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Comparison of Efficacy of Oral Hypoglycemic Agents in Diabetic Patients

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Abstract: ***Diabetes is a group of metabolic disorders characterized by persistent hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Besides symptoms related to hyperglycaemia itself such as thirst, polyuria and weight loss, it may also cause potentially life-threatening acute hyperglycaemic emergencies. With good control of hyperglycemia established early on and continued life-long, an individual with diabetes can enjoy a good quality of life and reduce the risk of these long-term complications that are so detrimental to their life and wellbeing. The Objective of the study is to compare the efficacy of anti-diabetic agents among type-2 diabetic patients. A total of 60-80 male and female patients with type-2 diabetes are selected and patients are randomly divided into groups based on their disease and treatment. Efficacy of medications with respect to patient demographics such as age, weight and gender are compared. Patients with the age ranging from 40-70 years are taken into study. In our study vildagliptin with metformin showed greater reduction of fasting and post-prandial blood glucose levels when compared to pioglitazone and glimeperide combinations.No weight gain is reported in patients using vildagliptin and only mild hypoglycaemic episodes are reported in some patients. Our study concludes that Vildagliptin combination is more effective in controlling fasting and post-prandial blood glucose levels when compared with pioglitazone and glimeperide combinations.***

Keywords: Diabetes Mellitus, Hyperglycemia, Hypoglycemics, Vidagliptin

1. Introduction

Diabetes is a group of metabolic disorders characterized by persistent hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels. (American diabetes association)

Besides symptoms related to hyperglycaemia itself such as thirst, polyuria and weight loss, it may also cause potentially life-threatening acute hyperglycaemic emergencies. It is a major cause of morbidity and premature mortality from long term complications such as cardiovascular disease, blindness, renal failure, amputations and stroke. With good control of hyperglycemia established early on and continued life-long, an individual with diabetes can enjoy a good quality of life and reduce the risk of these long-term complications that are so detrimental to their life and wellbeing.

Types of Diabetes Mellitus

a) Type 1: β-cell destruction, usually leading to absolute insulin deficiency
   - Immune-mediated diabetes.
   - Idiopathic diabetes.

b) Type 2: Ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretary defect with insulin resistance.

c) Other specific types:
   1) Genetic defects of the β-cell
   2) Genetic defects in insulin action
   3) Diseases of the exocrine pancreas
   4) Endocrinopathies
   5) Drug or chemical-induced diabetes
   6) Infections
   7) Uncommon forms of immune-mediated diabetes
   8) Other genetic syndromes that may associate with diabetes (E.g. Down's syndrome, klinefelter syndrome
   9) Gestational diabetes.

2. Literature Review

Jaber et al assessed the effectiveness of a pharmaceutical care on the management of non-insulin-dependent diabetes mellitus (NIDDM) in urban African-American patients. Patients were randomized to either a pharmacist intervention or control group and followed over a 4-month period. Patients in the intervention group received diabetes education, medication counselling, and instructions on dietary regulation, exercise, and home blood glucose monitoring. Patients in the control group continued to receive standard medical care provided by their physicians.

Outcome measures included fasting plasma glucose and glycated haemoglobin concentrations and Quality-of life assessments were performed in both groups at baseline and at the end of the study. Thirty-nine patients (17 interventions, 22 controls) completed the study and Significant improvement in glycated haemoglobin (p 0.003) and fasting plasma glucose (p =0.015) were achieved in the intervention group) and no change in glycaemia were Observed in the control subjects. The study data demonstrated the effectiveness of pharmaceutical care in the reduction of hyperglycaemia associated with N1DDM in a group of urban African-American patients[6].

Timothy et al investigated the impact of a pharmaceutical care program in a community-reductions in BMI, blood pressure, fasting plasma glucose, and glycosylated haemoglobin were greater in patients participating in pharmaceutical care than in the usual-care patients. 180 patients with type 2 diabetes who participated in the program were received usual care. The pharmaceutical care

group also experienced non-significant improvements in serum lipid parameters and urine albumin creatinine ratios. The median 10-year risk of coronary heart disease decreased in the pharmaceutical care group but did not change significantly in the usual-care group, the results indicate[7].

Joan M.Rider (2004) emphasized on 3 major treatment components for Type 2 Diabetes Mellitus that include Diet (Medical Nutrition Therapy, MNT), Exercise and Pharmacological therapy. Further in this article the author focused on the Pathophysiology, etiologic classifications, and diagnosis and treatment options for Diabetes Mellitus. The author concluded that the Diabetes management requires multidisciplinary approach that is well organized and systematic[8].

Susan Cornell and Amber Briggs in their article entitled "Newer treatment strategies for the management of Type 2 Diabetes Mellitus" reviewed the treatment option for managing type 2 diabetes. They alone indicated that the Sulfonylureas and Biguanides are insufficient at effecting the treatment goals (achieving and maintaining near blood glucose levels and Glycosylated Hemoglobin Levels (HbA1c) particularly if used long term hence need to explore newer and better treatment options that provide long lasting glucose control. They suggested that a general guidelines or algorithm must be needed to initiate anti-diabetic therapy, though diabetic treatment strategies should be individualized. These algorithms are based on blood glucose levels and are divided into 3 categories: mild, moderate and severe Type 2 Diabetes Mellitus[9].

Kenyetta N. Nesbitt overviewed the Diabetic Nephropathy and the American Diabetes Association (ADA) recommendation for early detection and treatment guidelines. The scope of this article was to review pathophysiology screening and treatment of Diabetic Nephropathy. Author emphasized glycemic control and blood pressure control as the key aspects to prevent Diabetic Nephropathy progressing to end stage renal disease (ESRD). The overall recommendations of ADA as highlighted by the author include the use of ACE inhibitors (ACEI) or Angiotensin Receptor Blockers (ARB's) in the treatment of nephropathy[10].

Giuseppe Derosa, pioglitazone and metformin co-administration improves glyceamiccontrol,insulin sensitivity and lipid profile which remains the cardinal points of diabetes care. The two different mechanism of action of insulin sensitizing agents leads to optimized control of different pathways that leads to insulin resistance, inflammation and atherosclerosis. The evidence of a possible effect of pioglitazone on pro-inflammatory markers, adipocytokines and pro-coagulative state supports its use in the treatment of metabolic syndrome.[11]

IftekarHMd,Vildagliptin is a specific and potent DPP-4 inhibitor that has demonstrated weigh neutrally, and improbes B-cell as well as CV function in patients with type-2 diabetes in multiple, monotherapy and combination. However hypoglycaemic event reported with metformin and sulfonylureas but safe with pioglitazone and combination of insulin reduced it. Vildagliptin also shows feedback inhibition of GLP-1 secretion which reduces the risk of CV and hypoglycaemia.[12]

3. Materials and Methods

Study population

A total of 60-80 male and female patients with type-2 diabetes are selected and patients are randomly divided into groups based on their disease and treatment. Efficacy of medications with respect to patient demographics such as age, weight and gender are compared. Patients with the age ranging from 40-70 years are taken into study. Patients with ideal body weights are taken into study. Patients with co-morbid condition such as hypertension are also included in the study. Parameters such as fasting and post-prandial blood glucose levels are taken and changes in the blood glucose levels are observed during the study period. Efficacy of anti-diabetic medications in controlling blood glucose levels in hypertensive patients are studied.

Groups based on diseases:-

- Diabetes mellitus.
- Diabetes associated with hypertension

Groups based on treatment:-

- Patients treated with pioglitazone+metforminHcl (30mg+500mg)
- Patients treated with glimepiride+metforminHcl (2mg+500mg)
- Patients treated with vidagliptin+metforminHcl (50mg+500mg)

Inclusion criteria

Adults (>18years) male and female patients suffering from type-2 diabetes mellitus and diabetes along with hypertension.

Exclusion criteria

- Diabetes mellitus patients having other co-morbid conditions are excluded from the study(except those stated in inclusion criteria)
- Pregnant diabetic patients and lactating mothers.
- Patients with eclampsia.

4. Results

Table 1.1: Fasting and Post Prandial Blood Glucose Levels (mg/dl) of Various Groups of Anti-Diabetic Medications Before and After 30days Treatment

Drugs	FBS		PPBS	
	Before	After	Before	After
G+M	142.3±4.6	111.2±4	252±3.9	202±4.2
P+M	135±5.3	95±4.6[a, b]	268±5.2	190±4.7
V+M	168±6.1	136.5±5.7	272±4.9	202±6.5

n=10, All the values are blood glucose expressed in Mean±SD.

a-Signicant decrease in BG compared to G+M; **b**-Signicant decrease in BG compared to P+M; **c**-Signicant decrease in BG compared to V+M

Table 1.2: Percentage Reduction in Blood Glucose Levels after Treatment.

Drug	FBS(%)	PPBS(%)
G+M	21.85	18.69
P+M	25.54	24.76
V+M	30.1	27.1

Combination of glimeperide with metformin showed a reduction of 21.85% in fasting blood glucose,pioglitazone with metformin showed a reduction of 29.54% and vildagliptin when with metformin showed a reduction of 30.1% in fasting blood glucose. The reduction in post-prandial blood glucose levels with glimeperide and metformin combination is 18.69% while with pioglitazone and metformin combination is 26.76% and with vildagliptin and metformin combination is 27.1%. The above 3 combinations vildagliptin with metformin shows better reduction in fasting and post prandial blood glucose levels when compared to glimeperide, pioglitazone in combinations.

Table 2.1: Efficacy of Anti-Diabetic Drugs in Various Age Groups

Age	40-50(YEARS)				50-60(YEARS)				60-70(YEARS)			
Drugs	FBS(Avg)		PPBS(Avg)		FBS(Avg)		PPBS(Avg)		FBS(Avg)		PPBS(Avg)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
G+M	203±5.8	145±6.6	255.5±7.1	202.5±5.8	164.8±7.2	134.2±6.5	252.1±5.3	203.4±6.9	167.8±7.3	141.4±6.4	246.6±7	200.8±6.5
P+M	157.5±5.1	125.5±5.3	191±5.6	158±5.5	171.5±4.6	132.5±5.2	294±3.8	189.5±5.7	200±5.3	124.5±6.3	269.5±5.9	193.5±5.5
V+M	151±4	133±6.7	248.6±6.4	159.6±4.3	156.5±5.8	140±4.2	276.5±4.1	230±	192.6±4.3	151±4.2	293±4.9	225.3±4.6

Table 2.2: Percentage Change in Blood Glucose Levels in Various Age Groups

Drugs	FBS			PPBS		
	40 -50(Y)	50 -60(Y)	60 -70(Y)	40-50(Y)	50 -60(Y)	60 -70(Y)
G+M	28.3%	18.5%	15.7%	21.73%	19.3%	18.5%
P+M	33.5%	26.54%	28.2%	25.5%	21.3%	16.1%
V+M	21.2%	21.87%	17.7%	25.8%	21.9%	17.8%

The efficacy of glimeperide,pioglitazone and vildagliptin in combination with metformin, in controlling fasting blood glucose decreases with increase in age of the patient. With increase in age of the patient no significant reduction in post prandial blood glucose is observed with the above combinations.

Table 3.1: Efficacy of Anti-Diabetic Drugs in Patients with Different Body Weights

Body weight	40-50(kgs)				50-60(kgs)				60-70(kgs)			
Drugs	FBS(Avg)		PPBS(Avg)		FBS(Avg)		PPBS(Avg)		FBS(Avg)		PPBS(Avg)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
G+M	172.7±5.3	155.5±4.3	272.5±4.8	230.7±5.5	172.9±4.6	143±5.5	246.3±5.2	203.6±5.1	205.2±5.4	117.5±5.2	246.7±4.7	110.5±4.6
P+M	157.5±3.8	125.5±4.1	191±4.6	158±4.7	175.1±5.1	132.5±4.4	294±4.8	189.5±5.5	200±4.7	124.5±3.8	269.5±4.2	193.5±5.2
V+M	151±6.7	153±5.9	248.6±4.6	159.6±5.5	156.5±4.8	140±6.1	276.5±6.3	230±6	192.6±5.6	151±4.9	293±4.5	225.3±6.3

Table 3.2: Percentage Change in Blood Glucose Levels in Patients with Different Body Weights

DRUGS	FBS			PPBS		
	40-50(Kgs)	50-60(Kgs)	60-70(Kgs)	40-50(Kgs)	50-60(Kgs)	60-70(Kgs)
G+M	34.7%	30.4%	27.6%	30.1%	28.3%	27.6%
P+M	37.7%	34.3%	29.3%	33.7%	30.1%	28.2%
V+M	39.3%	36.6%	32.6%	36.7%	33.9%	28.9%

The combination of glimeperide, pioglitazone and vildagliptin in combination with metformin showed no significant effect in controlling blood glucose levels with respect to the weight of the patients.

Table 4: Efficacy of Anti-Diabetic Drugs in Male and Female Patients

DRUGS	MALE				FEMALE			
	FBS(Avg)		PPBS(Avg)		FBS(Avg)		PPBS(Avg)	
	Before	After	Before	After	Before	After	Before	After
G+M	169.3±2.8	154±3.5	263.9±2.6	221.2±3.1	191.2±4.3	136.7±4.5	238.6±3.1	176.5±4.2
P+M	193.6±5.3	140.6±4.8	299.4±3.9	190.4±3.6	172.5±5.5	118.7±4.7	244.7±5	138.8±3.7
V+M	152±4.6	125±6.8	242.5±5.5	203.5±6.2	173.3±5.9	157±5.1	272.1±4.9	201.3±6.3

Table 4.2: Percentage Change In Blood Glucose Levels in Male and Female Patients

Drug	FBS		PPBS	
	MALE	FEMALE	MALE	FEMALE
G+M	23%	28.4%	20.1%	26%
P+M	27.3%	31.2%	26.4%	34.8%
V+M	27.7%	39.4%	28%	37%

The efficacy of glimeperide,pioglitazone and vildagliptin combination with metformin in controlling fasting and post-prandial blood glucose levels in female patients is good when compared to male patients.

Table 5: Effect of Systolic and Diastolic Blood Pressure In Various Anti-Diabetics With Anti-Hypertensive Treated Groups

DRUG		Systolic B.P		Diastolic B.P	
	G+M	Before	After	Before	After
Glimeperide + Metformin	Telmisartan	150±8	122±7.5	80±7.3	80±6.9
	Metoprolol succinate50mg	158±6.8	130±6.5	86±5.8	80±5.7
	Amlodipine-2.5 mg + Metoprolol-12.5	145±4.9	130±4.7	85±6.9	80±5.4
Pioglitazone + Metformin	Telmisartan	152.5±4.9	125±4.6	85±3.9	80±5.5
	Metoprolol succinate50mg	156.6±5.4	126.6±4.8	90±5.3	80±4.1
	Amlodipine-2.5 mg, Metoprolol-12.5 mg	147.5±6	127.5±6.7	90±5.8	80±5.5
Vildagliptin+ Metformin	Telmisartan	160±3.9	130±3.6	95±5.6	82±4.5
	Metoprolol succinate-50mg	160±6.5	123.3±5.3	93.3±4.9	80±5.7
	Amlodipine-2.5 mg, Metoprolol-12.5 mg	147.5±4.3	125±5.1	82.5±5.8	80±4.6

Table 5.2: Percentage Change in Blood Pressure

DRUG	SYSTOLIC B.P(%)			DIASTOLIC B.P(%)		
	G+M	P+M	V+M	G+M	P+M	V+M
Telmisartan	18.66	18.03	18.75	2.43	5.82	10.52
Metoprolol succinate-50mg	17.72	19.14	22.91	6.97	11.11	14.28
Amlodipine-2.5mg Metoprolol-12.5mg	10.34	13.55	15.25	5.88	11.11	3.03

5.3 Fasting and Postprandial Blood Glucose Levels in Diabetes Associated with Hypertensive Patients

	DRUGS	FBS		PPBS	
		Before	After	Before	After
G+M	Telmisartan	165	142	253.5	215.25
	Metoprolol	168.8	133.6	205.4	170.4
	Amlodipine5mg + Metoprolol-50mg	215	175.5	370.5	296.5
P+M	Telmisartan	176.25	149.5	245.5	198.75
	Metoprolol	185.6	165	257.3	205
	Amlodipine5mg+ metoprolol-50mg	206	155.6	137.6	280.3
V+M	Telmisartan	188	163	258.5	207.5
	Metoprolol	194.5	162.7	323.2	282.75
	Amlodipine5mg+metoprolol-50mg	208.6	168.6	253.3	188,6

5.4 Percentage Change in Blood Glucose Levels in Diabetes Associated with Hypertension

	DRUGS	FBS(%)	PPBS (%)
G+M	Telmisartan	13.93	15
	Metoprolol-50mg	15.85	17
	Amlodipine5mg+metoprolol-50mg	18.3	11.9
P+M	Telmisartan	15.1	19.4
	Metoprolol-50mg	21.1	20.3
	Amlodipine5mg+metoprolol-50mg	24.4	25.7
V +	Telmisartan	13.2	15.7
	Metoprolol-50mg	16.3	12.5
	Amlodipine5mg+metoprolol-50mg	19.1	19.5

The combination of pioglitazone and metformin in patients using anti-hypertensive medications showed better control of fasting and post-prandial blood glucose levels when compared to glimeperide and vildagliptin in combination with metformin.

5. Conclusion

Vildagliptin combination is more effective in controlling fasting and post-prandial blood glucose levels when compared with pioglitazone and glimeperide combinations. No weight related changes in controlling blood glucose levels is observed. Efficacy of these combinations decreases with increasing age of the patients.Pioglitazone combination effectively controlled blood glucose levels in patients with hypertension co-morbidity.

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