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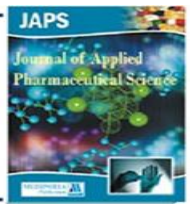

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Adherence to the Standard Guidelines for Prescription of Antidiabetic Agents in Patients with Type 2 DM

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ABSTRACT

Prescription of appropriate antihyperglycemic agent depending on the standard guidelines has an important role in controlling diabetes and improving patient health. The aim of the present prospective study is to follow-up the adherence of prescribers to the standard guidelines for the prescription of anti-diabetic drugs in patients with type 2 diabetes mellitus. A prospective clinical trial was carried out on 64 individuals (43 patients and 21 healthy volunteers) of both sexes with the age range from 40-70 years. Parameters followed-up were fasting blood glucose (FBG), lipid profile, liver and renal function tests. The values of these parameters (at admission and after 3 months of follow-up) were calculated and compared with that of the control group and with the recommended treatment goals stated by American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE/ ACE). Despite of continued treatment, no improvements were seen regarding followed-up parameters. It has been suggested that the adherence of prescribers to the standard guidelines for prescription of anti-diabetic agents is poor in our center, all patients evaluated have highly uncontrolled hyperglycemia where different anti-hyperglycemic drugs fail to attain glycemic control, and therapeutic strategy followed should be reconsidered.

Keywords: Type 2 DM, Diabetes guidelines, Hyperglycemia, oral hypoglycemic agents.

INTRODUCTION

T2DM is a global epidemic with an estimated worldwide prevalence of 6% (246 million people) in 2007, and forecast to rise to 7.3% (380 million) by 2025 (IDF 2006). The health, social, and economic burden is great (De Groot, 2001; Derek Wanless, 2002; Jacobson, 2004), consequently, T2DM presents a major challenge to healthcare systems around the world.

T2DM is characterized by fasting and postprandial hyperglycemia and relative insulin insufficiency. If left untreated, then hyperglycemia may cause long-term microvascular and macrovascular complications, such as nephropathy, neuropathy, retinopathy, and atherosclerosis. This disease causes significant morbidity and mortality at considerable expense to patients, their families and society. It is a complex disorder in which the interaction between environmental and genetic factors results in the development of insulin resistance (IR) and β-cell dysfunction (Facchini *et al.* 2001; Stumvoll *et al.* 2005). The development of IR precedes the onset of T2DM by many years (Facchini *et al.* 2001; Shanik *et al.* 2008) and is influenced by many factors including puberty, ageing, pregnancy, physical activity and oral intake (Kahn *et al.* 2006). To an extent, there has been some disappointment in that most of the observed initial improvements in glycemic control are not sustained because of the progressive nature of the disease (Kahn *et al.* 2006; Del et al.2007). These treatments may also have undesired side effects, such as hypoglycemia, weight gain, gastrointestinal symptoms and peripheral oedema, in addition to variable effects on β-cell function (Del et al.2007; Black *et al.* 2007) .

Treatment guidelines and algorithms for patients with type 2 DM

Current guidelines by ADA (ADA 2010; Nathan *et al.* 2009), the AACE (Rodbard *et al.* 2007), the International Diabetes Federation (IDF, 2005), the UK National Institute for Clinical Excellence (NICE, 2010), and the Canadian Diabetes Association (CDA,2008) for the pharmacologic management of type 2 diabetes recommend lifestyle modifications (weight reduction, dietary adjustments, and physical exercise) followed by initial monotherapy and, subsequently, a stepwise intensification of therapy if glycemic control is inadequate.

These associations have recommended treatment goals (as illustrated in table 1 (ADA 2010; AACE, 2007) for patients with T2DM to be included in a comprehensive approach to patient care. Table 1 lists target values for HbA1c, blood pressure, and lipids as suggested by the (ADA, 2010) and (AACE /ACE 2007).

The ADA/ the European Association for the study of diabetes (EASD) recently published a consensus statement on the medical management of hyperglycemia. The new recommendations were derived from integrating information on multiple aspects of therapy, including outcomes, synergistic effects, costs of therapy, and potential for adverse events (AEs) (Nathan *et al.* 2009).

Metformin monotherapy is uniformly designated as the preferred initial intervention (NICE, 2010) . The potential utility of early pharmacotherapeutic combination therapy is recognized, but only for patients whose hyperglycemia is quite severe (HbA1c > 8.5% in the ADA / EASD guidelines and ≥ 9% in the CDA guidelines) (CDA, 2008). Patients with excessive HbA1c levels after initiating metformin should introduce additional anti-hyperglycemic agents into their treatment regimens until target glycemia (whether defined as < 6.5% or < 7.0%) is achieved (Shah *et al.* 2005). ADA/EASD consensus statement is unique in suggesting the initiation of both lifestyle changes and metformin at diagnosis - a form of combination therapy - but also continues to advocate the stepwise therapeutic philosophy.

Table. 1: Comparison of treatment targets for the treatment of patients with type 2 diabetes mellitus.

Target treatment goals	AACE / ACE 2007	ADA 2010
HbA1c	≤ 6.5%	< 7%
Fasting glucose	Fasting plasma glucose; < 110 mg/dl	Pre-prandial capillary plasma glucose; 70-130 mg/dl
Postprandial glucose	2-hr postprandial glucose; <140 mg/dl	Peak postprandial capillary plasma glucose; < 180 mg/dl
Blood pressure	< 130 / 80 mm Hg	< 130 / 80 mm Hg
Cholesterol (lipids)	LDL-C <100 mg/dL (< 70 mg/dL for patients with diabetes and coronary artery disease)	LDL-C < 100 mg/dL
	HDL-C < 40 mg/dL in men, < 50 mg/dL in women	HDL-C < 40 mg/dL in men, < 50 mg/dL in women
	Triglycerides (TG) < 150 mg/dL (1.7 mmol/L)	Triglycerides < 150 mg/DL (1.7 mmol/L)

LDL= low density lipoprotein; HDL= high density lipoprotein

Table. 2: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Subjects of either sexes, with the age range between 40 and 70 years	Diabetes other than type 2
Patients taking oral hypoglycemic agents	History of keto-acidosis
Patients have type 2 DM	Hepatic or renal disease
	Nursing or pregnant women
	Patients on lipid lowering agents

Table. 3: General data information of the patients included in the study.

Groups	Number	Sex		Age	Weight	Smoking history	Positive Family history
		M	F				
Group 1	21	18	3	50.65 ± 2.23	75.1± 3.08	8	8
Group 2	22	11	11	58.66 ± 1.57	81.09 ± 2.88	6	11
Group 3	21	10	11	56 ± 1.2	79.15 ± 3.46	4	10

Data were expressed as Mean ± SEM

AIM OF THE STUDY

The aim of the present prospective study is to follow-up the adherence of prescribers to the standard guidelines for the prescription of anti-diabetic drugs in tertiary health care setting; and to compare the hypoglycemic effect of two different antihyperglycemic drugs regimens; namely Glibenclamide and combination of Glibenclamide with Metformin in type 2 diabetic patients. Furthermore, to clarify the effect of long standing disease and / or drugs on lipid profile, liver and renal functions, and on serum Ca level, moreover.

PATIENTS AND METHODS

The present prospective study was carried out on 64 individuals (43 patients and 21 healthy volunteers) of both sexes with the age range from 40-70 years. The inclusion and exclusion criteria of patients in the present study were listed in table 2.

Study design

The individuals included in the present study were divided into 3 groups depending on the type of drug regimen they take as follow:

Group1: twenty-one healthy subjects serving as control.
Group2:twenty-two diabetic patients taking Glibenclamide.
Group3:twenty-one diabetic patients taking a combination of Glibenclamide with Metformin.

Study procedure

The groups of patients taken were referred from private clinic to the hospital for following-up and assessment of glycemic control. So, our study did not involve addition or deletion of drugs into or from patients regimens but just to follow-up the adherence of prescribers to the guidelines depending on the existing drug regimens. A special form was designed to take the general information from the patients regarding age, family history, time elapsed from the onset of the disease, no. of emergency admission, drugs taken (the group in which the patients fall was determined by this item)…etc as shown in table 3. Thereafter, 10 ml of blood was withdrawn from each patient for analysis. Subsequently, a date was set for each patient for reevaluation after 3 months. The adherence of patients to their regime was ensured by arranging a weekly visit to the institution.

The parameters followed-up were as follow

- FBG
- Lipid profile (cholesterol, TG, LDL, HDL)
- Liver function tests (alanine transaminase (ALT), aspartate transaminase (AST), and total serum bilirubin (TSB))
- Renal function tests (S. Urea and Creatinine)
- S. Ca

The values of these parameters were calculated and compared with that of the control group and with the recommended treatment goals stated by ADA and AACE/ ACE.

The adherence of the institution to the standard guidelines for prescription of antidiabetic drugs was assessed by comparing our treatment options with the AACE / ACE diabetes algorithm recommendations for glycemic control of patients with T2DM.

Statistical analysis

All the results were expressed as mean ± SEM. The significance of difference between the control and test groups was determined using single factor ANOVA and unpaired t-test (between the test groups and control group), followed by paired t-test (for the same group at admission and 3 months thereafter). P-values < 0.05 were considered significant.

RESULTS

Table 4 and fig. 1 clearly show that there is significant difference (P < 0.05%) between the control group (1) and the test groups (2 and 3) regarding the value of FBG. Other parameters (S. Cholesterol, S. TG, HDL and S. Ca) were approximately equal in their values (i.e. non-significant differences exist between them). Furthermore, there are no any significant differences within the values of each group at admission and after 3 months of follow-up (i.e. no improvements were seen on the patients in spite of continued treatment).

Table 5 shows renal and liver function parameters for the followed-up groups. In this table, significant differences were noticed between the values of S. urea, S. Creatinine and TSB of the test groups and that of the control group although all these values fall within the normal range.

In addition to that, time elapsed for the onset of disease was nearly comparable and non-significant difference exists between the two groups as in table 6. Moreover, the doses of Glibenclamide (in group 2) and the doses of Metformin (in group 3) were not reached to the maximum effective dose which is necessary in patients not responding to the initial doses. Furthermore, non-significant differences were existed between the two groups regarding number of admissions to emergency ward because of hypo or hyperglycemia as in table 6.

Table. 4: Parameters studied at admission and after 3 months.

GROUPS		**FBS** mmole/L	**S. Cholesterol** mmole/L	**S. Triglyceride** mmole/L	**S.HDL** mmole/L	**S. Ca** mmole/L
GROUP 1	At admission	5.80±0.38	4.10±0.09	2.55±0.23	0.95 ± 0.02	2.04±0.02
	After 3 months	5.51±0.37	4.05±0.08	1.94±0.07*	0.97 ± 0.02	2.03±0.01
GROUP 2	At admission	12.19±1.25[a]	4.31±0.13[a]	2.23±0.26	0.93 ± 0.02	2.03±0.02
	After 3 months	12.25±0.86[a]	4.22±0.11	1.82±0.10	0.94 ± 0.02	2.06±0.01
GROUP 3	At admission	10.81±1.18[a]	3.92±0.13[b]	2.25±0.2	1± 0.03	2.05±0.02
	After 3 months	12.17±1.19[a]	4.07±0.12	2.14±0.18	1± 0.03	2.03±0.01

Data were expressed as Mean ± SEM, *P < 0.05 with respect to at admission group., [a, b] P < 0.05 with respect to control group. ,Values with non-identical subscription (a, b) are considered significantly different (P < 0.05).
Group 1= Control group
Group 2= Glibenclamide group
Group 3= Combination group (Glibenclamide + Metformin)

Table . 5: Renal and liver function tests of the evaluated group at admission and after 3 months.

GROUPS		S. Urea mmole/L	S. Creatinine µmol/L	S. ALT U/L	S. AST U/L	TSB µmol/L
GROUP 1	At admission	4.52±0.15	75.4±1.47	9.7±0.44	8.8±0.45	9.6±0.40
	After 3 months	5.37±0.30*	80.75±2.36	10.8±0.56*	10±0.48*	11.05±0.33*
GROUP 2	At admission	5.88±0.34[a]	85.66±2.46[a]	10.57±0.58	9.47±0.67	11.62±0.35[a]
	After 3 months	5.99±0.40	88.04±5.06	10.71±0.49	9.33±0.38	11.66±0.30
GROUP 3	At admission	6.56±0.38[a]	104±10.03[b]	11.4±0.73[a]	10.3±0.56[a]	11.15±0.43[a]
	After 3 months	5.99±0.40	94.15±8.7	11.55±0.61	10.05±0.54	11.00±0.39

Data were expressed as Mean ± SEM., *P < 0.05 with respect to at admission group., [a, b] P < 0.05 with respect to control group. ,Values with non-identical subscription (a, b) are considered significantly different (P < 0.05).
Group 1= Control group
Group 2= Glibenclamide group
Group 3= Combination group (Glibenclamide + Metformin)

Table. 6: Time elapsed from the onset of disease, doses of drugs / day and number of emergency admission (as a result of diabetes) for the studied groups .

Groups	Time elapsed from the onset of disease (year)	The dose of Glibenclamide / day	The dose of Metformin 500 mg / day	No. of emergency admission
Group 2	6.85±0.53	20 patients 1 tab / day 2 patients 2 tab / day		0.9±0.06
Group 3	7.60±0.48	17 patients 1 tab / day 4 patients 2 tab / day	20 patients 2 tab/ day 1 patient 1 tab/ day	1.5±0.07

Data were expressed as Mean ± SEM.

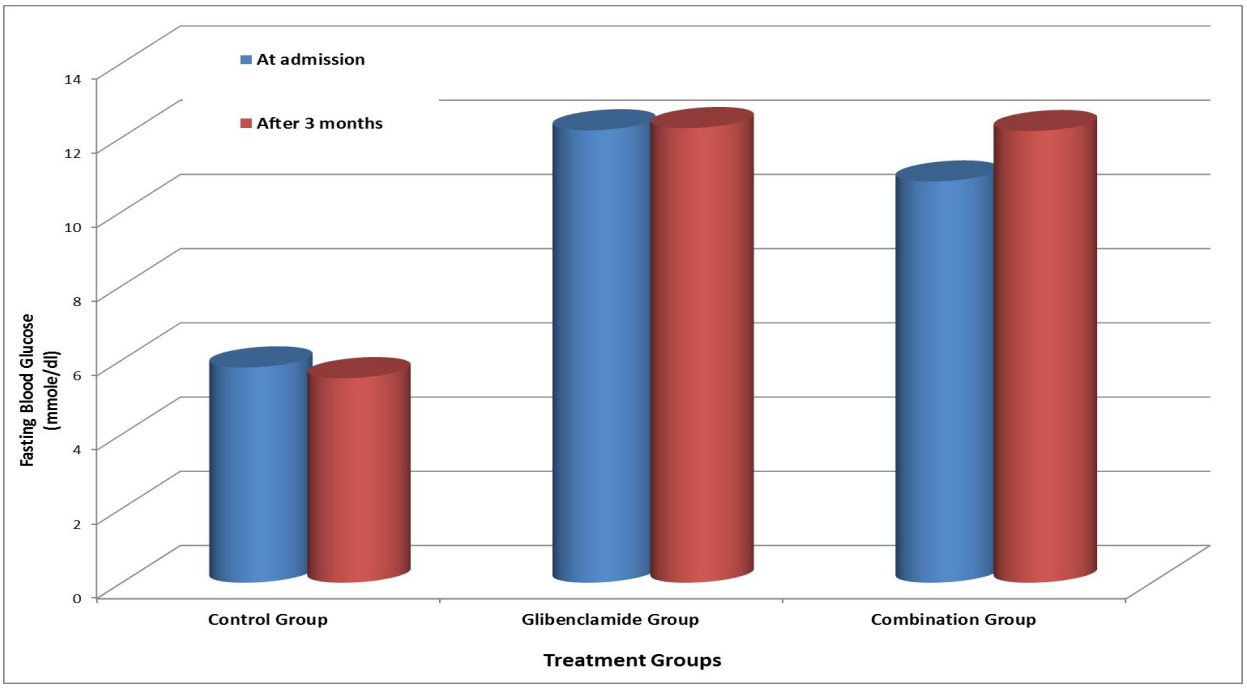

Fig. 1: Fasting blood glucose level in different treatment groups.

DISCUSSION AND CONCLUSION

Some studies showed poor adherence of patients with chronic diseases like DM to their treatments(Santhosh *et al*. 2011). In contrast, the main objective of our study is to assess the adherence of prescribers to the standard guidelines for prescription of antidiabetic drugs through follow-up of therapeutic outcome that result from prescription of antidiabetic agents. The second objective is to compare the hypoglycemic effect of Glibenclamide alone and in combination with Metformin with respect to glycemic control. It is obvious that there is no significant difference between Glibenclamide group and combination group regarding FBG. Furthermore, there is no any noticeable difference within the same followed up groups at admission and after 3 months of assessment. At the same time, highly significant differences exist between treatment test groups (group 2 and 3) and control group (group 1) which clearly indicates inefficacy of the treatments to achieve therapeutic goal stated by ADA and AACE / ACE.

A number of currently available antihyperglycemic therapies are associated with unmet needs, including the potential for weight gain, increased risk of hypoglycemia, and the inability to optimally control postprandial hyperglycemia. Wide glycemic fluctuations may persist despite treatment, and many therapies fail to maintain long-term glycemic control.

The pathophysiologic components of type 2 diabetes include insulin resistance, at least a relative impairment of insulin secretion, inappropriate glucagon secretion, and a decreased incretin effect (AACE /ACE 2007). Newer treatments for type 2 diabetes, including those that target the incretin system (incretin-based therapies), have improved glycemia while providing weight maintenance or loss (Stonehouse,2006).

To overcome deficiencies in diabetes management, we must become more proactive in minimizing long- and short-term exposure to hyperglycemia. The traditional approach to managing patients with type 2 diabetes includes prescribing a period of lifestyle intervention, followed by introduction of a single oral agent. As glycemic control deteriorates, a second oral agent is added, followed eventually by a third (Nathan ,2002).

In some cases, patients are inappropriately threatened with warnings suggesting that the use of insulin is "just around the corner" unless they become more diligent about their own care; if they return to their physician with a further increase in HbA1c, they may be labeled as "non-adherent."

Frustration, misunderstandings concerning the inevitability of certain complications such as painful peripheral neuropathy being inaccurately attributed to aging, and depression, all limit patients' empowerment in diabetes self-management (Unger ,2006).

Regarding the second objective, all the values of the lipid profile, renal and liver function tests and S. Ca levels fall within the normal ranges except for TG values where these values slightly higher than the normal ranges (< 2.2 mmole/L) and there is no significant difference with that of the control group.

According to the guidelines stated by AACE/ ACE, the prescription of one, two or more than two anti-diabetic drugs depends on the value of HbA_{1c}. A specific HbA_{1c} can be calculated from average blood glucose by using the following formula:
Hemoglobin A_{1c} value = (Average blood glucose (mg/dl) + 46.7) / 28.7 (Lenters-Westra and Slingerland ,2008).

Accordingly, the approximate value of HbA_{1c} for the control group (group 1) = 5.08%

The approximate value of HbA_{1c} for Glibenclamide Group (group 2) = 9.31%

The approximate value of HbA_{1c} for Combination Group (group 3) = 9.26%

So, HbA_{1c} is > 9% for group 2 and 3 in fasting state (the values of HbA1c calculated were approximate values because we calculated them from fasting blood glucose level (not average blood glucose level) and if the average blood glucose level were considered, surely it would be higher than fasting blood glucose level). Accordingly, all the patients should take at least three antihyperglycemic drugs or a combination of insulin with one of the antihyperglycemic drugs if we follow the AACE / ACE diabetes algorithm recommendations.

In the long-term treatment of type 2 diabetes, advancement of the disease often necessitates alteration of therapy when previous monotherapy with oral anti-diabetic drugs ceases to be effective. It has become increasingly clear that combination therapy is often necessary in order to achieve ADA targets of glycemic control in type 2 diabetes. Combination of oral agents is a frequent approach for restoring glycemic control when the response to oral monotherapy declines over time (Luna and Feinglos 2001). because of the progressive nature of the disease process, none of the traditional oral hypoglycemic agents maintain glucose levels indefinitely (Stefano and Pulizzi 2006); (Adler *et al.* 2000). With time, many type 2 diabetics require exogenous insulin therapy as illustrated by the study conducted by (Harikrishnan *et al.* 2012) because they either didn't respond to the oral hypoglycemic agents or they might show decreasing of the response during therapy. For encompassing this need, recent studies have evaluated different combination therapies. Individuals with T2DM will ask for more effective therapies to treat the complications associated with this disease. Society will also demand more cost effective treatments for this disease. However; these drug combinations have limitations in their application to late stage type 2 diabetics. To overcome these issues new treatment strategies are being developed. For example, islet cell transplantation and glucagons like peptide-1 (GLP-1) or GLP-1 analogues are being used for the replacement and proliferation of islet cells. Islet cell transplantation is better suited for type 1 diabetics, while the GLP-1 or GLP-1 analogues are more suitable for type 2 diabetics, and it also can promote pancreatic islet cell proliferation in diabetic animals (Youn *et al.* 2007).

Regarding adherence of the institution to the guidelines stated by ADA and AACE / ACE, in fact, there are no specific guidelines in our institutions concerned with the prescription of the antidiabetic drugs. Instead, the prescription of these drugs depending on the symptoms of the patients. In other words, if the patient has blood glucose level above 500 mg/dl and still asymptomatic, the patient continues to take his medications which may be one or two oral hypoglycemic agents. On the other hand, if the patient seems symptomatic and has blood glucose level ranging from 200 to 600 mg/dl, then the patient is hospitalized and shifted to insulin therapy and after stabilization of situation, the patient is returned to the initial treatment. Also the initiation of lifestyle changes and the prescription of Metformin at the time of diagnosis was absent from our dictionary and nearly all the patients started with Glibenclamide at first, and then Metformin is added after that.
In conclusion, the adherence to the standard guidelines for prescription of antidiabetic agents is poor in our center, all the patients evaluated have highly uncontrolled hyperglycemia (different antihyperglycemic drugs fail to attain glycemic control) and therapeutic strategy followed should be reconsidered (antidiabetic drug combinations should be prescribed and some patient should be converted to insulin therapy, instead). Furthermore, the effect of longstanding disease and / or antidiabetic drugs on lipid profile, renal and liver functions, and on serum Ca level was (were) non significant because the time elapsed from the onset of disease was not long enough (6.85 and 7.6 years for group 2 and 3, respectively).

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