EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 9
444-448
Year: 2018

TO TEST A) ASSOCIATION OF HBA1C % AND THE FREQUENCY OF T2 DIABETIC COMPLICATIONS B) T2 DIABETES TREATMENT (ALGORITHM AACE VS ADA+ EASD REGIME)

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Article Received on 05/07/2018 **Article Revised on 26/07/2018** **Article Accepted on 15/08/2018**

ABSTRACT

Background: D.M is a metabolic disorder characterized by the presence of hyperglycemia due to impaired insulin action/sensitivity and β cell defect. India occupies the second position, after China, in the global list of countries with a total of 66.8 million cases. Standardised HbA1C cut off values are taken for the diagnosis, treatment and to assess prognostic outcome of T2 Diabetes. **Methods**: The cut off **HbA_{1c} value ≥6.5%** (NSGP standards) is taken as new criteria to diagnose T2 Diabetes and it can be used for predicting the complications. Efficacy of Incretin based therapy (AACE) was compared with other hyopoglycemics (ADA+EASD) as second line of drugs. **Results** Of the 165 cases of complicated T2 Diabetes 72% of the cases with HbA1C level >7% showed complication like Diabetic retinopathy and microalbuminuria After Rx means patients after receiving hypoglycemic drugs showing improvement in the form of reduced HbA1C, Fasting and PP glucose levels. Out of 155 cases on GLP1 agonist, 120 cases(77.40%) shows considerable reduction in HbA1C% (0.5- 1%)& Of 145 cases on other hypoglycemics, 100 cases (68.9%) reduction of HbA1C % but the average reduction was <0.5% of HbA1C. **Conclusion**: Studies shows a direct & linear correlation of HbA1C with the diabetic retinopathy and micro-albuminuria. It is very safe to say that HbA1C is better parameter than FBS & 2 hour PP plasma glucose level in diagnosing & predicting the complications of diabetes. The formulations of AACE guidelines for treatment of T2 Diabetes mellitus appears to be better as it in includes weight reduction stratigies, obesity & prediabetes management. GLP1 agonists as 2nd line drugs (AACE) are more effective as compared to other hypoglycemic.

KEYWORDS: Type 2 diabetes, HbA1C, Diabetic retinopathy, Incretin therapy, microalbuminuria.

Abbrevations
AACE (American association of clinical endocrinology), ADA (American association of diabetes mellitus), EASD (European association of study of Diabetes, D.M.(Diabetes Mellitus).

INTRODUCTION

"It was first reported in Egyptian manuscript about 3000 years ago. It is estimated that, by 2030 there would be 552 million cases of DM of which 439 million people would be type 2 DM[1]. Diabetes mellitus (DM) is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion or action, or both.

Diagnostic criteria for T2 Diabetes[1,2]

1) Glycated haemoglobin **(HbA_{1c}) value ≥6.5%** - (NSGP standards).
2) **FPG ≥126 mg/dl (7.0 mmol/L) (8 hours fasting) & 2hPG ≥200 mg/dl (11.1 mmol/L)** (WHO:- OGTT using 75g Glucose).
3) **Random PG > 200 mg/dl (11.1 mmol/L).**[1]

Any one of the above Criteria + Typical Symptoms = DM
If patient is Asymptomatic, then repeat the test.

Setting the diagnostic thresholds

a) ADA **(**Aleast 1 or more criteria)
b) WHO recommends the use of FPG + 2hPG (OGTT) especially in asymptomatic individuals
c) FPG and 2h OGTT showed a linear increase in diabetic retinopathy at glucose levels beyond these two values.
d) Normal Fasting PG level is < 110 mg/dl (6.1 mmol/L) & 2h PG Is < 125 mg/dl
e) IFG (impared fasting glucose) - 110 mg/dl (6.1 mmol/l) to < 125 mg/dl (6.9 mmol/l)

f) IGT - 2hr OGTT value > 140 mg/dl (7.8mmol/L) to 199 mg/dl (11.0mmol/L).

Table 1

MATERIALS AND METHODS

Inclusion criteria

To assess HbAIC level with complications the study group included 165 cases of complicated diabetes.

To evaluate the effect of Incretin based therapy Vs other hypoglycemic

Uncomplicated Type-2 DM diagnosed on the basis of the ADA 2015 guidelines were included in study.

Patients were categorized into 3 types based on HbA1C level (7- 7.5), (7.6 – 8.0), (8.1- 8.5)

Exclusion criteria

Type 1 DM, congestive heart failure, tuberculosis, gout, rheumatoid arthritis, renal failure and on insulin therapy were excluded from the study.

Statistical analysis of data: All data were expressed as Mean ± SD. Statistical analysis was done using unpaired students t test. A level of p value <0.05 was used to indicate statistical significance in all analyses.

RESULTS

Table 2

Of the 165 cases of complicated T2 Diabetes, 72% of the cases with HbA1C level >7% showed complication like Diabetic retinopathy and microalbuminuria

A total of 300 cases of umcomplicated T2 Diabetes were studied

Of 300 cases 155 were on Incretin based (GLP1 agonists) therapy and 145 were on other hypoglycemics.

Patients were categorized into 3 groups

Group I includes HbAIC (7 -7.5)% with a total number of 125 cases

Group II includes HbAIC (7.6- 8) % with a total number of 100 cases

Group III includes HbAIC (8.1 – 8.5) % with a total number of 75 cases

Table 3: The statistical calculation showed a p value of < 0. 05

After Rx means patients after receiving hypoglycemic drugs showing improvement in the form of reduced HbA1C, Fasting and PP glucose levels.

For 2nd line drugs AACE formulates usage of INCRETIN (GLPI Agonists) and ADA prefers other drugs on the basis of HbA1c- lowering efficacy, Weight-Changes, Hypoglycaemia

Out of 155 cases on GLP1 agonist, 120 cases(77.40%) shows considerable reduction in HbA1C% (0.5- 1%)

Of 145 cases on other hypoglycemics, 100 cases (68.9%) reduction of HbA1C % but the average reduction was <0.5% of HbA1C.

DISCUSSION

1) Metformin :- Safest drug, Most essential drug

2) **GLP-1 Agonists - exenatide and liraglutide (inject)**

3) DPP- **4 inhibitors** - sitagliptin, - (safest for CVS), vildagliptin, saxagliptin linagliptin

4) SGLT-2 Inhibitors (Newest) :- **dapagliflozin, canagliflozin, empagliflozin**

5) Sulfonylureas – Glipizide gliclazide glimepiride

6) Glitazones

The most widely accepted strategy at diagnosis is the[3,4,5]

- ✓ Basically Start with Lifestyle modifications in the form of healthy eating and increased physical activity.(most important step)
- ✓ IF HbA1c < 7% Start single drug therapy, if > 7.5% then Dual / triple drug
- ✓ IF HbA1c > 8.5 % directly start insulin

1) Step :- Always start with single drug **" Metformin"**

2) Step :- If Blood glucose (fasting + PP) & HbA1c target is not achieved then

Next step is start with 2 drugs combination:- Metformin + Second hypoglycemic agent (which may be a sulfonylurea / thiazolidinedione / DPP-4 inhibitor / **GLP-1 agonist** / basal insulin**.**

The choice between these five agents is decided by

HbA1c- lowering efficacy, Weight-Changes., Hypoglycaemia, Cost of therapy.

Besides being an insulin sensitizer, metformin has favourable effects on body weight, blood lipids and fibrinolytic system (AACE guidelines preferred GLP-1 agonist as the second line agent (bcoz it has superior PP glucose control & significant Wt loss) along with metformin for patients who need dual therapy (A1C target of ≤ 6.5%,)

Step 2 = Metformin + GLP-1 Agonists

Step 3: In the third step, an agent that has not been used in step 2 is added

At any time only 3 Drugs can be used in combo if goal not achieved

Step 4: Start with basal insulin & 3 drug combo if it fails to achieve the desired HbA1c target, one must proceed to a complex insulin strategy of multiple daily injections. One or two non-insulin agents may be continued along with insulin. According to ADA-EASD Committee & other guidelines

Note : (Newer combine a DPP-4 inhibitor with a GLP-1 agonist

Role of Incretins (GLP1 agonists) in T2DM treatment[8,9]

A) AACE guidelines preferred GLP-1 agonist as the second line agent (bcoz it has superior PP glucose control & significant Wt loss) along with metformin

for patients who need dual therapy (A1C target of ≤ 6.5%,)

- For example, the weight-lowering effect of GLP-1 agonists might be beneficial in T2DM patients who are overweight or obese. DPP-4 inhibitors are weight neutral. Sulfonylurea, thiazolidinedione, and insulin which promote weight gain.
- DPP-4 inhibitors can be considered as monotherapy in patients who are intolerant or have contraindications to metformin (eg. In CKD-linagliptin as an initial choice, whereas other DPP-4 inhibitors can be used with dose adjustment with CKD 3 or 4).
- DPP-4 inhibitors reduces pre and post meal blood sugars without causing hypoglycaemia, may be preferred as add-on therapy to Oral antidiabetic drugs in T2DM patients who are not overweight or in those patients who are reluctant on initiating injectable therapy.
- In elderly T2DM patients with multiple comorbidities such as CKD and CAD, DPP4 inhibitors are preferable as compared to other agents who has potential to cause hypoglycaemia. In patients with slowing of gastric emptying (gastroparesis) worsened by GLP-1 agonists may make DPP-4 inhibitors preferable.

Cardiovascular outcome trials for incretin based therapies

- TECOS (sitagliptin) shows CV safety (published in 2015). SAVOR TIMI (saxagliptin) and EXAMINE (alogliptin) showed an increased risk of heart failure.
- Liraglutide showed a significant reduction in cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke in patients with diabetes and increased cardiovascular risk in the LEADER trial

Many prospective studies that used to predict the progression to diabetes demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8-12 years), those with an A1C between 5.5 and 6.0% had a substantially increased risk of diabetes with 5-year incidences ranging from 9 to 25%. An A1C range of 6.0-6.5% had a 5-year risk of developing diabetes between 25 and 50% and relative risk 20 times higher compared with an A1C of 5.0%.[4,5]

Table 1: HbA1C Merits and Demerits.

Merits	Demerits[3]
➢ More convenient to perform, as patients are not required to fast, and can be performed at any time of day ➢ HbA_{1c} has greater preanalytical stability ➢ No variation to acute illness or stress Linked with microvascular (Diabetic retinopathy) and (to a lesser extent) macrovascular complications	➢ The test is more costly & should be NGSP certified, and standardised to Diabetes Control and Complication Trial (DCCT) assay ➢ HbA_{1c} may vary with age and ethnicity of the patient ➢ Falsely Low HbA_{1c} - associated with increased RBC turnover (Hemolysis, hemorrhage recent BT, G6PD def. Rx of IDA, dapsone & anti-retroviral drugs. ➢ Haemoglobinopathies like Beta-thalassaemia. ➢ Falsely high HbA1C - associated with decreased RBC turnover like IDA

Table 2: Shows relation of HbA1C level vs complications.

Authors	Complications	HbAIC cut off values
Massin et al (2015)	DR, MA	>6
Colagiuri et al (2011)	DR, MA, Nephropathy	>6.3
Tapp et al (2007)	DR, MA, DN	>6.1
Expert committee (1997)	DR, MA	>6.2
Engelgau et al (1997)	DR	>6.7
Present study	DR, Nephropathy, MA	>6.5 for Diagnosis >7 for complications

Table 3: GLP1 Agonist vs Other hypoglycemic.

	Group I (125 cases)		Group II (100 cases)		Group III (75cases)	
	After	Rx	After	Rx	After	Rx
GLP1 Agonist (AACE 2013)	50	45 (90%)	60	40 (66%)	45	35 (78%)
Other hypoglycemic (ADA-EASD 2015)	75	50 (66%)	40	30 (75%)	30	20 (66%)

Table 4: Comparison AACE vs ADA-EASD.

AACE (2013)[2]	**ADA-EASD (2015)**[4]
AACE guidelines preferred GLP-1 agonist as the second line agent (because it has superior PP glucose control & significant Weightt loss) along with metformin for patients who need dual therapy (A1C target of ≤ 6.5%,)	Second line of drugs are other hypoglycemics
Prediabetic treatment is outlined	Not outlined
Guidelines mentions weight reduction stratigies, obesity management	No such inclusions
Algorithm covers safedrugs in green and risky drugs in yellow	No clear mention of safety of drugs

AACE COMPREHENSIVE DIABETES MANAGEMENT ALGORITHM 2013[4]

Table 5: Comparative analysis of Hypoglycemic drugs.

HbA1c- lowering efficacy	**Highest efficacy INSULIN**	**High efficacy Sulphonylurea GLP 1**	**Modest efficacy DPP -4 Inhibitors & glitazone**
Weight loss	Marked GLP-1 Analoges	Modest Metphormin	Weight neutral DPP -4 Inhibitors
Hypoglycaemia	Insulin +++	sulphonylureas ++	No hypoglycemia GLP -1, Met.
Weight gain[1,6]	Insulin & sulphonyl ureas		

Chronic Renal Failure	Safely given	Given with dose Adjustment	Contraindicated
	GLP I Linagliptin Liraglutide	DPP-4 inhibitors (preferred in elderly with CRF) SGLT -1 (hypotension)	Metformin
Effect on Cardiovascular system	Cardioprotective	Can Safely given	Contraindicated
	Metphormin Acarbose SGLT-1 (Empagliflozn canagliflozin CANVAS, EMPA-REGA	Sitagliptin (TECOS)	Liraglutide[1,7,8,9]

Table 6: To choose between GLP-1 agonist & DPP-4 inhibitors[6,7]

DPP-4 Inhibitors	**GLP-1 agonist**
Oral	Injectable
Limited by endogenous incretin secretion	Not limited by endogenous incretin secretion
Moderate efficacy	Enhanced efficacy
Weight neutral	Weight loss
Well tolerated	GI side effects

CONCLUSION

The various conclusions draws from this study are:

1) HbA1C can be used effectively for the diagnosis of type 2 DM. There is an inherent logic to using a more chronic versus an acute marker of dysglycemia and it has preanalytical stability.
2) HbA1c can be used for predicting the complications of type 2 DM. It shows a direct & linear correlation with the diabetic retinopathy and microalbuminuria. The formulations of AACE guidelines for treatment of T2 Diabetes mellitus appears to be better as it in includes weight reduction stratagies obesity & prediabetes management. GLP1 agonists as 2nd line drugs (AACE) are more effective as compared to other hypoglycemic.

It is established fact that the Complications are directly related to level of chronic hyperglycemia in T2 Diabetes

This study highlights

- Relation of HbA1C level to the complications of T2 Diabetes.
- This study shows a direct & linear correlation with the diabetic retinopathy & microalbuminuria.

The new findings are

- **AACE regime/algorithm is better as compared to ADA+ESD** as it in includes weight reduction stratagies obesity & prediabetes management.
- GLP1 agonists as 2nd line drugs (AACE) are more effective as compared to other hypoglycemic.

Future scope of Research

New studies based on the prediabetics cutt off values & GLP1 agonists efficacy & safety over
Other drugs & insulin levels are warranted.

- "This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors".
- The authors have no competing interests to declare.
- The Author Anil K. Sirasagi has done the statistical part in this study.
- "Data Sharing Statement" :- No additional unpublished data from the study is available

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