid level and body weight better than any other oral anti-diabetic drug, is main therapeutic choice for type II diabetes in over-weight patients.[26]

A study reported that AMP kinase, which increases with depletion in energy store of cells and results in uptake of glucose in muscles, is activated by metformin in rat hepatocytes.[27]

Diabesity is term used to describe correlation of obesity and type II diabetes. Evidences showed that patients of type II are more prone to complications if they are obese too.[28]

Metformin plays a vital role in success of treatment involving combination therapy.[29] Weight reduction, carbohydrate rich, fat poor diet and exercise should be first

recommendation for high risk patients, then metformin and then combination therapy.[30]

Metformin works more efficiently when combined with sulfonyl urea.[31] Some of clinical conditions, in which oral anti-hyperglycemic drugs are used, involve diabetes of young, elderly diabetes, patients with cardiac and renal disease and in pregnancy.[32] A clinically well supported newer approach, to make combinations in a single tablet, can be good for glycemic control.[33] Thiazolidenediones are unique in improving insulin resistance and make skeletal muscles, liver and adipose tissues sensitized for insulin. It can produce synergistic effect with other oral anti hyperglycaemic drugs.[34] Patient education, counseling on the therapy, proper and regular monitoring of blood glucose and HbA1c level, proper diet planning and adherence to medication are points of consideration in obtaining desired outcomes from therapy.[35]

Methodology

A retrospective study was conducted in Services Hospital Lahore (Department of Endocrinology and Metabolism). By using convenient sampling technique 75 patients were randomly selected during a period of 3 months. . A structurally designed data collection form was used to interview subjects and record this data. Patients (males/females) suffering from Diabetes Mellitus Type II with age limit above 30 years were included in study while children, addicts, out of age limit, patients with other diseases and those who did not give consent were excluded from study.

RESULTS AND DISCUSSION

Table 1: Diabetes Diagnosis

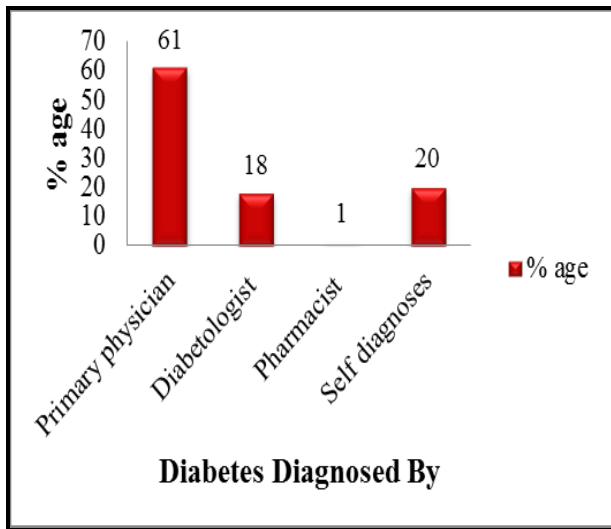| Diabetes diagnosed by	Frequency (n=75)	% age
Primary physician	46	61
Diabetologist	13	18
Pharmacist	1	1
Self diagnoses	15	20

Figure 1: The Diagnosis of Diabetes Type II Was First Made By Primary Physician in Patients (61%), By Diabetologist (18%), By Pharmacist (1%) And Self Diagnosed By (20%) of Patients

Table 2: Duration of Diabetes

Duration of diabetes	Frequency (n=75)	% age
Less than 5 years	55	73
Less than 10 years	14	19
More than 20 years	6	08
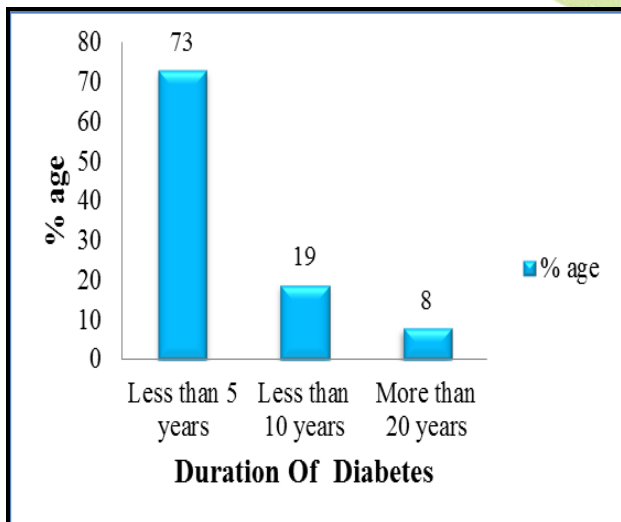
Figure 2: The Duration of Diabetes In Patients Was Found To Be Less Than Five Years (73%), Less Than Ten Years (19%) and More Than Twenty Years (08%)

Table 3: Medicines Prescribed

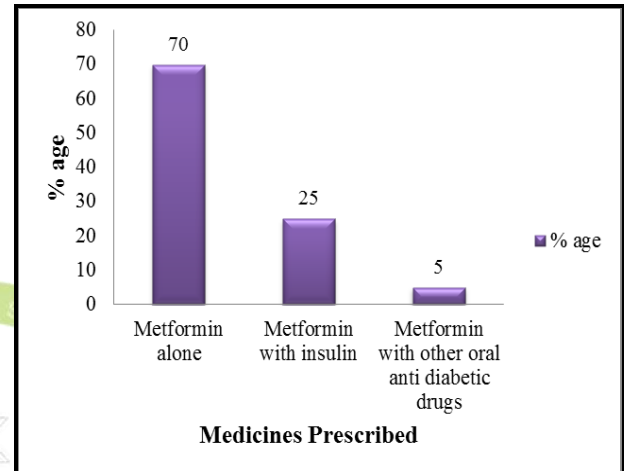| Medicine prescribed	Frequency (n=75)	% age
Metformin alone	53	70
Metformin with insulin	19	25
Metformin with other oral anti diabetic drugs	03	05

Figure 3: Metformin Was Prescribed Alone To (70%) of Patients, in Combination with Insulin to (25%) Other Oral Anti Diabetic Drugs to (05%) of Patients

Table 4: Dose of Metformin Prescribed

Dose of metformin prescribed:	Frequency (n=75)	% age
500mg/day	01	1
1000mg/day	08	11
More than 1g/day	66	88

Table 5: Side Effects of Metformin Experienced by Patients

Side effects	Frequency (n=75)	% age
Gastrointestinal irritation	50	67
Diarrhoea	07	9

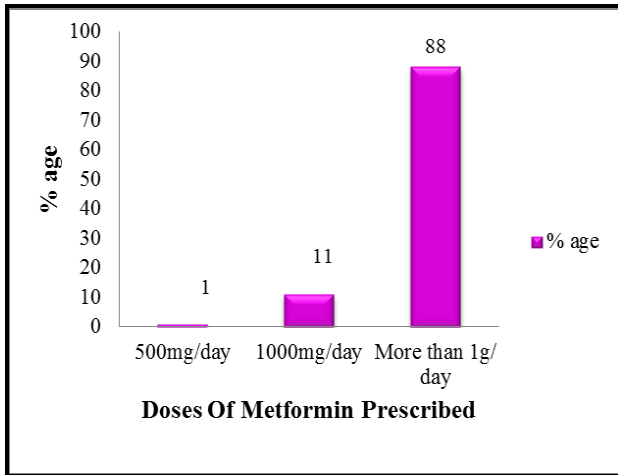|		
Nausea /vomiting	04	5
Flatulence	00	00
More than one	09	13
More than two	5	6

Figure 4: Dose of Metformin Prescribed 500mg/Day (1%), 1000mg/Day (11%) And More than 1G/Day to (88%) of Patients
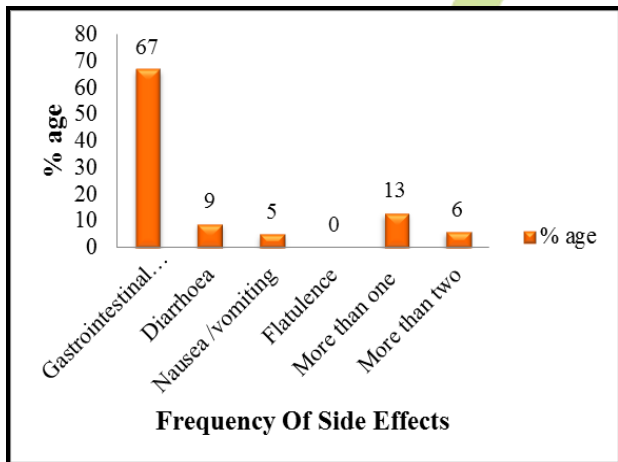

Figure 5: Patients Observed Side Effects with Use of Metformin i.e. Gastrointestinal Irritation (13%), Diarrhoea (02%), Nausea /Vomiting (23%) and Flatulence (02%)

Table 6: Any Herbal or Homeo Medicines Patients Are Taking Along With Metformin

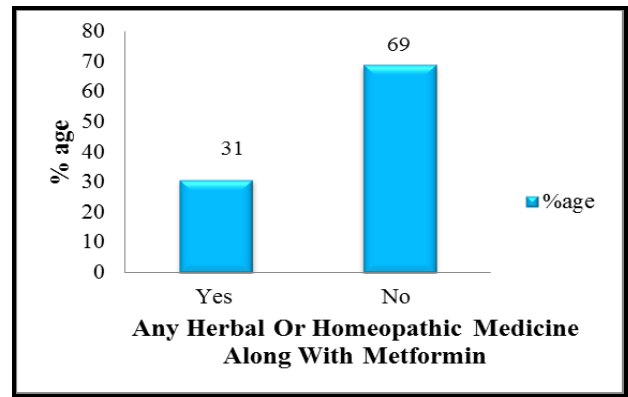| Taking medicine	Frequency (n=75)	% age
Yes	23	31
No	52	69

Figure 6: The Patients Who Used Any Herbal or Homeo Medicine (31%) along with Metformin and (69%) Of Patients Did Not Take Any Herbal or Homeo Medicine

Table 7: Patient Knowledge about Why to Take Metformin

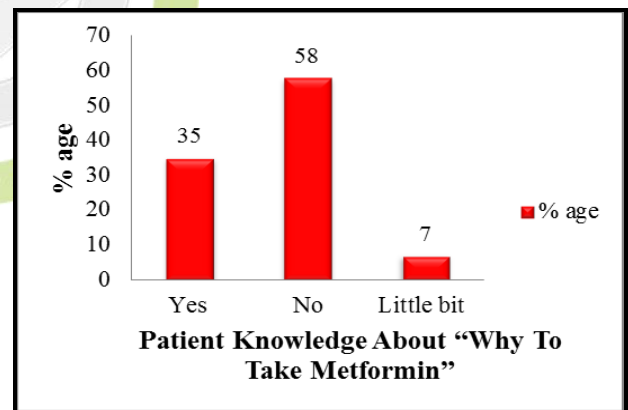| Patient knowledge	Frequency (n=75)	% age
Yes	26	35
No	44	58
Little bit	5	7

Figure 7: Among Diabetic Patients Only (35%) Were Aware Of "Why to Take Metformin" 58% of Patients Did Not Know and Only (07%) Patients Knew A Little Bit

Table 8: Patient Counseling About Use of Metformin:
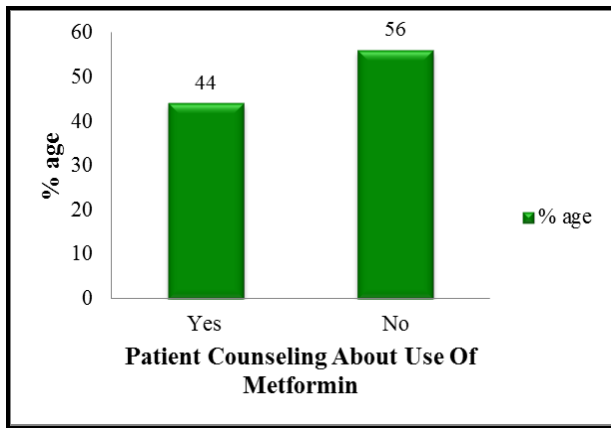
Patient counseling	Frequency (n=75)	% age
Yes	33	44
No	42	56

Figure 8: Among Patients Only (44%) Patients Were Well Counseled about Use of Metformin While (56%) were not

Table 9: Patients Buy Medicine From

Purchasing of medicine	Frequency (n= 75)	% age
Hospital vicinity	05	07
Pharmacy	13	17
Medical store	57	76

Figure 9: Patients Used To Buy Medicines from Hospital Vicinity (07%), Pharmacy (17%) and Medical Store (76%)

Table 10: Information about Difference between Doctor and Pharmacist

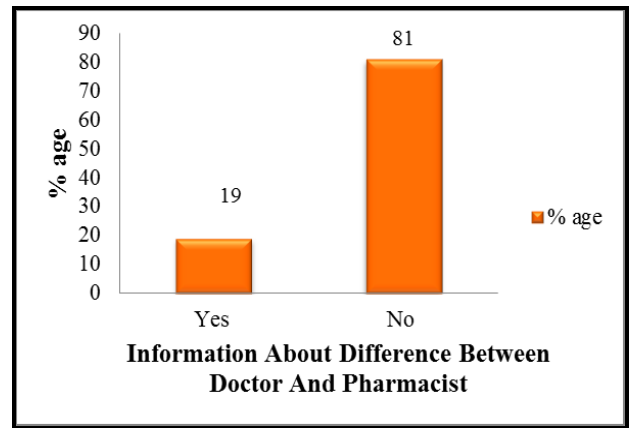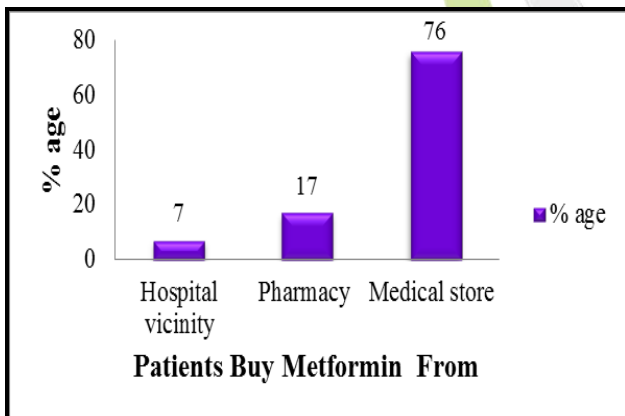| Difference between doctor and pharmacist	Frequency (n=75)	% age
Yes	14	19
No	61	81

Figure 10: Patients Who Knew the Difference between Doctor and Pharmacist (19%) And (81%) Patients Did Not

Table 11: Frequency of Missing Dose

Frequency of missing dose	Frequency (n=75)	% age
Yes	31	41
No	44	59

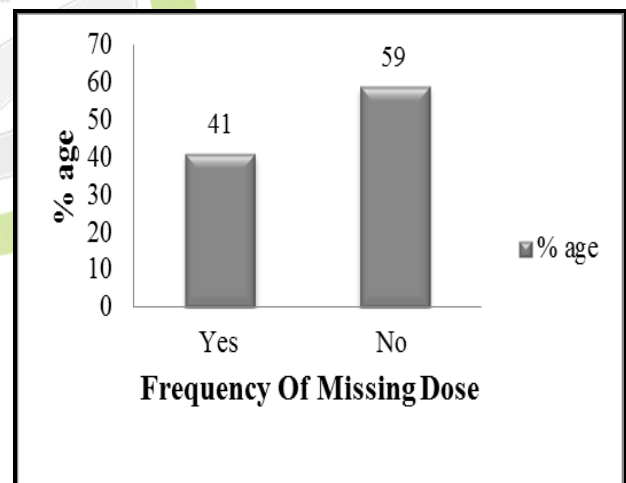
Figure 11: Among Patients Taking Metformin (41%) Often Used To Miss Doses While (59%) Take Metformin Regularly As Prescribed

Table 12: Frequency of People Who Discuss Their Medication Problems with Doctor

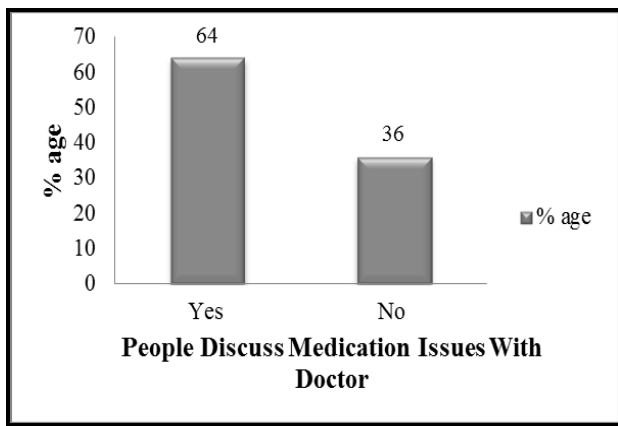| Discuss medication problems with doctor	Frequency (n=75)	% age
Yes	48	64
No	27	36

Figure 12: The Patients Who Used To Discuss Their Medication Problems with Doctor Were Found To Be (64%) While (36%) Did Not

Table 13: Feeling of Improvement in Disease Severity

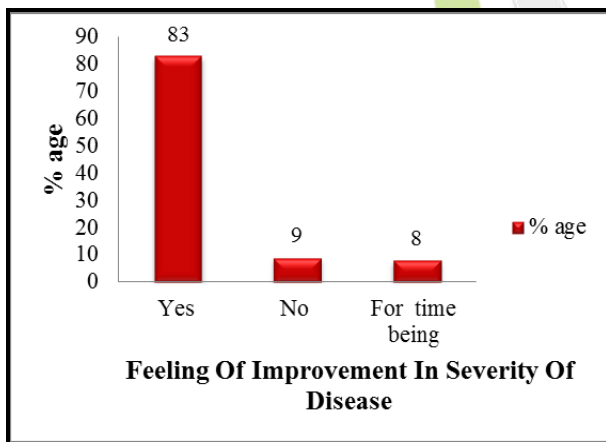| Improvement in disease severity	Frequency (n=75)	% age
Yes	62	83
No	07	09
For time being	06	08

Figure 13: Among Patients (83%) Felt Improvement, (09%) Did Not While (08%) of Patients Felt Relief for a Time Being

Table 14: Follow Up

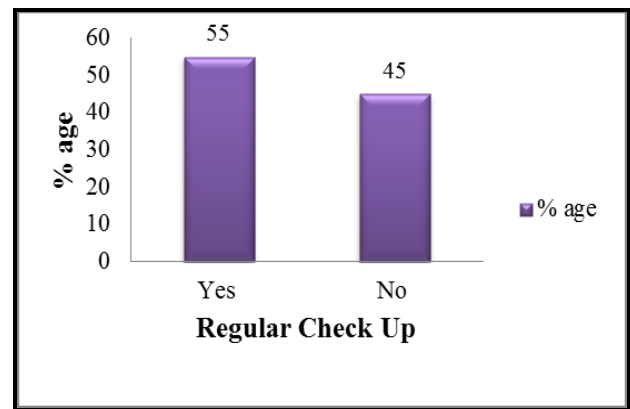| Regular check up	Frequency (n=75)	% age
Yes	41	55
No	34	45

Figure 14: The Patients Who Go For Regular Check Up (55%) While (45%) Only Then Go for Checkup When They Feel Sick

DISCUSSION

A questionnaire based survey was conducted in a re-known hospital of Lahore Services Hospital Lahore (Department of Endocrinology and metabolism) to assess the rational use of metformin in management of diabetes type II. The results of survey revealed that diabetes is disease that is very much common among patients of age above 40 years (83%) while cases below age of 40 years and 30 years were also reported 16% and 1% respectively. The diabetes was first diagnosed in patients by primary physician 61%, by diabetologist 18%, by pharmacist 1% and self-diagnosed in 20% of patients. Genetically determined insulin resistance played a key role in incidences of non-insulin dependent diabetes mellitus (NIDDM). Most of patients were having family history of diabetes 65% while 35% did not. McCarty also concluded the genetic evidence of incidence of NIDDM. The age of diabetes was found to be less than 5 years in 73% of patients, less than 10 years 19% and more than 20 years in 08% of patients. The patients were recommended lab tests HbA1c (88%), eye examination (7%), renal function test (87%) and fasting lipid profile (83%).

About 3/4th of the patients used to monitor their glucose level at home (93%) rather than at pharmacy or at private sector (07%). Metformin was prescribed alone to (70%) of patients, in combination with insulin to (25%) and with glycosidase inhibitors (Glucobay) [R] (05%) of

patients. Blood sugar level was not monitored on daily or weekly basis but patients checked their blood sugar level occasionally. The reasons behind this may be the scarcity and distant availability of medical facilities and economy of patients. Survey showed dose of metformin prescribed 500mg/day (1%), 1000mg/day (11%) and more than 1g/day to (88%) of patients. Minor side effects experienced by patients were gastrointestinal irritation (13%), Diarrhoea (02%), Nausea /vomiting (23%) and Flatulence (02%). These findings also have similarity with research results of Hermann and Pongwecharak et al. There was opinion among patients that herbal or homeopathic drugs can enhance the cure so 31% of patients were reported to take herbal or homeopathic medicines while 69% of patients relied on prescription.

In health care settings nearly all patients were counseled about the proper use of medicine but due to time shortage and huge mass of patients seeking medical care resulted in poor understanding by patient and some of the patients remain neglected in this regard. Many patients failed to produce any information or knowledge about mechanism of action of metformin, why to use metformin and the difference between doctor and pharmacist. Most of the patients were found to have trust (92%) in medical stores in regard of purchasing and counseling. Another aspect revealed that Patients were illiterate and had no knowledge about pharmacist and its importance. Few educated patients showed positive response and satisfaction from work of pharmacist.

As the compliance is considered the key factor in control of progression of disease and in minimizing disease symptoms and it was displayed that patients taking metformin (41%) were used to miss doses while (59%) take metformin regularly as prescribed. The factors resulting in noncompliance were found to be psychological, social and economic because some of patients who belong to lower middle class they were mostly non-compliant due to economic issues. Some reported that their

attendants unintentionally cause them to miss the doses.

During study it revealed that control of the blood glucose level in patients was due to diet consciousness and restricted use of sugar as about 53% abstained from sugar use in their diet, while 34% patients sometimes became careless. Among those the 65% of patients preferred to take diet drinks or canderel as sugar alternative. Although, patients have showed positive behavior towards diet control but also felt emotional and psychological deprivation regarding food and meal that others can consume sugar items while they cannot. Unrestricted sugar use in food was found to be a significant cause of severity of disease symptoms.

Along with medicines it's a healthy attitude in disease management that patients preferred to take exercise regularly while others did not bother to develop exercise habits. In case of DM the medications and life style modifications can play very effective role in prevention as well in control of severity of disease progression. Yoon et al also concluded that life style modification can be helpful in prevention of NIDDM. An irrational behavior towards therapy was that 44% of patients had not get check-up on time but they prefer the need basis. The possible reasons were found to be the psychological, economic and social factors. Regular blood sugar monitoring, properly prescribed medication, compliance to that medication and proper check-up are key factor to live a healthy and quality life along with NIDDM. Questioning about medical and medication related personal problems can ensure efficacy of treatment plan. Besides patients were reluctant to discuss their medication related problems with doctors but some of them were observed to participate actively in counseling. Diet plans were explained to every single patient to aid in managing life with diabetes. Since high glucose level leads to many complications so patients suffered retinopathy, numbness in feet and nephropathy. The patients who used metformin for a long time and all those who were recently prescribed with metformin experienced

improvement in their disease condition and showed confidence on the drugs prescribed. With round the clock hard work and dedication of team of doctors, and other paramedics in hospital were found to manage this disease efficiently.

CONCLUSION

Metformin is the drug that is most commonly prescribed (70% alone and 30% in combination) to treat early stages of NIDDM, which occurs usually after 40s, with life style modifications, patient counseling, assurance of compliance, regular blood sugar monitoring and follow up to ensure quality life. The most frequent dose of metformin prescribed is more than 1g, about 41% patients miss the doses knowingly, 47% take sugar, 65% use sugar alternatives and 51% feel deprived. The side effects reported are GIT irritation, nausea & vomiting, diarrhea or combined. A low percentage of patients were counseled by pharmacist and 92% trusted them.

ACKNOWLEDGEMENT

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