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IDEAL ORAL DRUGS IN MANAGEMENT OF TYPE 2 DIABETES MELLITUS -OPTIONS LEFT OPEN WHEN METFORMIN MONOTHERAPY IS INEFFECTIVE

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ABSTRACT

The trend towards personalized management of diabetes mellitus has focused attention on the differences among available pharmacological agents in terms of action, efficacy and most importantly the safety. Clinicians must develop individualized drug therapy regimens which covers these features. Because of the low cost sulfonylurea's (SU's) are the mostly used oral drugs in the management of type 2 diabetes mellitus (T2DM) after the metformin. A treatment paradigm shift is suggested in which conjunction management is employed by agents that correct known pathophysiological defects in T2DM and produce consistent reduction in HbA_{1c} rather than just focusing on the glucose-lowering ability of the drug. Unfortunately, sulfonylureas lost their durability very early and are sometimes associated with management related severe hypoglycaemic attacks leading to hospitalization's which had limited their outmost utilization presently. Not long ago, in cretin-dependent treatments like dipeptidyl peptidase-4 inhibitors (DPP-4I) and glucagon-like peptide-1 (GLP-1) agonist (GLP-1A) are obtaining vogue principally because of their advantage of Glucose-dependent effect on insulin secretion, weight reduction which is probably related to delayed stomach emptying and minimal hypoglycaemia. Sodium glucose transporter 2 inhibitors (SGLT-2I) called gliflozins, lead to a reduction in blood glucose levels. Canagliflozin, a member of gliflozins enhance blood glucose control as well as dwindle weight, systolic and diastolic blood pressure reduction is another new promising molecule currently searching for its arena in the management of T2DM. Insulin could be utilized at any place when required. This review will discuss what could be the best second line oral drugs for T2DM, once the metformin mono-therapy becomes in effective. Although all the guidelines suggested metformin as first line, there was no definite consensus on the second choice of drugs as a variety of medication categories were strongly suggested. When all options are comparatively well and safe given the benefits they converse, medicinal resolution should depend on a customized approach, taking into account patients, clinical situations, constitution, pathological effects, predilection, abilities and costs.

KEYWORDS

Sulfonylureas, Type 2 diabetes, Incretin dependent treatment, Dipeptidyl peptidase-4 inhibitors, Glucagon-like peptide-1 (GLP-1), Sodium glucose transporter 2 inhibitors (SGLT-2I) and Gliflozins.

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INTRODUCTON

The cause and pathogenesis of Type-II Diabetes Mellitus (T2DM) is chiefly centered on insulin resistance and insulin deficiency over the past years. Currently, the guidelines were updated with newer generation of anti-diabetic drug classes. Diabetes mellitus has affected 382 millions of individuals in the

world and also the prevalence was calculable to rise[1]. Accompanied by the climbing pervasiveness, it increases the economic burden particularly in developing country[2]. The healthcare price of polygenic disease was calculable to be USD612 billion globally in year 2014[3]. Besides, it's a chronic malady which led to complications that accumulated the high price of management[4-6].

Drug therapy management of Type 2 diabetes mellitus has additionally emotional from being "gluco-centric" to "patient-centric." The comprehension of the pathology of type 2 diabetes (T2DM) is vital for efficient treatment. In the last decades, main reason behind T2DM was centered on two metabolic defects particularly beta-cell dysfunction and the defiance of insulin[7]. Immensely, the β-cells of pancreas had started to fail way before T2DM was diagnosed[8,9]. Overly the β-cell will degenerates and then it advances to diminish glucose tolerance (IGT)[10]. Therefore, efficacious and affordable drugs are paramount in the diabetes therapy. There have been a paradigm shift in treatment modalities and presently entire focus is shifted from classical "triad" of beta-cell failure and insulin resistance to ominous "octet" idea as the pathophysiology expands to alpha-cells, gastrointestinal tract hormones, kidney, fat cells and brain. The danger factors for T2DM are fatness, stationary lifestyle[11].

Hereditary had precipitated hypoglycaemic agent resistance whereas obese individuals lived in hyperinsulinemia state to counter the hypoglycaemic agent resistance[12]. Further insulin deficiency emanated in increased fasting blood glucose level and eventually overt diabetes[13]. The last 20 years have witnessed the development of a good variety of new therapeutic choices to treat T2DM. Although every class of these medications broadly shows indistinguishable efficacy as monotherapy with hardly variations in glucose-lowering efficiency at least in short term, each therapeutic category has well outline dad verse-event profile that either can be relating to their specific pharmacological action and/or any harmful adverse effects. A number of these adverse effects (in particular hypoglycaemia and weight gain) could be clinically mean to the patients and general physicians, and it is conceivable that these adverse events may in future precipitate the cardiovascular (CV) risk in T2DM or may negate the potential CV benefits of few of the hypoglycaemic drugs[14].

This review article will mostly provide the information that what would be possibly the best option as a next oral hypoglycaemic drug when Glucophage (Metformin) mono-therapy becomes in efficacious, based on the evidence available through the different studies published recently. Even after 3 to 6 months, if the target range/ level of HbA1c was not achieved guidelines suggested addition of second line agent which may be of sulfonylurea, glucagon-like peptide-1 (GLP-1) receptor agonist/insulin, dipeptidyl peptidase-4 (DPP-4) inhibitor[7]. However, the American Association of Clinical Endocrinologists (AACE) recommends use of metformin as first line treatment unless contraindicated in advance kidney disease or liver problems[15]. Every guidelines recommend metformin as the 1st line drug of choice, as it is inexpensive (low cost) and has durable efficacy and safety data particularly on cardiovascular safety[16,17]. However, glycaemic target should be different from one person to another person (individualized) to circumvent hypoglycaemia. Stiff target of 6.0%-6.5% was recommended for younger and healthier patients whereas the glycaemic target of 7.5%-8.0% was strictly recommended for geriatrics, patients with co-morbidities or hypoglycaemia prone patients[18].

Brief Summary of Type II DM: Pathophysiology and General Management Approach

Type-II Diabetes Mellitus is distinguished by a combination of resistance of insulin (peripherally) and insufficient insulin release by the pancreatic β cells. Insulin resistance, which has been attributed to increase in the level of free fatty acids and pro inflammatory cytokines in plasma which further leads to decreased glucose transport into the cells of muscles, increased hepatic glucose production and increased breakdown of fat. Excess intra-cavity adipose tissue causes the over secretion of some cytokines (adipokines or adipocytokines) associated with endothelial dysfunction, leads to inflammation and furtherly thrombosis. Classical examples of such

type of adipokines include plasminogen activator inhibitor-1 (which is prothrombotic), TNF-α and interleukin-6 and resisting (which causes insulin resistance). Abdominal fat, in type 2 diabetes, is metabolically different from subcutaneous fat and can cause 'lipotoxicity', as it is resistant to the antilipolytic effects produced by the insulin, emanating in the liberation of excessive amounts of free fatty acids, leading to insulin resistance in the liver and muscle. The effect is an increase in gluconeogenesis in the liver and suppression of insulin-mediated glucose uptake in the muscle[19]. Type 2 diabetes is an islet paracrinopathy within which the mutual relationship among the glucagon-secreting alpha cell and also the insulin-secreting beta cell is lost, resulting in hyperglucagonemia and therefore the resultant hyperglycemia[20]. In addition to muscle, liver, and β-cells ("triumvirate"), lipocytes and fat cells (accelerated lipolysis), GI tract (incretin deficiency/resistance), α-cells (hyperglucagonemia), renal tubules/ urinary organ (increased glucose reabsorption) and brain (insulin resistance and neurochemical dysregulation) play necessary roles in the development of glucose intolerance in T2DM people. Jointly, all these eight players will comprise the "ominous octet"[21] (Figure No.1).

β-CELL FUNCTION AND DYSFUNCTION

Beta-cell dysfunction develops early in the pathological process and does not essentially follow the stage of insulin hormone secretion resistance[22]. Initial-or starting-phase insulin release unleash in response to glucose often is reduced, and pulsatile insulin secretion is absent, leading to postprandial hyperglycaemia. Endocrine glucagon response to carbohydrate consumption is altered in patients with type 2 diabetes who have a defective or absent early insulin response secondary to β cell pathologic dysfunction or failure. For patients with type 2 diabetes, un treated fasting and following a meal hyperglycaemia provoked by declined glucose uptake and increased liver glucose production, hyperinsulinemia and insulin resistance result in a regeneration that inflicts on going harm to tissues and organs[23]. With time, β cells lose their ability to retort to increased glucose concentrations, leading to increasing loss of glucose management. In patients with burdensome high plasma sugar levels, the quantity of the hormone insulin emanated in response to glucose is diminished and insulin resistance is worsened (glucose toxicity). β-cell dysfunction is initially characterized by an impairment in the first phase of release of insulin during glucose invigoration/stimulation and should antedate the onset of glucose insularity in T2DM[24].

Emergence of the insulin reaction mainly depends upon the transmembrane transport of the glucose and coupling of glucose to the glucose sensing element. The glucose/glucose sensor complex then induces a rise in glucokinase by stabilizing the protein and impeding its ignominy. Glucokinase ordination is the first step in linking intermediary/ negotiant metabolism with the framework of insulin secretion. Glucose delivery inβ-cells of type 2 diabetes patients seems to be greatly diminished, thus transposing the sway tip for the release of insulin from glucokinase to the glucose transport system[25,26]. The 2nd period delivery of freshly combined insulin is impaired. This secondary event, termed desensitization or pancreatic beta cell glucose toxicity (glucotoxicity), is the result of a incomprehensible restrictive glucose effect upon secretion of the insulin and may be referable to the storage of the glycogen within the pancreatic beta-cell as a sequel of sustained hyperglycemia[27]. Other defects in β-cell function in T2DM encompass flawed glucose enhancement in reaction to non-glucose insulin secretagogues, nonparallel insulin secretion and a delittled conversion of proinsulin insulin[28, 29].

Insulin Resistance

The presence of hyperinsulinism in type 2 diabetes mellitus and insulin resistance has been thought about to play a crucial role within the pathophysiology of the disease[30]. As chronic hyperinsulinemia inhibits both insulin emanation[31] and activity[32] and the increased plasma glucose highness (hyperglycaemia) can hinder both the insulin secretory response to glucose[33] as well as cellular insulin sensitivity[34,35]. Similarly, in most of the insulin resistant T2DM patients, obesity is virtually always present[36,37]. Grandiosity in the adipose tissue within the abdomen is related with insulin resistance in

the absence of diabetes, it is assumed by some researchers that the resistance of insulin inT2DM was entirely due to the coexistence of magnified adiposity[38]. Longitudinal type of studies have established the existence of one of two insulin insufficiency or resistance of the insulin prior to the onset of T2DM[39]. In T2DM mostly the hepatocytes and the muscles are extremely resistant to the insulin in T2DM[40,41]. The flexibility of insulin to vanquish the liver glucose synthesis both in the empty stomach (fasting state) and after a meal (postprandial) is traditional in first degree blood relatives of T2DM[42]. Resistance of insulin by the liver is characterized by a marked decrease in glucokinase activity and a chemical change magnified conversion of substrates to glucose in spite the existence of insulin[43]. Thus, in T2DM the liver is organised for both higher production and diminished utilisation of glucose. The increased free fatty acid levels found in type 2 diabetes may additionally play a role in larger amount of glucose production by the liver[44]. After an overnight fast, the liver produces glucose at ∼2 mg/kg/min. In T2DM, the speed rate of basal Hepatic Glucose Production is increased, averaging ∼2.5 mg/kg/min. This amounts to the addition of an extra amount/quantity (25-30 grams) glucose to the integral circulation nightly and is liable for the towered empty stomach (fasting) blood glucose concentration[45].

Choice of Second - Line Oral Drugs After Metformin: Option Left Open When Metformin Becomes Ineffective

Currently, varied choices are available as a second - line agent after metformin becomes ineffective. Agents which can be used orally embrace sulfonylureas (SUs), pioglitazone, DPP-4I and SGLT2I. Agents which may be utilised in injection type include GLP-1(Glucagon - like peptide -1) agonist and the insulin. As pioglitazone is insulin hormone sensitizer, this could not be a awfully appropriate second - line drug because once one sensitizer like metformin becomes ineffective and therefore this will not be mentioned further during this review. Although, alpha glucosidase inhibitors is additionally utilized in treatment of T2DM but its utility is restricted with poor tolerability and it should not be considered as preferred second-line agent and thus won't be discussed further in this review.

Best second line oral drug when metformin becomes ineffective: comparing sus versus dpp-4 inhibitors

Sulfonylureas were the most customarily handed-down 2nd line drug therapy because of their well - established potency and low or economical or affordable cost excluding with accustomed side effects of hypoglycaemia and attaining of extra weight[46] (Table No.1).

Results from some studies (RECORD and ADOPT) have also guided to the apprehension regarding their permanence and long - lasting Cardiovascular (CV) safety (UGDP), which may likely be allied to the actuality that Sulfonylureas moreover cohere to the Sulfonylurea receptor (SUR) subunit1 (subtype SUR1) of the potassium adenosine triphosphate (KATP) channel in the cell membrane of the pancreatic beta cells, but may also adhere to the Sulfonylurea receptor (subtype SUR2) on cardiomyocyte and also on the simple squamous cells called endothelial cells and can put up direct effects on CV function[47]. The controversy regarding the cardiovascular safety outline of Sulfonylureas initiated mainly with the UGDP, performed in the 1960s that fist gave rise to examine about the protection of the 1st generation sulfonylurea, tolbutamide[48]. In this study, outstandingly enlarged threat of all - cause and CV mortality was witnessed between members who have taken this sulfonylureas vs place bo drug[49]. Nevertheless, as a consequence of these data, each of the sulfonylureas approved for treatment in the United States, mentioned in its label of product that Sulfonylureas use has been associated with increased CV mortality[50]. Uncertainty exists whether the conclusions of UGDP were relevant to the current state clinical practice, where modern diabetes management encompasses the several factors (multifactorial) approach/proceed towards to lower the threat of Cardiovascular complications[51]. Beside this, majority of the large Cardiovascular outcome (result/consequence) trials have necessarily analysed the influence of several combinations of glucose - lowering agents as part of an overall therapy course of treatment (e.g. United Kingdom Prospective Diabetes

Study, Action To Control Cardiovascular Risk In Diabetes, Advance, Veterans Affairs Diabetes Trial) [52]. Very few of the long - term head - to - head trials have differentiated the consequences of single anti-diabetic agents on Cardiovascular outcomes (PRO active) or CV surrogates (CHICAGO, PERISCOPE, AND APPROACH)[53-55]. Thus, a comparative interpretation of the cardiovascular impact of this most widely used diabetes drugs is actually lacking[56].

DPP4I are already in utilisation for past 7 years and results of few larger cardiovascular studies like VIVIDD, SAVOR TIMI were disseminated not long ago.The beginning effect of increasing nasopharyngeal infection and urinary tract infection (UTI) has largely been concluded out in these research studies[57]. These studies unveiled Cardiovascular neutrality of these drugs, few concerns abided in the idiom of outstandingly to were hospitalization due to heart failure seen in SAVOR TIMI trials and this drift sustained in EXAMINE trial whilst insignificantly[58] (Table No.2).

CV: Cardiovascular, DPP-4: Dipeptidyl peptidase-4, UTI: Urinary tract infection, VIVIDD: Vildagliptin in ventricular dysfunction in type 2 Diabetes, SAVOR: Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus, TIMI: Thrombolysis in myocardial infarction.

It should be noted that there were several Dipeptidyl Peptidase-4 substrate independently from glucag on-like peptide-1(GLP-1) that can influence the vascular outcomes (Table No.3). Some of them could be worthwhile like factor derived from stroma called as stromal - derived factor-1α (SDF-1α), Natriuretic peptide of Brain (BNP) and substance P, remaining can be injurious like neuropeptide Y (NPY) and peptide YY (PYY). Interestingly, substance P is a potential vasodilator but it does elevate the sympathetic activity. Substance P is degraded in to inactive metabolite both by ACE and DPP-4. Recent review cites substances P as a putative agent inducing increased sympathetic activity and in succession raising inactive heart failure, when the Dipeptidyl Peptidase-4Inhibitors was used in conjunction with the Angiotensin Converting Enzyme inhibitors[59].

CV: Cardiovascular, DPP-4: Dipeptidyl peptidase-4, UTI: Urinary tract infection, GLP: Glucagon - like peptide-1, SDF1-α: Stromal - derived factor-1α, BNP: Brain natriuretic peptide.

There have been indirect differentiation between Sulfonylureas and Dipeptidyl Peptidase-4 inhibitors from their independent trials as noticeable from several systemic reviews and meta - analysis done by Arjona Ferreira *et al*, 2013, Gallwitz *et al*, 2012 and Rosen stock *et al*, 2013. Because of the substantive inflation in data on the Dipeptidyl Peptidase-4 inhibitors vs Sulfonylureas as a additional therapy to metformin or as monotherapy, expanded data was necessary. Not long ago, 12 head-to-head trials of a meta-analysis between the Sulfonylureas versus Dipeptidyl Peptidase-4 inhibitors disseminated is explored here below[60] (Table No.4).

This meta - analysis have proposed a minimal precedence of SUs especially glimepiride in A1c reduction. DPP4I showed better efficacy with contrast to 2ndgeneration SUs like glipizide and gliclazide and also in most of the patients with chronic renal failure (CRF). DPP4I was clearly superior to SUs in any adverse effects, hypoglycaemia, weight gain, and CV events (Tables No.5).

#DPP4I showed better efficacy when compared to 2nd generation SU and also in CKD patient, *Same percentage of patient had A1C<7% when trial was >32 weeks, DPP-4: Dipeptidyl peptidase -4, SUs: Sulfonylureas, CV: Cardiovascular.

In concisely, Dipeptidyl Peptidase-4Inhibitors and sulfonylureas were both insulin otropic, yet with different mechanisms. SUs may cause (severe) hypoglycaemia, whereas DPP-4I does not. By direct (head -to - head) comparison, DPP-4I are associated with less cardiovascular events than Sulfonylureas. Because of the benefits of (no weight gain and no hypoglycaemia) and some expectations regarding CV benefit, DPP-4I were mostly used globally but the price is remnant as a major limitation with DPP-4I, SUs still remains a valuable drug in developing countries like India.

Comparing SUs versus SGLT-2 inhibitors

Recently SGLT -2 inhibitors class of agents are used in the management of T2DM. Both Canagliflozin and

Dapagliflozin primarily inhibit glucose re absorption in renal tubules through Sodium glucose transporter 2 (SGLT-2) receptors and diminishes the blood glucose level by escalating glucosuria. Because of this glucosuric effect, this class of agents decreases the BP and the leads to reduction in the body weight but at the cost of increasing genito-urinary infections (Table No.6). Only few head -to - head studies have compared SUs with SGLT-2 inhibitors. Both this study shown non - inadequacy of Sodium Glucose Transporter -2 inhibitors in HbA1c diminution in contrast to Sulfonylureas but with the prominent loss of weight and reduction of the blood pressure[61, 62].

CV: Cardiovascular, SU: Sulfonylureas SGLT: Sodium glucose transporter 2 inhibitors, PTH: Parathromone, LDL: Low density cholesterol, CANVAS: CA Nagliflozin cardiovascular assessment study, RASB: Renin angiotensin receptor blocker.

In the comparison study of Dipeptidyl Peptidase -4 inhibitors vs Sodium Glucose Transporter -2 inhibitors four head - to - head study compared DPP4I with SGLT2I either in therapy of unaffected suffering patient (Roden *et al.*) or on backdrop metformin therapy (Rosen stock *et al.*) or backdrop SU plus metformin therapy (Schernthaner *et al.*)[63].

There was no significant difference among this agent in A1c reduction but Sodium Glucose Transporter-2Inhibitors were allied with steady weight reduction and BP reduction. In fact in one study, 300mg of canagliflozin has shown superior efficacy when compared with sitagliptin 100 mg. Although SGLT2I seems to have certain advantage from weight and blood pressure point of view but some contemporary studies demonstrated deprivation of its potency/efficacy after its chronic or long tern use. SGLT2I were associated with paradoxical increase in internal glucose productivity caused by an increase in glucagon to insulin ratio[64].

Table No.1: Sulfonylureas: Advantages and Disadvantages

Advantages	Disadvantages
• Time tested • Robust glucose reduction in early stage • Cheap • Randomized trials did not give bad CV signal	• Gluco-centric without disease-centric properties • Durability - less • Hypoglycaemia - big issue • Weight gain • Possible beta cell apoptosis • Observational studies and overall meta - analysis shows increasingly bad CV signals and mortality

Table No.2: DPP-4 inhibitors: Lessons learnt so far

Advantages	Disadvantages
• A1c reduction at par with SUs • Minimal hypoglycaemia with weight neutrality or loss • Possible pleiotropic benefit and beta cell protection • Meta - analysis of pooled data from phase 2/3 showed CV benefit • Randomized trials—VIVIDD, SAVOR TIMI, and EXAMINE suggested CV neutrality • Issues of pancreatitis and UTI/ Nasopharyngitis do not seems to be any large issue from these results	• Cost • Slightly higher mortality in VIVIDD trial • Issues of increased hospitalization due to heart failure in SAVOR • TIMI needs further clarification Possible off - target effects

Table No.3: DPP-4 substrate which can potentially influence CV outcome

DPP-4 SUBSTRATE	CV ACTION	METABOLITES	CV ACTION
GLP-1 (7–36)	Decrease apoptosis and promotes preconditioning	GLP-1 (9-36)	Vasodilator
SDF-1α	Stimulates bone marrow mobilisation of endothelial Progenitor cell (repair of endovascular damage)	Inactive metabolites	Inactive
BNP	Natriuretic and vasodilator	BNP (3–36)	Minimal vasodilator
Substance P	Vasodilator and increase sympathetic activity	Substance P (5-11)	Inactive
Peptide YY (1–36)	Vasoconstrictor via Y1R	Peptide YY (3-36)	Vasodilator via Y2R
Neuropeptide Y (1-36)	Vasoconstrictor via Y1R	Neuropeptide Y (3-36)	Vasodilator via Y2R

Table No.4: Meta - analysis of 12 head- to -head studies: SUs vs DPP-4I

Study, year weeks	Intervention	HbA1c (%)	HbA1c<7% (%)	Body Weight	Hypoglycaemia (%)	CV events (%)
Arjona Ferreira et al.	Sitagliptin	−0.72−0.87	44	−0.2	6.3	7.8
2013* 54 week	Glipizide		56	0.8	10.8	9.2
Gallwitz et al.	Linagliptin	−0.16−0.36	30	−1.4	7	1.5
2012 104 week	Glimepiride		35	1.3	36	3.4
Rosenstock et al.	Alogliptin	−0.14−0.09	49	−0.6	5.4	0.5
2013* 52 week	Glipizide		45	0.60	26.0	0.9

*Life style intervention, all others were on background metformin

Table No.5: Results of the met - analysis of 12 head -to - head studies: SUs vs DPP-4I

Parameters	Dpp‑4 inhibitors (dpp4i) versus SUs
• A1C reduction# • A1c<7%* • Hypoglycaemia • Weight • Any adverse effect • DPP4I • CV events	• DPP4I produced less A1c reduction by 0.11% • 9% less with DPP4I when trial<32 weeks • 87% less with DPP4I • 1.65 kg less with DPP4I • 21% less total adverse event with • 47% less with DPP4I • Better PI/I ratio and HOMA-IR with DPP4I

Table No.6: SGLT-2 inhibitors: Advantages and disadvantages

Advantages	Disadvantages
• A1c reduction at par with metformin, SU, Gliptins • Durability seems superior to SU • Wt loss superior to metformin and gliptins • BP reduction robust than metformin and gliptins	• Genital and urinary infection • Volume depletion with loop diuretics • Postural hypotension with RASB and diuretics • Safety in elderly>75 year • Increase in endogenous glucose production (EGP) due to increased glucagon/insulin ratio • CV safety: Increase LDL and fatal and nonfatal stroke with Canagliflozine in CANVAS trial. • Malignancy: Increased breast AND bladder cancer with Dapagliflozin

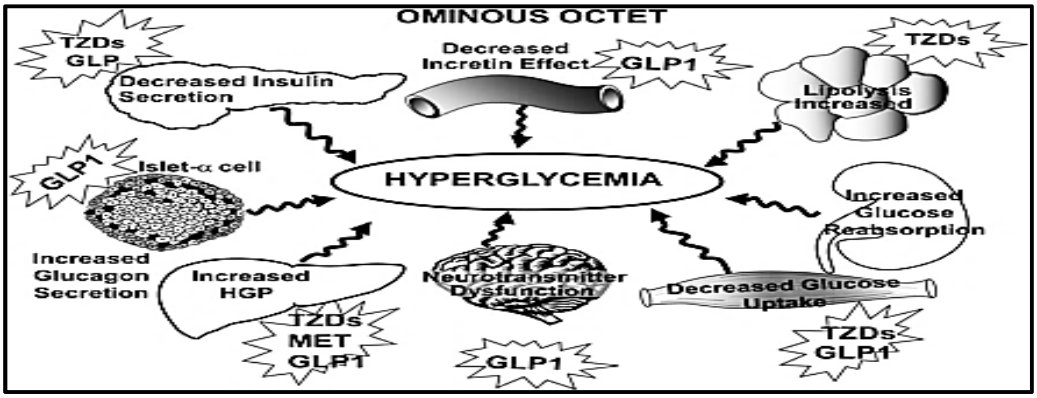

Figure No.1: The ominous octet depicting the mechanism and site of action of antidiabetes medications based upon the pathophysiologic disturbances present in T2DM

CONCLUSION

SUs remains the most prominent second - line drug once Glucophage (Metformin), over the years primarily due of its low cost value but however it will carry the luggage of severe hypoglycaemia at a time, with vital weight gain and secondary failure. SUs conjointly appear to own some of the Cardiovascular safety concern seen in retrospective case-control, experimental and prospective studies. In contrast, Dipeptidyl Peptidase-4 inhibitors are safer oral alternative with additional or less same HbA1c reduction without the luggage of severe hypoglycaemia and weight gain. DPP-4 inhibitors conjointly looks to be sensible good alternative especially within the light weight of encouraging results from two recently published giant Cardiovascular trials like SAVOR TIMI and EXAMINE that neither gave any vital dangerous signals of increased pancreatitis nor showed magnified CV mortality in such high - risk CV cases but however these medications are limited with their cost compared to SUs.

SGLT-2 inhibitors appears to be an additional propitious oral drugs as their HbA1c (Glycated haemoglobin) reduction capability is as at par with SUs and DPP -4I with additional advantage of the reduction of weight and reducing the blood pressure which seems to be steady. However, recent study suggesting the loss of efficaciousness in chronic utilisation due to increment in the endogenous aldohexose production derived from increase in

glucagon/insulin quantitative relation. If this elevation in integral glucose production is further validated in larger studies with SGLT2I, than previous use of glucagon lowering medications with incretin primarily based therapies alongside with metformin (which directly reduces EGP), makes additional sense. Type 2 diabetes includes a complex etiopathogenesis as evident from its "ominous octet" idea or opinion. No individual anti - diabetic drug will correct all of the pathophysiologic disturbances present in T2DM and therefore multiple agents are to be required for optimal glycaemic control and management. It is choice for the physician to choose which combination outfits/suits the individual (specific to one person) needs of the patient at certain given point of time with due considerations of the disease condition/ illness and the co-morbidities which makes the diabetes uncontrolled. So the drugs which are considered to be of outmost safe and effective are to be utilized in the management of type 2 diabetes mellitus.

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CONFLICT OF INTEREST

There is no conflict of interest.

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