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The Efficacy of Pharmacological Intervention in a Subset of Hyperglycemic Pakistani Population

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Treatment of type II diabetes with oral anti-hyperglycemic drugs is initially successful, but the inclusion of insulin in the treatment regime is eventually inevitable under poor control. This paper aims to provide an overview of anti-hyperglycemic drugs and their use in Pakistan population coupled with their efficacy in treatment of diabetes type II. Literature search identified 140 clinical trials and 26 observational studies that compared mono or combination therapies. Further a retrospective review of 1518 patients which were undergoing treatment for type II diabetes mellitus in outpatient department (OPD) of endocrinology unit of Aga Khan University Hospital during 2007-2010 was done. The inclusion criteria for study subjects favored of age between 35-65 years with duration of diabetes between 5-35 years. The data was collected from hospital record department and was analyzed for efficacy of the medications using SPSS.V16. Prescribed oral anti-hyperglycemic drugs were independent of diabetes duration. Insulin, Biguanides, Sulfonylureas, Thiazolidinediones and Alpha-glycosidase were preferred to use singly or in combination. Overall insulin usage with other combination was in 56% of patients while overall Biguanides and sulfonylureas usage was in 61% and 45% of patients respectively. In response to therapy, the achieved FBS level, below 110 mg/dl, was in 21% of patients, levels as >110 to <126 mg/dl were found in 13% of patients (CI 95%, OR 0.58, p=0.098) while 66% of patients had >126 mg/dl (CI 95%, OR 2.74, p=0.0006). Insulin and Biguanides were found efficacious in only 34 % of selected population to bring the glycemic levels at normal limits when employed singly or in combination. Poorly controlled glycemic levels in 66% of population indicate co-morbidities and future complications of diabetes. All the current anti-hyperglycemic medications existing in global market were not being used in Pakistani population. Further genetic variation affecting drug metabolism may be the cause of decreased efficacy of drugs. The results can aid diabetologists, physicians and patients in making informed choices for better management of type II diabetes.

Key words: Diabetes type II, *Anti-hyperglycemic drugs, Efficacy of Anti-hyperglycemic agents,*

1. Introduction

Type II diabetes mellitus is a multifactorial and heterogeneous metabolic condition, which will be affecting nearly 366 million individuals worldwide by 2030 [1]. Maintenance of near normal blood glucose levels in patients with type II diabetes mellitus has been shown to be associated with a reduced risk of micro and macro-vascular complications [2]. Treatment with oral antihyperglycemic drugs is initially successful in type II diabetes mellitus, but it is often associated with a high secondary failure rate. Drug use patterns and clinical efficacy in a "real-world" situation may differ significantly from the information provided from such trials. In particular, agent acceptability, drug-drug interactions, and the use of complicated drug regimens may lead to poor compliance or discontinuation with prescribed medications, resulting in reduced clinical effectiveness. The inclusion of insulin to the treatment is eventually necessary to restore an acceptable glycemic level for many patients [3], [4].

Type II diabetes mellitus has been found to be the consequence of Insulin resistance, Impaired Insulin Secretion, Increased hepatic glucose production (gluconeogenesis) and reduced Glucagon-like peptide-1(GLP-1) levels [5]-[8]. Insulin secretion is regulated by blood glucose, certain amino acids and hormones e.g. GIP [9], [10]**.** The process of insulin secretion begins when glucose enters the B cells in the Islets of Langerhans, via GLUT-2 channels; this glucose is phosphorylated here by glucokinase to form glucose-6-P [11]. The phosphorylated glucose is converted into large amounts of ATP via glycolysis & oxidative phosphorylation. ATP inhibits the

K+ ion channels & therefore prevents the leakage of K+ ions out, which in turn increases the membrane potential i.e. makes it more positive. Ca++ ion channels are sensitive to this alteration in membrane potential, they open up & allow large influx of Ca++ into the B cell. The insulin filled vacuoles are exocytosed as a result of this Ca++ influx [12]. This is a first-phase secretion which consists of pre-formed vacuoles; constant stimulation leads to insulin synthesis and therefore secretion which constitutes second-phase of secretion**.** Type II diabetes mellitus can be treated with a range of antihyperglycemic drugs. The oral anti-hyperglycemic drugs used in the management of type II diabetes mellitus may target either one of the stages of insulin secretion. In this paper an extensive review of the literature for classes of anti hyperglycemic drugs was conducted and identified 140 clinical trials and 26 observational studies that compared mono or combination therapies. A part from insulin, drugs that are employed in treatment of diabetes type II in Pakistani population is given

Sulfonylurea

These are known as insulin secretagogues as they target the impaired insulin secretion [13], [7]**.** The mechanism of action of sulfonylureas is the inhibition of ATP-sensitive K+ ion channels from opening. They have also shown to reduce serum glucagon levels & increase insulin sensitivity by increasing binding of insulin to its receptors [5]. Recently it has been reported that sulfonylureas interact directly with

Epac2. "Epac2 is a guanine nucleotide exchange factor for small GTP Rap1", member of Ras super family of small GTP binding proteins. Thus sulfonylurea activates Rap1 through Epac2. Mice lacking Epac2 showed decreased insulin secretion despite administration of sulfonylurea [14].

Sulfonylureas are the first-line oral antihyperglycemic drugs excluding obese patients [7]. It has first, second & third generation agents which differ in potency, safety & pharmacokinetics [6]. The 1st generation drugs e.g. chlorpropamide have the longest half-life. 2nd generation drugs e.g. glyburide have greater potency, are safer & have better pharmacokinetics. Whereas, the 3rd generation drugs e.g. glimepiride are used as part of combination drug. All sulfonylurea's are giving orally and bind strongly with albumin in plasma. They are metabolized in liver & excreted via kidney.

Adverse effects include hypoglycemia, hyperinsulinemia, obesity & hypersensitivity reaction in people with sulfa allergies [5], [7]. In rare conditions dermatological disorders, GI disturbances & CVS complications have been reported especially with tolbutamide where there is a 2.5 times greater risk [6]. Drug interaction also takes place with medication that might displace sulfonylurea from plasma protein e.g. sulfonamides, decrease excretion e.g. probenecid, or reduce metabolism in liver e.g. warfarin [15], [16]. Loss of efficacy with time is overcome by increasing dose.

Biguanides

Biguanides are the most commonly prescribed oral antihyperglycemic agents. Metformin is an example of this class of medication and controls the progression of type II diabetes mellitus by controlling the metabolic glucose products. Patients with known insulin resistance benefit the most & it is also the most commonly prescribed anti-diabetic medication [17]. In obese type II diabetes mellitus patients, metformin reduces the risk of MI more than sulphonylureas or insulin [18]. Metformin significantly lowers the gluconeogenesis, approximately by $1/3^{rd}$, when compared to non-medicated patients [19].

Mode of action of the drug is by activating AMP-activated protein kinase (AMPK), a liver enzyme that plays a significant role in the signaling pathways involved in insulin secretion & activity, along with the inhibitory effect on the production of glucose by liver cells [20]. Besides suppressing hepatic glucose production, metformin enhances peripheral glucose uptake by increasing insulin sensitivity and insulin binding to its receptors [5]. Research shows that activation of AMPK leads to an increase in the expression of small heterodimer partner (SHP), which inhibits the expression of gluconeogenic genes PEPCK and Glucose-6-phosphatase [21]. The mechanism of metformin which increase activity of AMPK remains indefinable.

Metformin also increases AMPK activity in skeletal muscle causing increased GLUT-4 translocation, resulting in an increased insulin-independent glucose uptake [22]. The metabolic actions of metformin in the heart muscle are independent of changes in AMPK activity and may be mediated by p38MAPK and PKC-dependent mechanisms [23]. Metformin reverses the detrimental effects of high glucose blood concentration on osteoblast function, as it decreases intracellular reactive oxygen species (ROS) and apoptosis, thus having osteogenic effects on osteoblasts, conversely treatment with Thiazolidinedione (TZD) inhibits osteoblastogenesis via stimulation of peroxisome proliferator-activated receptor- γ 2 (PPAR- γ 2) [24], [25]. A decrease in incidence of prostate cancer is reported in patients taking metformin [17]. Decrease in absorption of glucose from the gastrointestinal tract is responsible for side effects such as nausea, metallic taste, diarrhea & abdominal discomfort. These can be avoided if dosage is increased slowly & taken with meals. Contraindications include patients that are at high risk of lactic acidosis i.e. serum creatinine over 150 micro mol/l, hepatic impairment, respiratory insufficiency, severe infection and alcohol abuse [26]. It should be used cautiously in elderly patients above 80 years and is recommended to monitor renal function and hematological parameters upon initiation and termination of therapy. Dosage should be stopped before a procedure with radio contrast dye and surgery. Caution should be taken that co-administration of Alpha-glucosidase inhibitors (AGIs) lowers the bioavailability of metformin.

Alpha-glucosidase inhibitors (AGI)

These drugs regulate the absorption of glucose from the diet and are not only used for diabetic patients but are also beneficial in pre-diabetic cases [27]. Some available AGIs in the market are Acarbose, Mitligol & Voglibose, these drugs are structurally saccharides which act as competitive, reversible inhibitors of various enzymes that are responsible for digestion of carbohydrates [5]. Acarbose has been shown to decrease the risk of progressing to diabetes in subjects with impaired glucose tolerance (IGT); some studies have also suggested that Acarbose could decrease the risk of cardiovascular disease both in IGT and diabetes [27].

Alpha glucosidases enzyme is physiologically present in the lumen of the small intestine. These enzymes are responsible for the catabolism of disaccharides, trisaccharides & oligosaccharides. AGI inhibit these glucosidases, thereby reducing the post-prandial spikes in blood glucose levels. Production of insulin by beta cells is not affected neither is the action of insulin on peripheral cells, therefor hypoglycemia does not occur. Apart from acting on alpha glucosidases, AGI also act on maltase and sucrase, which physiologically hydrolyze complex starch to oligosaccharides and sucrose to glucose respectively [28].

AGI are generally prescribed to be taken before meals and dosage should be adjusted according to meal times. Patients that have irregular eating habits along with very high post-prandial glucose levels benefit the most from AGI therapy. Side-effects are pertinent to the GI tract such as flatulence and abdominal cramping due to excessive unabsorbed fats. These are however dose related and tolerance develops over time, thus gradual increase in dosage would prove to be most beneficial [29].

Thiazolidinedione (TZD):

Rosiglitazone and pioglitazone are members of a sub-class of TZD. They are known to modulate the peroxisome proliferator-activated receptor-γ (PPAR-γ), which is a nuclear hormone receptor, leading to an increase in insulin sensitivity [5], [30]. Ligands to the PPAR-γ receptor are capable of regulating adipocyte production, secretion of fatty acids and glucose metabolism, as well as achieving beneficial effects on insulin action & beta-cell function [31]-[33]. Glycemic control is achieved relatively easily when TZD is used therapeutically as compared to other anti-diabetic drugs especially sulfonylureas [34].

The Adverse effects associated with TZD are weight gain, headache, anemia, and edema, especially with co-administration of insulin is the increased propensity to fractures [25]. Heart failure is a very alarming potential adverse effect as treatment with TZD increases the likelihood of morbidity by two folds. Meta-analyses have reported a 30-40% increase in the risk of myocardial infarction in patients that were treated with rosiglitazone.

On the contrary pioglitazone is shown to be associated with lower risk of cardiovascular events as compared to any other anti-diabetic therapy [35]-[37]. Rosiglitazone treatment is also associated with increased LDL & decreased HDL cholesterol levels, where as pioglitazone is linked with improved lipid profile [38]. On the contrary there is no data conclusively indicated the beneficial affects of pioglitazone or harmful effects of rosiglitazone-on the cardiovascular system. American Diabetes Association & European Association for the Study of Diabetes on the management of type II diabetes mellitus recommends the use of pioglitazone as opposed to rosiglitazone [39]. Lower dose of TZD when co-administered with metformin creates an ideal combination for glycemic control with low risk.

Meglitinides

This class of anti-hyperglycemic drugs is comparable to sulfonylurea in action where as it is analogous to AGIs in terms of routes of administration of the medication. Unlike sulfonylurea, however, meglitinides are short-acting drugs, implying they have rapid onset with short duration of action [41]. Therefore it is always prescribed to take one to thirty minutes before a meal, often requiring several doses daily. Repaglinide & Nateglinide both act through stimulation of a "distinct site" on the sulfonylurea receptor (SUR). This receptor is essentially an ATP-sensitive K+ channel, which on stimulation results in insulin secretion, thus their action solely depends on functioning pancreatic beta-cells [40], [41].

Both drugs undergo hepatic metabolism by CYP3A4, member of cytochrome P450 family, to inactive products, consequently any medication that enhances e.g. rifampin, or inhibits e.g. fluconazole, the activity of these enzymes, accordingly depresses or increases the glucose lowering effect [42]. Side effects are comparatively similar to that of sulfonylureas, but with decreased incidence of hypoglycemia & weight loss.

GLP-1 analogs

Glucagon is a hormone that is secreted by the alpha cells of the islets of Langerhans, as a consequence of hypoglycemia. Glucagon increases glucose levels in the blood, by initiating several processes like gluconeogenesis, glycogenolysis & lipolysis. Therefore it has actions that completely oppose that of insulin, yet a very peculiar fact is that glucagon also increases the secretion of insulin. Glucagon-like peptide-1(GLP-1), as the name suggests, are structurally similar to glucagon. It has been reported that oral glucose administration compared to same equal dose given intravenously, results in higher levels of insulin in blood. This effect, called "incretin effect" is due to the secretion of gastrointestinal hormones, notably GLP-1. Patients with type II diabetes mellitus, have a reduced "incretin effect". Recently, a new drug, exenatide which has about fifty percent homologous polypeptide sequence to GLP-1, has been developed. Exenatide mediates its action through stimulating the GLP-1 receptor. This drug not only acts as an insulin secretagogue, but also slows down gastric emptying, reduces weight, lowers blood pressure & glucagon levels, improves lipid profile & HbA1c and promotes myocardial functions [43], [44]. The loss of beta cells is also decreased as GLP-1 promotes beta cell regeneration, thus halting disease development [45], [46]. Being a polypeptide, GLP-1 can only be administered parentally, which is a disadvantage, as repeated injections are required due to its short duration of action. Gastrointestinal side effects such as nausea, diarrhea, hypoglycemia & pancreatitis have been reported [44]-[47].

Amylin analogs

These are principally synthetic analogues of the human hormone amylin. Physiologically, levels of amylin increase after food intake, this hormone serves to decrease gastric emptying & glucagon secretion [48]. Analogs of amylin, such as the prototype drug, Pramlintide functions in the same manner as amylin. Analogous to GLP-1s, amylin analogs must be administered parentally only in concurrent insulin users, which is a major problem. Adverse effects include nausea, weight loss and hypoglycemia [44].

DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that degrades incretin in the human body. Incretins e.g Glucagon-like peptide-1 (GLP-1) & gastric inhibitory polypeptides (GIP) are hormones that are essential for digestion & absorption of nutrients like glucose [45]. Thus, DPP-4 inhibitors allow increased incretin levels [46]-[48]. As greater insulin secretion is achieved via increased incretin, DPP-4 inhibitors indirectly permit glycemic control. Sitagliptin is prototype of DPP-4 inhibitors; it is orally administered & is well tolerated. DPP-4s are widely believed to ultimately improve beta cell function [49]. Undesirable effects include Upper Respiratory infections (URI), nasopharyngitis, headache & Urinary Tract infections (UTI) [50], [51].

Bile acid sequestrants

Bile acid sequestrants, originally used for hyperlipidemia,

have been shown to control normal glycemic levels [52]. Its mechanism of action is unknown. Bile salts have membrane and nuclear receptors, thus it is postulated that modification of the related pathways by bile acid sequestrants leads to glycemic control & improvement in lipid profile [53]. For instance, bile acids are ligands for intestinal farnesoid X receptors. Binding of bile salts sequestrant down regulates the activity of the farnesoid X receptors, therefore lead to decreased SHP. SHP inhibits liver X receptor activity; hence bile salt sequestrants indirectly increase the liver X receptor activity. Liver X receptor has been depicted as a "glucose sensor", reduced glucose levels are seen with increased liver X receptor activity [54], [55]. Colesevelam Hydrochloride (Hcl) is a prototype drug that was approved in January 2008, as part of a combination therapy, when used with sulfonylurea, metformin or insulin [56], [57]. Research has shown that treatment with colesevelam Hcl leads to a reduction in fructosamine, fasting blood glucose (FBG), total cholesterol, HbA1c & high-sensitivity C-reactive protein (hsCRP), on the contrary, levels of triglyceride (TG) & ApoA-I lipoprotein are considerably increased [53], [58]. Gastrointestinal side effects such as constipation, vomiting, and abdominal pain have been documented.

Dopamine receptor agonists

In 2009, the US Food and Drug Administration (FDA) approved yet another anti-hyperglycemic drug. Bromocryptine, a prototype drug, acts on the hypothalamic centres, which control the post-prandial insulin mediated glucose & lipid metabolism. By this means, it reduces post-prandial hyperglycemia & hyperlipidemia [59]. Side effects include nausea, vomiting, orthostatic hypotension, dizziness & headaches.

2. Method

This study is a review of literature and descriptive, retrospective cohort review of 518 patients with type II diabetes mellitus, which were under treatment at the Aga Khan University Hospital (AKUH) Karachi during 2007-2010. We selected the age group 35 to 65 years with duration of diabetes between 5 to 35 years as inclusion criteria, rest of the patients were excluded. Information from medical records was collected which included age, gender, duration of diabetes, class of anti-hyperglycemic medication prescribed, fasting blood sugar (FBS) at 2-4 month follow up. Statistical analysis was done using SPSS V.16 program. Further web based information for the drugs review was collected from different data bases through reviews, papers and books. The boundaries used are arbitrary values for FBS levels to differentiate a pathological condition from a normal one in our population. FBS values of less than 110 are considered normal, values between 110 and 126 are considered impaired FBS levels and levels above 126 are considered to be hyperglycemic. This is according to WHO criteria generally followed at the time of patient treatment in Pakistan Patients were further classified on initial oral hypoglycemic agent monotherapy or initial combination therapy

3. Results and Discussion

Total of 518 type II diabetics met the inclusion criteria consisted of age group of 35-65 years, and duration of diabetes from 5-30 years. Among the subjects 261 (50.4%) were male and 257 (49.6%) were female. Mean age of all the patients was 55± 10 years and the median duration of diabetes was 18 years. Results showed that four classes of oral anti-hyperglycemic drugs were being employed in our population in order to treat chronic hyperglycemia in type II diabetes. These were Biguanides (61%), Sulfonylurea's (45%), Thiazolidinediones (5%) and Alpha-glycosidase inhibitors to 2% of patients.

Figure 1

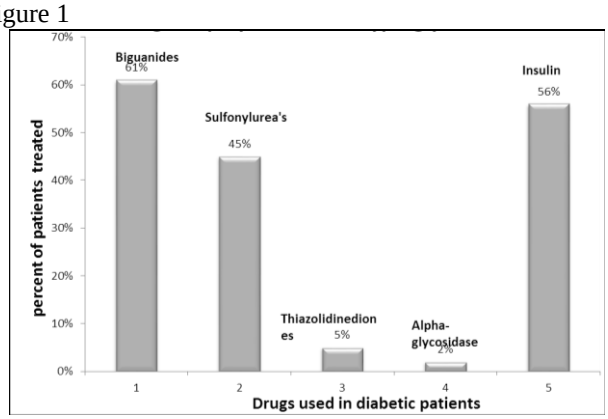

Figure1: Drugs employed to control Hyperglycemia

Furthermore, insulin was utilized in 56% of the selected population which represented the fact that more than 50% of our population depended on insulin for management of blood glucose at times.

In 21% of the sample size glycemic levels reached to normal as <110 mg/dl after treatment. While 13% reached to impaired FBS level >110-<126 (95 %CI, OR 0.58, p= 0.098) and 66% of population were in undesirable range (95 % CI, OR 2.74, p= 0.00026) as shown in fig 2.

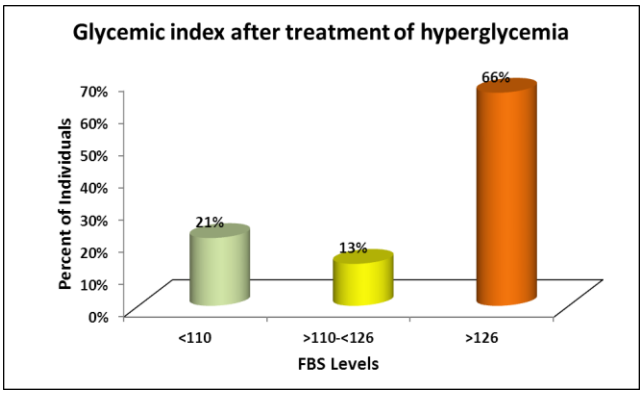

Figure 2: Glycemic index after treatment of Hyperglycemia

Treatment with a single drug in case of Insulin only was given to 17% of patients, could gain controlled levels high effect in 4% patients of total population. Biguanides only was given to 11% of patients and 45% out of these got their hyperglycemic levels controlled (p= 0.006). The sulphonylurea's alone were given to 4% of patients which could not bring them to desired glycemic levels of < 126 mg/dl (Fig 3).

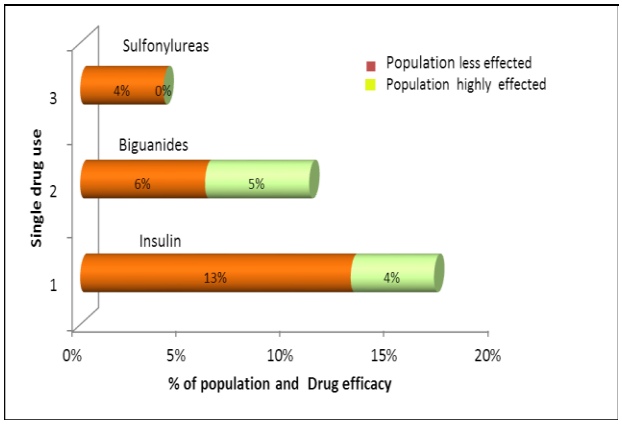

Figure 3: Efficacy of single drug treatment

The drugs were used in combination to control hyperglycemia as well Total of 90% population with hyperglycemia of type II was treated with anti-hyperglycemic dugs, while 10% were advised for non-drug therapy such as diet and exercise. Treatment with diet and exercise was effective on 5% of population
table1

Table 1: Response of Patient Population to reduce glycemic level by Treatment

Treatment	*Population treated (%)*	*% population attained*		
		FBS: <110	*FBS: >110 - <126*	*FBS: >126*
No medication Diet and exercise	10	4	1	5
Ins	17	2	2	13
Big	11	3	2	6
Thi	0	0.53	0	0
Sulf	4	0	0	4
Ins+Big	12	3	2	7
Ins+Sulf	5	3	0	2
Ins+Thi	2.53	0.53	0	2
Big+Sulf	16.00	2.00	2	12
Ins+Big+Sulf	16.00	2	3	11
Big+Sulf+Thi	2	0	0	2.0
Big+Sulf+Alpha1	1	0	0.53	0.53
Ins+Big+Sulf+Thi	1.06	0.53	0	0.53
Ins+Big+Sulf+Alpha1	1	0	0	0.53
SUM		20.56	13	66

Among the mono-therapy Insulin was used most of the time, however the efficacy of the biguanides was significant (95% CI, OR 2.71). Insulin used was in the form of humulin, Mixtard and Lantus. Bigunides were taken in the form of Metformin or Glucophage. Sulphonylureas were taken in the form of gliclazides (diamicron) glimepirides (amaryl, getryl) and glibn clamide (daonil). Alphaglucosidase inhibitors were given in the form of acarbose (glucoby). Thiazinolidiones were given in the form of pioglitazones: actos, piozer: avandia and zolid.

Over all in response to single oral medications given to 32 % of population, the results of FBS at 2-4 month follow up was such that 5% of the patients attained FBS <110 mg/dl± 3.3 SD, 4% of the patients attained FBS >110 mg/dl to <126 mg/dl± 3.1 SD and 23% of the patients could not acquire desirable levels but attained FBS values >126± 14 mg/dl (95% CI, OR 2.24, p=0.048) Combination therapy that was adopted usually consisted of two medications, but three and more were also being used for patients with unregulated blood glucose. In combination, insulin with biguanides and sulfonylureas was used in 16% population while sulfonylureas and biguanides use was also in 16% of the population. Difference in bringing the glycemic control with both of these drugs at the reasonable level was not significant as 3% vs. 2%, indicating the fact that combinatorial effect is synergistic. None of the drugs provided the additive effect. Since these drugs have different pathways to control the hyperglycemia this also indicate the complex mechanism of signaling interaction, perhaps all required mechanisms cannot be switched on at one time.

In response to double therapy 9% of population was able to achieve the glycemic levels to 110mg/dl, and 4% reached to gain levels <126 but >110mg/dl while 23% of the patients could not reach to desirable levels and were found having levels > 126mg/dl (95% CI, OR 1.48, p=0.029) . Regarding treatment given with triple therapy could gain 110 mg/dl in only 2% of patients and FBS levels were >110-<126 in 4% of patients while 14 % remained with FBS levels higher than 126mg/dl (95% CI, OR 1.92, p=0.23). Further significantly low number of population was given additional add on therapy with four drugs among these 0.53 % could achieve levels <110 mg/dl and levels >110-<126 mg/dl each, while around 2% population could not achieve the desirable levels Overall 32% of patients were on mono therapy 365 of patients were on doule combination of medication and 19% was on triple therapy .While 2% was on combination of four oral hypoglycemic drugs

Moreover observations indicated that prescribed medications were independent of duration of diabetes as shown in figure 4**.** In the interval of 6-15 years, biguanides were employed the most in 68% of the patients. Drug remained effective for large number of patients likely due to not causing hypoglycemic actions and also of low risk of CVD events. Further as diabetes became chronic approaching 30 years, biguanides usage decreased. Sulfonylureas usage increased from 38% in the interval 6-10 years and peaked at 58% in patients with less than 15 years of diabetes. A drastic decrease was observed in the interval 16-20 years, as it declined to 28%; as it may be causing frequent episodes of hypoglycemia, increased weight gain and risk of myocardial ischemia. Another rise was seen in the interval 21-25 years. Thiazolidinediones were infrequently utilized, always as a part of combination therapy. They were gradually used more and more in combination therapy as the disease became chronic, peaking at 19% in patients with diabetes for 27 years. Less usage is because of disadvantages associated with the drug, such as edema, heart failure, and risk of bone fracture. Alpha- Glucosidase inhibitors were seldom used in patients with diabetes of less than 20 years. Probably because of its moderate cost not affordable by many patients. Drug choice is based on preferences to keep side effects minimum, while reducing the hyperglycemic condition.

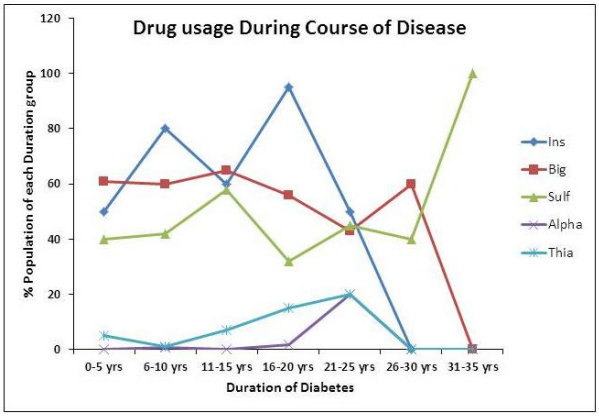

Figure 4: Pattern of Drug usage in diabetes duration

In the interval 21-25 years AGI usage increased significantly, reaching 18%. Insulin inclusion in the treatment regimen was the last resort. In the interval 16-20 years, greatest amount of insulin usage was observed, peaking at 96% to bring hyperglycemia in control.

The uninformed values of FBS are used to diagnose Type II diabetes mellitus in undiagnosed patients but we used them to equate it with drug efficacy since the objective of hyperglycemic drugs is to keep blood glucose levels within a normal range. Insulin and biguanides turned out to be efficacious in this selected population and therefore were employed more than other classes.

Also, not all the current anti-hyperglycemic medications are being used in our population possibly due to the increased cost of newer medications such as GLP-1 analogs and meglitinides being not easily affordable in majority of population in the developing countries. Selection of the drugs was also moving around the patients clinical relevant issues. Awareness amongst the GPs, lack of availability of the medications and compliance issues are another factor. Factors such as patients' beliefs, attitudes and adherence also contributed to the result, as disparity was found between socio-economic class and outcome of treatment, which is in accordance with reports in literature **[**60]

4. Conclusion

Diabetes requires life-long treatment and constant vigilance with regards to dietary habits and regular medications. Insulin and biguanides were one of the mainstays of therapy in the first two decades of diabetes treatment, whereas sulfonylureas were prescribed throughout the course of the disease. Alpha-glucosidases and thiazolidinediones were not used as commonly as biguanides and sulfonylureas. Higher levels of glycaemia in 66% of population after treatment regimens indicated requirement of intensification in therapy.

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