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Journal of Diabetes Education

To Dispel Darkness Of Diabetes

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JOURNAL OF DIABETES EDUCATION

To Dispel Darkness of Diabetes

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Incretins

Shaival Chandalia

Incretins are hormones produced by the gut which help to regulate glucose metabolism. These hormones were identified through the so called 'incretin effect'. If glucose is given orally to an individual, it produces a grater stimulation of insulin release then when it is given intravenously. This lead researchers to identify these hormones which are secreted by endocrine cells of the gut in response to oral nutrient intake.

The two main incretin hormones are GLP1 (glucagon like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). Of these two, GLP1 and its effect have been harnessed in the development of innovative drugs for type 2 diabetes. Type 2 diabetes is associated with a reduction in the incretin effect, alluded to earlier. GLP1 has been manipulated to enhance the incretin effect in type 2 diabetics.

What are the effects of incretin hormones, GLP1 and GIP on the body? The effects are four fold in controlling nutrient homeostasis.

1. These peptide hormones stimulate the beta cells of the pancreas to increase insulin secretion in a glucose dependent manner.
2. They inhibit the alpha cells of the pancreas to reduce glucagon secretion.
3. They affect the motility of the stomach to slow down stomach emptying
4. They suppress the appetite and induce satiety.

The result of this four pronged effect (insulin stimulation, glucagon inhibition, slowing down of gastric emptying and appetite suppression) is that blood glucose levels are regulated. Insulin, as you know helps reduce blood glucose, glucagon helps to increase blood glucose. Glucagon suppression will lead to lower blood glucose levels. Slowing down stomach emptying reduces the spike in blood glucose levels that are seen just after a meal. Lastly, suppressing appetite curbs the total quantum of food eaten and therefore consequent rise in blood glucose levels.

GLP is a peptide hormone which is inactivated by an enzyme in the blood called DPP4 or dipeptidyl peptidase 4. This is the reason that GLP1 cannot be used directly for therapeutic purposes. If GLP1 is injected into a patient, it is inactivated by DPP4 in a matter of minutes. So to produce a therapeutic effect, it has to be infused continuously which is not feasible. This prompted the synthesis of two classes of compounds to exploit the therapeutic effect of the GLP1 axis. These 2 classes of compounds are called

1. GLP1 analogs or incretin mimetics
2. DPP4 inhibitors or incretin enhancers

    1. GLP1 analogs or incretin mimetics - As the name suggests this class of compounds mimic the action of incretin hormones, examples are exenatide or Byetta and liraglutide or Victoza.

        Exenatide is the first molecule to exploit the GLP1 axis and prototype of its class. Discovery of this peptide was made serendipitously. A biologist by the name of John Eng was studying a lizard called the Gila monster which is found in the United states. He found that the saliva of this lizard has glucoregulatory properties (see Fig.1). Exendin-4 was the protein he isolated from the saliva of the lizard. Exenatide is a synthetic version of the same protein – exendin 4. How does it work? In one of nature's bountiful ways it so happens that exenatide has 50% similarly in structure to GLP1. The difference is that it is resistant to degradation by DPP4 because of a 50% change in structure. This makes it convenient to inject exenatide twice a day i.e. its half life is extended to 12 hrs (from that of GLP1 which is few minutes). It reduces blood sugar levels by the four different mechanism described above. This discovery further sprouted research in this area of medicine.

Dr.Shaival H Chandalia, Endocrinologist & Diabetologist at Dr.Chandalia's Diabetes Endocrine Nutrition Management and Research Center (DENMARC) & Jaslok and Bhatia Hospitals and Research Centre, Mumbai, Email Id: **shaivalc@hotmail.com**

Fig: 1

Development of Exenatide: An Incretin Mimetic

Exenatide (Exendin-4)

– Synthetic version of salivary protein found in the Gila monster

– Approximately 50% identity with human GLP-1

- Binds to known human GLP-1 receptors on β cells in vitro
- Resistant to DPP-4 inactivation

Adapted from Nielsen LL, et al. **Regulatory Peptides.** *2004;117:77-88. Reprinted from* **Regulatory Peptides,** *117, Nielsen LL, et al, Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycaemic control of type 2 diabetes, 77-88, 2004.*

Liraglutide was the result of this research. This second protein molecule was synthesized in the lab and has 97% similarity in structure to native GLP1. The difference of 3% makes it resistant to degradation by the enzyme DPP4. Thus liraglutide can be injected only once a day for its effect. Both these compounds are called GLP1 analogs because they are similar in structure to GLP1. They mimic the action of GLP1 - hence incretin (GLP1)mimetics. Both are injectable, as opposed to the next group of medicines called DPP4 inhibitors or incretin enhancers, which are given orally.

2. DPP4 inhibitors or incretin enhancers – We alluded to the enzyme called DPP4 which degrades native GLP1. This group of oral medications inhibit the enzyme DPP4. Hence they are called as DPP4 inhibitors. By doing so they enhance the action or prolong the action of endogenous GLP1, hence they are called as incretin enhancers. Examples in this group include sitagliptin, vildagliptin, saxagliptin and linagliptin. These are oral medications, hence the ease of administration.

What are the advantages of GLP1 analogs and DPP4 inhibitors?

Because this class of agents works through the physiological incretin axis, they have a number of advantages. While conventional medicines for diabetes have side effects of hypoglycemia and weight gain, this class of agents does not. Hypoglycemia does not occur because when the blood glucose level drops, insulin secretion is shut down. This is called as glucose dependent insulin secretion. In contrast, medications like sulfonylureas which produce severe hypoglycemia, because insulin secretion stimulation by the drug continues even when the blood sugar level is normal. As mentioned earlier, this class of medications suppresses appetite and influences satiety. Hence, as opposed to conventional medicines which produce weight gain, this new class of medicines is weight neutral or produces weight loss.

Does it influence the natural history of the disease? In other words, does it preserve the beta cell against the inexorable decline that is seen in long standing diabetes? This remains an unsettled issue. None of the conventional medicines prolong the life of the beta cell. We hope that this class of agents will change that aspect of the natural history of diabetes.

Another important consideration is whether using these agents reduces long term cardiovascular mortality (heart disease and deaths) in patients taking these drugs. Reassuringly, so far, at least there is good evidence that the incidence of heart disease and deaths does not increase.

What are the disadvantages of these agents?

These agents, first and foremost are expensive. They remain beyond the reach of a large population of our diabetic patients. Hopefully market forces will dictate lower prices in the long term. The main side effect of these agents is that they are sometimes associated with gastrointestinal symptoms like nausea and vomiting. This is usually temporary and by increasing the dose gradually, can be prevented.

There have also been cases of pancreatitis associated with the use of these agents. However, it is not clear whether these cases have been directly caused by these agents. Having diabetes, per se, increases the risk of pancreatitis, so the judgment is still not out on whether these agents contribute to pancreatitis or there are other reasons such as the increased pancreatitis risk due to diabetes. Other possible side effects are specific to certain molecules seen in the class of agents. Liraglutide has been associated with thyroid C cell tumors in mice and rats. However, in humans, equivalent tumors have not been found. Continued vigilance is required in this area.

To summarize, we now have in our armamentarium of agents to treat type 2 diabetes, a new class of agents. These agents are potent and have advantages over conventional agents like less hypoglycemia and weight gain. This is a fast developing field with numerous molecules lined up to be marketed. Once a week exenatide has also been marketed in western countries. Thus with one jab a week, you will soon be able to control blood sugars in selected cases. The potential in this field is immense and we hope that these agents stand the test of time.

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Myths & Facts in Diabetes

Sonia Kakar

MYTH 1: Diabetes is contagious

No. It is not contagious disease. Type 1 is due to absolute insulin deficiency and type 2 due to a combination of insulin resistance and deficiency.

MYTH 2: If children get diabetes, they'll eventually outgrow it

When children get diabetes, it is usually Type 1 or insulin dependent diabetes. This form of diabetes is caused by the destruction of the beta cells in the pancreas that produce insulin. Since beta cells cannot be regenerated, type 1 diabetes cannot be convert into type 2 diabetes neither can type 2 diabetes convert into type 1. Type 1 diabetes is irreversible and patients need insulin, lifelong.

MYTH 3: Kids with diabetes can't exercise

In fact, kids with diabetes should exercise. Physical activity or exercise along with diet and insulin are important in the management of diabetes. Exercise has many benefits. It lowers the blood glucose, which results in a person feeling better, helps to keep weight under check and lowers the chances of developing the long-term complications associated with diabetes. However, it is important to test blood glucose levels before and after exercise in order to avoid hypoglycemia.

MYTH 4: People with diabetes should avoid parties

There is no reason to do this since everyone needs to relax and socialize. In fact, parties are a great way to lower or avoid stress, which can affect blood sugar levels. People with diabetes just need to be careful about the amount of food or alcohol that they consume. It's important to discuss the amount of alcohol intake with your doctor, diabetes educator or dietitian. Your dietitian can also show you how to substitute various foods in your meal plan, and what types of foods to restrict.

MYTH 5: Insulin cures diabetes

No. Insulin itself does not cure diabetes, it only controls. When used correctly, insulin helps to keep the levels of blood sugar in the near-normal range. In Type 1 diabetes, insulin is essential because the pancreas is not producing any insulin. In Type 2 diabetes, diet (meal plan), exercise, and oral medications are used routinely, while insulin is used in some patients until long standing type 2 diabetes.

MYTH 6: Diabetes in women prevents them from having children

In the past, few technologies existed that would help people keep blood sugars in the normal range. We now know that if a woman with diabetes becomes pregnant, she can deliver a healthy baby by maintaining normal blood sugar levels both before conception and throughout the pregnancy.

MYTH 7: Urine and blood glucose testing are interchangeable (Both provide the same information)

Directly testing blood is the most accurate method of measuring the glucose level. The urine glucose test,

Dr. Sonia Kakar, PhD, MSc in Nutrition, Canada. Email Id: **kakarsonia25@yahoo.com**

measures the amount of glucose that 'spilled' into the urine. It is only an indirect method of determining the glucose level in the blood. The kidneys will not allow sugar to spill into urine until the blood glucose reaches a level above 180-200 mg/dl. Therefore, the urine will test negative for glucose if the blood glucose is at any level between 0 and 180 mg/dl. Thus, hypoglycemia cannot be detected by testing urine for glucose neither can the borderline elevated blood glucose in the range of 150-200mg%.

MYTH 8: Once insulin injections are started for treatment of type 2 diabetes, they can never be discontinued

During periods of acute stress (such as illness, infection or surgery) or when receiving certain medications that cause elevations in blood glucose, some patients with type 2 diabetes will require insulin. If the diabetes had been well controlled with diet alone or diet along with oral drugs, the patient should be able to resume previous methods of control for diabetes when the stress is resolved.

Myth 9: Starting insulin injections in Type 2 diabetes is the beginning of the end.

Not true, patients often panic and resist when told injections are necessary, but it's the next logical step if oral medications don't work. Emerging research suggests that starting insulin treatment early also can reduce strain on insulin-producing cells. And, the need for insulin injections is not always permanent; some patients with Type 2 diabetes eventually can stop taking insulin if they also make appropriate lifestyle changes.

Myth 10: Kids with Type 1 diabetes can't have anything sweet.

People with diabetes once were discouraged from having any sweets, but advances such as rapid-acting insulin therapies and monitoring protocols allow for the occasional treat. A child can have a piece of birthday cake, for example, as long as they receive the proper insulin dose beforehand and are monitored closely.

Diabetes only affects old people

False.In reality, diabetes affects all age groups. By 2007, 230 million people between the ages of 20 and 79 will have diabetes. In developing countries diabetes will affect about 30 million people between ages 20-39, roughly 70 million between ages 40-59 and over 40 million between ages 60-79. In developed countries, diabetes will affect some 5 million people between ages 20-39, roughly 30 million between ages 40-59 and over 40 million between ages 60-79.

Diabetes predominantly affects men

False. In fact, diabetes affects both men and women, and is rising among women. It is also increasingly dramatically among youth and threatening to decimate indigenous populations.

Diabetes cannot be prevented

False. In fact, up to 58% of type 2 diabetes is preventable by changing diet, increasing physical activity and improving the living environment.

Diabetes prevention is too expensive

False. Many inexpensive and cost-effective interventions exist. Proven strategies for improving the living environment, changing diet and increasing physical activity can reverse diabetes.

Effect of Oral Antidiabetic Agents on the Cardiovascular System

Debasis Basu

Introduction

Epidemiological evidence indicates that Type 2 diabetes(T2D) is an independent risk factor for Cardiovascular Disease (CVD) and the rate of CVD is higher in people with diabetes as compared to non-diabetes.[1] Type 1 DM patients possess a 10 times higher risk than the general population,[2] whereas type 2 patients have a 3 times higher risk of CVD related death.[3] Among individuals with T2D, every 1% rise in HbA1c is associated with a 30% increase in all-cause mortality and a 40% increase in CVD mortality. 4 It is CVD that worsens long-term prognosis in T2D[5], to the point that diabetes has been proposed as a CV risk equivalent. Diabetes increases case fatality rate after myocardial infarction, and worsens overall prognosis after CHD.[7]

Among diabetic adults, the cardiovascular-disease-related death rate remarkably declined by 40% and all-cause mortality declined by 23% from the 1997-1998 sample to the 2003-2004 sample. The excess CVD mortality rate associated with diabetes (i.e., compared with nondiabetic adults) decreased by 60% (from 5.8 to 2.3 CVD deaths per 1,000) while the excess all-cause mortality rate declined by 44% (from 10.8 to 6.1 deaths per 1,000).[8] Clinical treatment goals for patients with T2D ideally should include alleviating acute symptoms of hyperglycemia and forestalling diabetes-related complications, specially CVD (heart attack and stroke) which accounts for more than 80% of premature excess mortality.[9] But as several large trials in the recent past generated serious controversy, the role of glucose control in modulating CVD risk has posed as an equipoise akin to the “holy grail” in the management of clinical diabetes. It is well known that increases in glycemia are associated with a greater risk of cardiovascular disease. Studies like UKPDS showed that more aggressive glycemic control was associated with a 16% reduction in risk for myocardial infarction (MI), including fatal and nonfatal MI and sudden death and an estimate of 1% reduction in glycated hemoglobin resulted in a 14% reduction in MI risk.Yet, it has been difficult to prove whether reducing glycemia by any drug or treatment strategy has a direct cardiovascular benefit. Rather concerns have been raised that some antidiabetic agents may impart greater cardiovascular risk than was previously appreciated. A meta-analysis of clinical trials of rosiglitazone, pointed to an increased risk of myocardial ischemia (odds ratio, 1.43),[11] which fueled debate over whether long-term cardiovascular outcome trials should be part of the approval process for antidiabetic drugs. Soon followed the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that a treatment strategy designed to lower blood glucose to near-normal levels was associated with increased mortality with no apparent adverse cardiac effects of rosiglitazone.[12] In contrast, no change in the rates of death or cardiovascular events was demonstrated in the Action in Diabetes and Vascular Disease: A Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Thus, both macrovascular effects of antidiabetes agents and the optimal glycemic goals, as well as other aspects of combined treatment strategies, remain incompletely understood raising a serious concern of uncertain directions of management.[13]

The Big Fight

The journey which initially sparked of doubts and debates about the CV safety of SUs was done by the University Group Diabetes Programme,[14] indicating increased CV mortality with tolbutamide (Fig.1)

Other studies have resurrected the debate. Data from 5795 patients in the Saskatchewan Health database, identified by initiation of an OHA, revealed that first

Dr Debasis Basu, MBBS, MD, FICN, President and Lead Consultant, Preventive Cardiology and Metabolic Disease, Sugar and Health Clinic, Kolkatta. Email Id: **drbasu@yahoo.com**

generation SUs had the highest mortality (67.6 deaths per 1000 patient-years), compared with glibenclamide (61.4 deaths per 1000 patient-years) and metformin (39.6 deaths per 1000 patient-years).[15] Another study derived information from the Diabetes Audit and Research in Tayside, Scotland (DARTS) diabetes information system and the Medicine Monitoring Unit(MEMO) of Tayside, Scotland.[16] Patients newly prescribed with OHAs (n = 5730) were divided into five cohorts: metformin only; SU only; SU added to metformin; metformin added to SU and concomitant SU and metformin combination. SU monotherapy was associated with a higher CV mortality rate compared with metformin, and patients on combined SU and metformin were also at increased risk of CV mortality.

Unfortunately these studies had methodological flaws, with inadequate patient selection, randomization imbalance and poor compliance. On the contrary, UKPDS demonstrated that glibenclamide was not associated with any adverse CV events.[17] In fact, during 11 years of follow-up, glibenclamide maintained glycaemic control and reduced risk for macrovascular events, although this was not statistically significant. Furthermore, the 'A Diabetes Outcome Progression Trial (ADOPT)' study revealed that glibenclamide was associated with a similar risk to metformin, but significantly lower risk of CV events, including heart failure, compared with rosiglitazone.[18] A study from the Veterans Health Administration Diabetes Epidemiology Cohort of 39,721 patients investigated the impact of several classes of OHAs relative to SU monotherapy on all-cause mortality.[19] The adjusted odds ratios were 0.87 for metformin monotherapy, 0.92 for metformin and SU and 1.04 for TZDs; thus, the study did not show any significant effect on all-cause mortality for any OHA relative to SU monotherapy. A nationwide (French) registry of 1310 diabetic patients in 2005 with Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction hospitalized for acute MI revealed no hazard with the use of SUs before the acute episode. Infact, patients previously receiving gliclazide/glimepiride had improved in-hospital outcomes, compared with those on glibenclamide.[20] Following DARTS and MEMO report, Gulliford and Latinovic21 failed to show a significant hazard ratio for all cause mortality in diabetic subjects treated with SUs compared with those treated with metformin (HR 1.06, 95%CI 0.85 – 1.31; P = 0.616). In 2007, FDA issued a public safety black box warning about Rosiglitazone in response to a study published(meta-analysis report) by Nissen, et al.[22] where 86 out of 27,843 participants who took Rosiglitazone experienced a MI, compared with 72 of those who did not take the medication, a statistically significant 43% increased risk. In addition, the study also found that 39 participants who took Rosiglitazone died from cardiovascular events, compared with 22 of those who did not take the medication, an almost statistically significant 64% increased risk.

Potential cardiovascular effects of different antidiabetic drugs

Because different antidiabetic drugs lower blood

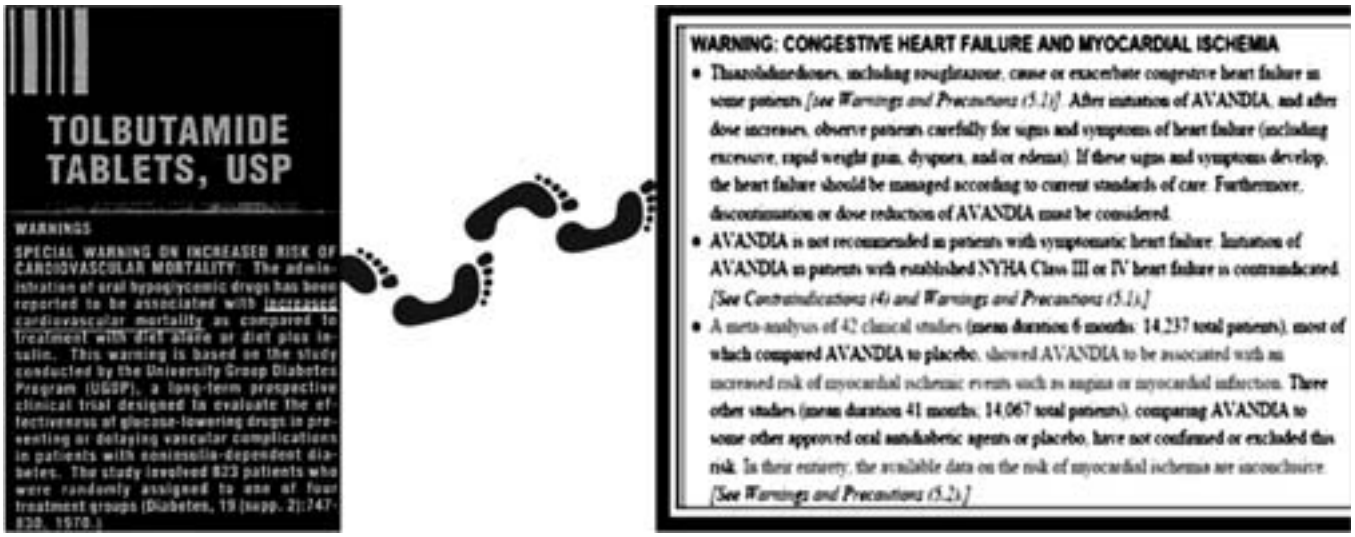

Fig.1: Blackbox labels from 1970 to 2007 (milestones during the journey from Tolbutamide to Thiazolidinediones)

glucose through different mechanisms, their effect on the cardiovascular system may differ. Several potential cardiovascular effects of different antidiabetic drugs have been postulated to explain how they may influence cardiovascular risk and outcome among patients with T2D (Table.1).

Sulfonylureas(SU):

SUs enhance insulin secretion upon binding with β-cell membrane receptors to close SUR1/Kir6.2 channels (Fig.2).

Table.1: Summary of the benefits, adverse effects and potential concerns of antidiabetic drugs

	Long-term data	Other benefits	HbA_{1c} decrease	Route	Hypoglycaemia risk change	Body weight	GI effects concerns	Other potential
SUs (1946)	Proven efficacy / safety	Low cost	0.8-2.0%	Oral	Yes	Gain	No	CV events?
Biguanides (metformin) (1957)	Proven efficacy/ safety	Low cost CV benefits?	1.0-1.5%	Oral	No	None or possible loss	Yes	Lactic acidosis (very rare)
Alpha-glucosidase inhibitors (1995)	Limited data	CV benefits?	0.5-0.8%	Oral	No	No	Yes	Unknown
Glinides (1997)	Limited data	Rapid acting	0.8-1.5%	Oral	Low	Gain	No	Unknown
TZDs (1997)	Improve β-cell function	Lipid profile (pioglitazone)	0.8-1.0%	Oral	No	Gain	No	Oedema, heart failure, fracture
GLP-1 agonists (2005)	Unknown	Improved β-cell mass? CV benefits?	0.6-1.0%	Injection	No	Loss	Yes	Risk of pancreatitis
Amylin Analogues (2005)	Unknown	–	~ 0.6%	Injection	No	Loss	Yes	Unknown
DPP- IV inhibitors (2006)	Unknown	Improved β-cell mass? CV benefits?	0.5-0.9%	Oral	No	Neutral	Yes	Unknown

HbA_{1c}, glycated haemoglobin; GI, gastrointestinal, SUs, sulphonylureas; CV, cardiovascular; TZDs, thiazolidinediones; GLP-1, glucagon-like peptide-1; DPP-IV, dipeptidyl peptidase-IV.

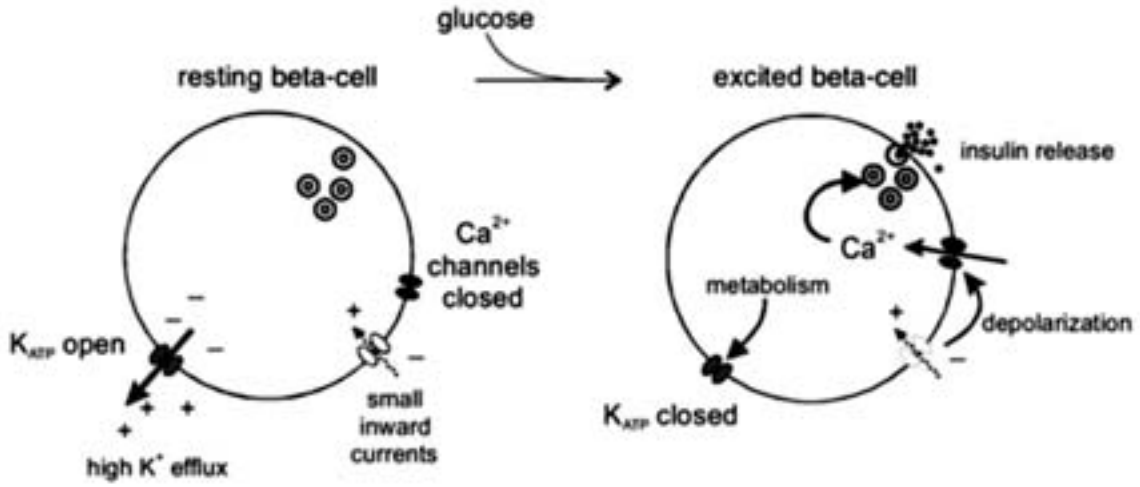

Fig.2 K-ATP channel activity modulates insulin secretion in pancreatic beta cells. Glucose-dependent KATP channel closure results in membrane depolarisation and insulin release.

Binding of the SUs to K-ATP channels in extra-pancreatic tissues may have a number of physiologic consequences. In cardiac myocytes, ischemia results in K-ATP opening, K^+ efflux, reduced Ca^{++} influx, and via these mechanisms a reduced contractility and consequently a decreased need for oxygen. Further, activation of K-ATP channels in the heart during ischemia is thought to minimize cardiac damage by "ischemic preconditioning". In vascular cells, K-ATP opening decreases muscular tone, resulting in increased flow. In the brain, opening of the K-ATP channels under metabolic stress has been suggested to protect against neuronal damage and neurodegeneration.[23]

Thus, SUs could at least theoretically be harmful by closing K-ATP channels. The impairment of ischemic preconditioning by some SUs (glibenclamide, glipizide) has been described both in experimental models[24-26] and in patients undergoing coronary angiography[27-29] and after direct angioplasty for acute myocardial infarction.[30] A similar effect has not been seen with other SUs (glimepiride, gliclazide).[25-28,31] The extra-pancreatic K-ATP channels are structurally different from the pancreatic isoform, giving a potentially different effect of SUs as their affinity for the different receptors differs. In a rodent model of ischemic stroke, this channel was upregulated, and post-event block by glibenclamide reduced mortality, cerebral oedema and infarct volume by half.[32] In addition, gliclazide may enhance fibrinolysis and reduce platelet activity and oxidative stress,33 properties that might reduce myocardial ischemic damage. Glibenclamide may reduce arrhythmias during ischemia.[34] Opening of even 1% of the total amount of channels in the sarcolemma can significantly shorten the cardiac action potential.[35] Therefore by inhibiting sarcK-ATP currents and preventing action potential shortening, the ensuing cellular calcium overload may promote gap junction closure and block re-entrant wave-fronts via cellular uncoupling finally preventing fatal arrhythmia.[36]

Glimepiride improves the lipid profile by reducing total and low-density lipoprotein (LDL) cholesterol and triglycerides and increasing high-density lipoprotein (HDL) cholesterol.[37]

Although SUR2A/Kir6.2 has no SU binding site, it has a benzamido binding site. Therefore treatment with SUs which have a benzamido group, during acute cardiac ischaemia may have a deleterious effect on the heart by interfering with K-ATP channel opening.[38,39] Study by Park et al. suggested that SU receptor 1 (pancreatic) has two binding sites, a benzamido site and a sulphonylurea site, whereas SU receptor 2 (cardiac) has only the benzamido binding site. Glibenclamide has both moieties, whereas Gliclazide has only the sulphonylurea moiety and so does not block cardiac channels with high affinity.[40,41] Inhibition of the Kir6.2/SUR1 channel by gliclazide was readily reversible, whereas the blocking by glibenclamide, glimepiride and repaglinide was only very slowly reversible. Inhibition of Kir6.2/SUR2 channels by repaglinide was also slowly reversible, whereas blocking by glibenclamide and glimepiride was rapidly reversible & gliclazide does not block that channel.[42]

Biguanides

Metformin decreases total and LDL cholesterol, plasma free fatty acids, and triglycerides, giving a beneficial effect with regard to the lipid profile. Metformin also decreases concentrations and activity of the antifibrinolytic factor plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA) antigen, von Willebrand factor, and platelet aggregation and adhesion, and increases tPA activity, each of which improves hypercoagulability. Metformin further improves vasoreactivity.[43] However, metformin may cause gastrointestinal disturbances such as nausea and diarrhoea, and during chronic therapy, it will impair the intestinal absorption of group B vitamins (mainly vitamin B12) and folate.[44] This effect leads to increased serum homocysteine, which may accelerate the risk for cardiovascular disease by adverse effects on platelets, clotting factors, and endothelium.[45] Metformin may lead to lethal lactic acidosis, especially in patients with clinical conditions that predispose to this complication, such as heart failure or recent myocardial infarction.[46] Metformin undergoes renal excretion, presenting undesirable pharmacologic interactions with several widely used cardiovascular drugs. The coadministration of nifedipine or furosemide leads to increased metformin plasma levels. Furthermore, digoxin, quinidine, and triamterene – which are eliminated by renal tubular secretion – may interact with metformin by competing for proximal renal tubular transport systems.[47]

Metformin therapy was found to be associated with a favorable cardiac outcome. As compared to SUs, lesser morbidity in patients with heart failure[48] and lesser cardiovascular hospitalization and mortality were reported[49] Many studies have shown that

metformin can reduce oxidative stress and lipid peroxidation, lower low-grade inflammation, and improve endothelial function. It is on the basis of these pleiotropic effects that the positive outcomes of the UKPDS have been accounted for. Secondary analysis of 342 overweight diabetic patients treated with metformin (Table.2) showed greater beneficial effect on all diabetes-related end points, including a 39% risk reduction for myocardial infarction (P = 0.01) compared with 951 patients treated with sulfonylureas or insulin.[50] Based on these results and retrospective analysis, a cardioprotective effect of metformin has been claimed[51] and metformin therapy has become a standard first-line treatment in almost all national and international guidelines. A recent systematic review and meta-analysis suggests that in patients with comorbid heart failure and diabetes, metformin is the only agent which has not been associated with harm.[52]

Alpha-glucosidase inhibitors

The primary mechanism of action of antidiabetic drugs like acarbose, voglibose and miglitol is based on competitive inhibition of several enzymes of the alpha-glucosidase group (maltase, isomaltase, sucrase, glucoamylase). These are membrane-bound enzymes that hydrolyze oligosaccharides and disaccharides to glucose in the brush border of the small intestine Thus, by delaying digestion of carbohydrates, these compounds shift their absorption to more distal parts of the small intestine and colon, and defer gastrointestinal absorption of glucose.[53] Unlike the SUs,they do not cause hypoglycaemia[54] Acarbose has been shown to lower triglyceride levels, total and LDL cholesterol levels, and blood pressure.[55] The STOP-NIDDM trial[56] is the largest randomized trial to date investigating the drug in subjects with prediabetes and early diabetes. This study suggests that acarbose treatment was associated with a reduction in hypertension and cardiovascular disease: this treatment resulted in a 25% relative risk reduction in the development of T2DM, in a 34% risk reduction in the development of new cases of hypertension, and in a 49% risk reduction in cardiovascular events. A 28-week Precose Resolution of Optimal Titration to Enhance Current Therapies (PROTECT) trial, which followed more than 6,000 patients with type 2 diabetes in a real-world setting, concluded that acarbose has an excellent safety profile.[57] Chronic treatment with voglibose stimulates GLP-1 secretion and decreases plasma DPP-4 activity by reducing its circulating levels[58,59] Similar features were documented for miglitol[60] Thus, the antihyperglycemic effect of

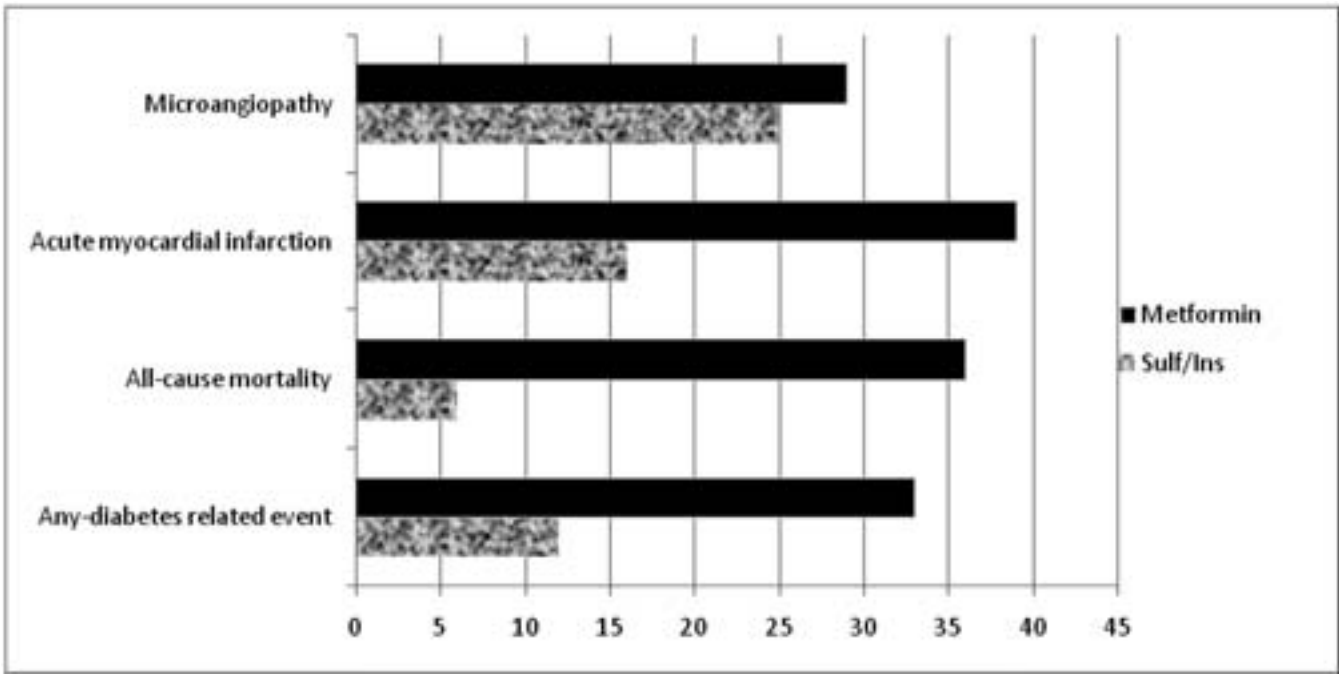

Table.2: Effect of Intensive Control with Sulfonylurea/Insulin (Sulf/Ins) and metformin versus conventional blood glucose control on the Relative Risk Reduction shown as Percentage of micro- and macrovascular diabetes complications in the UKPDS.

alpha-glucosidase inhibitors is likely achieved by two parallel mechanisms which are both direct and indirect. It directly reversibly inhibits the α-glucosidase enzymes, and secondly, induces GLP-1 secretion.

Thiazolidinediones

Thiazolidinediones (TZDs) are agonists of the peroxisome proliferator–activated receptor (PPAR)-γ, which enhances insulin action primarily on the adipose tissue with a favorable effect exerted on skeletal muscle and liver.[61] Glitazones improve endothelial function and markedly increase circulating concentrations of the good adipokine called adiponectin, which may have antiatherogenic properties. Glitazones increase HDL cholesterol and reduce triglycerides, free fatty acids, PAI-1, tumour necrosis factor-α, and the inflammatory markers C-reactive protein (CRP) and CD40 ligand.[62] TZDs can lower blood pressure, reduce microalbuminuria,[63] and exert anti-inflammatory, anti-oxidative action and cardioprotective effects at each stage of atherogenesis.[64] Vast majority of diabetic patients had regression of carotid intima-media thickness, and less re-stenosis after coronary artery stent implantation.[65] By intravascular ultrasonography in T2D patients with CAD, PERISCOPE study showed a significantly lower rate of progression of coronary atherosclerosis with pioglitazone when compared with glimepiride[66] Edema has been reported in 5% of patients, and glitazones are contraindicated in NYHA class III or IV.[67] The risk of heart failure is a class effect of the TZDs, whereas the ischemic cardiovascular risk is confined to rosiglitazone but not to pioglitazone with differential effects (rosiglitazone raising LDL cholesterol and pioglitazone lowering it) on metabolism explaining the apparent disparity in their impact on outcomes.[68] Other PPAR-γ agonists have also demonstrated adverse CV events. Muraglitazar, a dual PPAR-α and -γ agonist, increased adverse CV events, including MI69. This drug was not approved by the FDA and its further development was halted.

Meglitinides:

Because of their shared mechanism of action, meglitinides may exert effects similar to those of sulfonylureas on the extra-pancreatic K-ATP channels. They have also shown beneficial effects on cardiovascular risk factors by reducing total and LDL cholesterol, triglycerides, free fatty acids, PAI-1, CRP, fibrinogen, and thrombin-antithrombin complexes.[70] Nateglinide may exert a more physiologic effect on insulin secretion – i.e. a glycemia-dependent response – than repaglinide, presenting less propensity to elicit hypoglycemia in vivo. Regarding nateglinide, it appears to have less affinity for the potassium channels than repaglinide[71] and hence it is safer. It is interesting to mention a double effect of nateglinide: its action as a prandial insulin-releasing agent may partly rely on inhibition of GLP-1 degradation as well as beta-cell ATP-dependent potassium channels inhibition.[72]

Inhibitors of DPP-4 (DPP-4i)

Oral inhibitors of DPP-4(DPP-4i) have recently become available for patients with T2DM. They decrease the activity of the enzyme >80% for up to 24 hours, thereby enhancing meal related circulating concentrations of biologically active GLP-1 and GIP. In contrast to therapy with GLP-1 mimetics, DPP-4 inhibitors increase effective incretin levels into a more physiological range.[73] Their metabolic effects include the glucose-dependent stimulation of pancreatic insulin secretion and suppression of glucagon output.[74] Series of experimental and preliminary clinical data suggest that GLP-1 itself has favorable cardiovascular effects.[75,76] Studies showing vascular benefits of GLP-1 were carried out using either native GLP-1 or recombinant GLP-1 analogues at high concentrations or in a way that induced supraphysiological GLP-1 signaling. Even if DPP-4 inhibition may lead to similar effects, the effects of GLP-1 analogues and DPP-4i may be different, as DPP-4 inhibition restores GLP-1 signaling within the physiological range. But a pilot study indicated that DPP-4i (sitagliptin) acutely improved myocardial response to dobutamine stress and reduced features of myocardial stunning.[77] Although sitagliptin increased glucose load-induced GLP-1 concentrations, the link between GLP-1 and restoration of myocardial function remains speculative. A specific interest shifts therefore to the DPP- 4i effects beyond those carried out by GLP-1.This study is backed by experimental data using ex vivo hearts from obese, pre-diabetic rats: Huisamen et al. found that, after ischemia/reperfusion injury, treatment with a DPP4 inhibitor reduced the infarct size and was associated with activation of the cardioprotective PI-3K/Akt pathway.[78] In vitro, the authors found no evidence of increased glucose uptake by cardiomyocytes, an effect that is consistent with a GLP-1-independent mechanism.[79,80] Importantly, the beneficial effects of DPP-4i on left

ventricular function after MI may be mediated by the improved SDF-1α signaling. For instance, Zhang et al. implanted mesenchymal stem cell sheets with the DPP-4i diprotin over the surface of infarcted left ventricles and found an improvement in post-ischemic angiogenesis and myocardial performance, with concomitant SDF-1α upregulation.[81] A very important cardiovascular research has been a discovery that a subset of circulating cells contributes to endothelial homeostasis and vascular repair. These endothelial progenitor cells (EPCs) are derived from the bone marrow and can be mobilized into the blood stream in response to many stimuli.[82] Vascular damage or ischemia, through the release of growth factors and cytokines, inform the bone marrow of the need for EPCs, which then specifically home to damaged tissues. Locally, EPCs are able to form a patch at sites of endothelial denudation and reconstitute the anatomical integrity of the intimal layer.[83] Subsequently, EPCs differentiate into mature endothelial cells and complete functional reconstitution of the normal vasculature. One of the most important soluble regulator of EPCs is the stromal derived factor (SDF)-1α, which acts by binding to its receptor CXCR4. SDF-1αstimulates EPC mobilization from the bone marrow through induction of MMP-9, cleavage of membrane bound kit ligand and attenuation of progenitor cells/stromal cells interactions.[84] In the periphery, hypoxia-induced SDF-1α gradients guide EPC homing to ischemic tissues. Interestingly SDF-1α is a physiological substrate of DPP-4.[85] Therefore, DPP-4 inhibition is expected to increase SDF-1α bioavailability and activity, with the eventual stimulation of EPCs. A 4 week sitagliptin therapy, besides increasing EPCs and SDF-1α, was also associated with a significant reduction of the pro-inflammatory chemokine MCP-1.[86] MCP-1 plays an important role in regulating homing of activated monocytes into atherosclerotic plaques as well as into the inflamed visceral fat, thereby acting at two key pathologic processes frequently seen in diabetic patients.

Sitagliptin also reduced mRNA expression of a range of inflammatory genes, such as IL-6, TNF-alpha, and IL-12 in the adipose tissue, and MCP-1, IL-6, IL-12, and IP-10 in the endocrine islets.[87] DPP-4 activity and expression is increased in vitro by high glucose only in microvascular endothelial cells,[88] providing a rationale for the use of DPP-4i to protect endothelial cells from the detrimental effects of hyperglycemia. Very recently, effects of acute DPP-4 inhibition was sought on vascular tone, through an action on endothelial cells. They showed that pre-contracted aortic segments were dose dependently relaxed by the DPP-4i alogliptin. In cultured endothelial cells, alogliptin increased activation of the Akt-eNOS pathway and induced NO release. Therefore, these data suggest that DPP-4i regulates vascular tone through an action on the nitric oxide system.[89] This vascular relaxation effect of DPP-4i per se may have important clinical implications on blood pressure. Four weeks' treatment with vildagliptin improves endothelium-dependent vasodilatation in subjects with type 2 diabetes.[90]

Indeed, preliminary data in a small Japanese cohort suggest that the DPP-4i sitagliptin may lower blood pressure.[91] A retrospective meta-analysis of 8 phase II and phase III trials found no evidence that saxagliptin increases CV risk in patients with T2DM.[92] In a large preplanned, prospective and adjudicated meta-analysis, Vildagliptin was not associated with an increased risk of CCV events relative to all comparators in the broad population of type 2 diabetes including patients at increased risk of CCV events.[93] In another study, of 5239 treated patients 3319 received linagliptin once daily (5 mg) and 1920 received comparators (placebo, 977; glimepiride 1-4 mg, 781; voglibose 0.6 mg, 162). Primary CV events occurred in 11 (0.3%) patients receiving linagliptin and 23 (1.2%) receiving comparators. These results from a large Phase 3 programme support the hypothesis that linagliptin may have CV benefits.[94]

In a recently published pooled analysis, the RR of any adverse CV event with a DPP4 inhibitor was 0.48 (0.31 to 0.75, p 0.001), and the RR for nonfatal myocardial infarction or acute coronary syndrome was 0.40 (0.18 to 0.88, p 0.02). However, only Sitagliptin showed a significant risk decrease (RR 0.37, p 0.001), whereas risk decreases with saxagliptin and vildagliptin, although similar in magnitude to that noted with sitagliptin, were insignificant. Alogliptin, with the smallest patient sample, showed trends in the opposite direction.[95] A very recent publication summarized a total of 70 trials with various DPP4i, enrolling 41959 patients with a mean follow-up of 44.1 weeks, was collected and included in the analysis. The Mantel–Haenzel odds ratio (95% Confidence Interval) was 0.71[0.59;0.86], 0.64[0.44;0.94], 0.77[0.48;1.24] and 0.60[0.41;0.88] for Major Adverse Cardiac Events, MI, stroke and mortality, respectively. Infact, the reduction in the

incidence of myocardial infarction is greater than what predicted on the basis of conventional risk factors, suggesting a role for other mechanisms.[96]

Conclusion

With the passage of time there has been a substantial evolution of drugs (Fig.3) in the armamentarium for the treatment of diabetes.

Much water has flown under the bridge connecting antidiabetic drugs and cardiovascular safety recently and finally time has come when the navigators like US Food and Drug Administration (FDA) Strategic Priorities for 2011-2015[97] and the European Medicines Agency (EMA) Road Map to 2015,[98] promise to guide the movement of a drug on a straight and safe path and balance the desire for a "level playing field".[99] One has learnt reasonably well from the turmoil that intensive glycemic control may be more effective in patients with earlier diabetes and less extensive atherosclerosis. It has been proposed that glucose reduction in patients with established atherosclerosis may disrupt previously stable plaques and result in increased plaque rupture and clinical coronary events.[100] Further, hyperglycemia-induced tissue damage, including formation of advanced glycation end products, may not be readily reversible by restoration of normoglycemia and may contribute to the bad "legacy effect". On the contrary, the benefits of early tight glycemic control appear to persist for many years even after the control reverts to that of a standard treatment control group, as in the DCCT/EDIC study.[101,102] "Bad glycemic legacy" from years of poor glucose control may be what drives the risk of diabetes vascular complications and cannot be reversed by a relatively brief period (3–5 years) of improved tight glucose control.[103] Finally, as uncertainties of "cardiotoxic" management of diabetes plague the decision making among physicians and as patient compliance get affected when media sensationalism about controversial findings is misunderstood,[104] larger and long-term studies taken to hard endpoints and better reporting of cardiovascular events in short term studies are being undertaken to draw firm conclusions about major clinical cardiovsascular benefits and risks related to oral diabetes agents[105] (Fig.4). Proposed regulatory measures will ensure approval of safer drugs, but may also lengthen the drug development cycle or even deter development of potentially useful drugs.[106]

Trial	Drug	Sample Size	Stage
ORIGIN	Insulin glargine	12,500	Started 9/2003
TECOS	Sitagliptin	14,000	Started 12/2008
ACE	Acarbose	7500	Started 2/2009
TIDE	Rosi/Pio	16,000	Halted 9/2010
EXAMINE	Alogliptin	5,400	Started 09/2009
CANVAS	Canagliflozin	4500+ 14,000	Started 11/2009
T-emerge 8	Taspoglutide	2,000	Halted 4/2010
AleCardio	Aleglitazar	7,000	Started 2/2010
SAVOR TIMI-53	Saxagliptin	16,500	Started 4/2010
ELIXA	Lixisenatide	6000	Started 6/2010
EXSCEL	Exenatide LAR	12,000	Started 6/2010
C-SCADE 8	Empagliflozin	12,500	Started 7/2010
CAROLINA	Linagliptin	6000	Started 10/2010
LEADER	Liraglutide	9,000	Started 11/2010

Fig.4: Present Landscape of CVD outcomes Trials involving nearly 1.5 lakh Type 2 DM patients

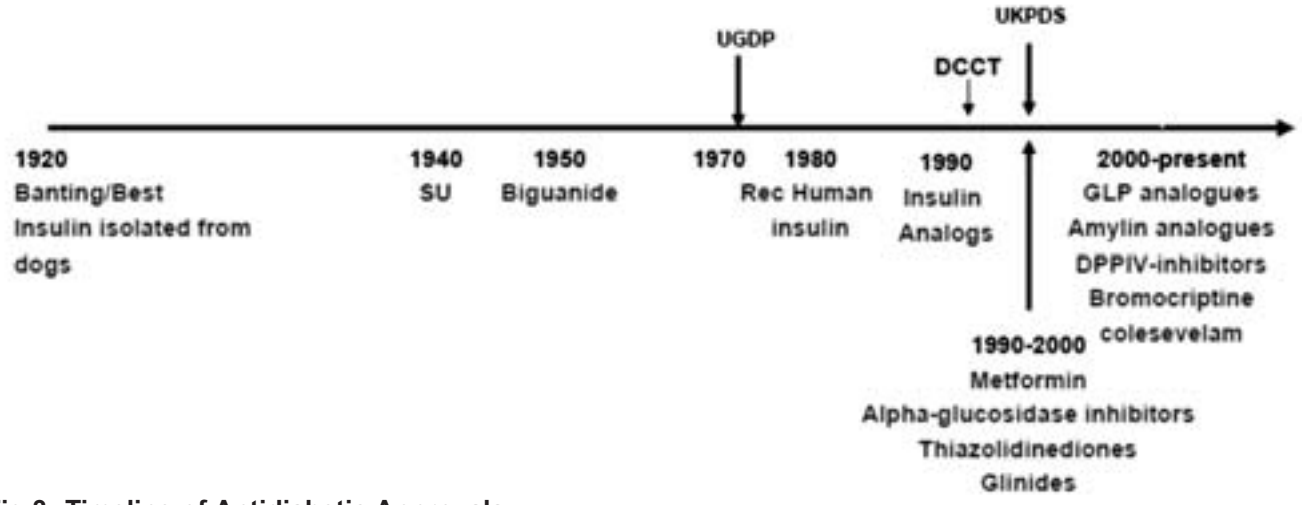

Fig.3: Timeline of Antidiabetic Approvals

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Sick Day Management in Type 1 Diabetes

Zankhana Shetty

When struck by an intercurrent illness, a diabetic has to shift to a flexible regimen called sick-day routine. A person with diabetes is required to be educated on this aspect of diabetes.

Sick Day management in Type 1 Diabetes:-

Type 1 diabetes is caused by an absolute insulin deficiency, as a result of the near complete destruction of the insulin-producing beta cells of the pancreas. There is some strong evidence of impaired leukocyte function in poorly controlled diabetes. Type 1 diabetic children with poor metabolic control may have altered immune function, which leads to increased susceptibility to infection and they frequently fall ill and experience delayed recovery from infection. A study clearly documented that adult patients with type 1 diabetes have a higher risk of urinary tract, skin and mucous - membrane infections (1).That's why it is important for the health care professional for carefully manage sick days in type1 diabetic patients.

What happens during illness?

Diabetes is affected not only by what you eat and the insulin you take, but also by other hormone s in the body. When a person with diabetes is ill or sick, his/her body is also under metabolic stress. To deal with this stress, body releases stress hormones like cortisol, epinephrine and growth hormone. These hormones counteract the effect of insulin and cause a rise in blood glucose level. These stress hormones trigger something called the 'fight or flight response'. Sickness, infections can cause diabetes to go out of control. During this state there in increase in cytokines increasing gluconeogenesis and cause insulin resistance.

Illness associated with vomiting and diarrhea like gastroenteritis may lower blood glucose and lead to hypoglycemia. Decreased food intake and poor absorption during gastroenteritis cause hypoglycemia.

Common causes of sick days include:

Colds, flu, sore throat, gastroenteritis, diarrhea and urine infections, or more serious illnesses like pneumonia or a foot infection. Extremely high blood glucose levels caused by illness can also lead to life threatening condition called diabetic ketoacidosis in people with type 1 diabetes. Hence controlling diabetes during acute illness is very crucial.

Evaluation of Sick Child with Diabetes:-

- Presence of fever, nausea, vomiting, diarrhea, Abdominal pain- location, severity
- Presence of hyperglycemia / Ketonuria
- Hydration status, able to eat or drink
- Signs of acidosis.

Management of diabetes during illnesses can be more difficult during illnesses that interrupt oral intake.

Special guidelines have been developed to manage diabetes when people with diabetes are sick.

✓ The underlying illness should be treated first

Further, just remember word **SICK** to remember the strategy for sick day management in type 1 diabetes.

S:- IS FOR BLOOD SUGAR TESTING

Blood glucose monitoring is especially important during any sickness. Patients should never stop insulin and oral diabetic medications during sickness although the dose can be modified. Advise patient to check their blood glucose every 2 to 4 hours, depending upon the severity of illness. Frequent blood glucose monitoring facilitates optimal management during illness.

I:- Is for Insulin

The most common mistake made by health care providers and caregivers who are unfamiliar with diabetes is to advise the omission of insulin because the child is ill and not eating and drinking anything, because of poor appetite, nausea and vomiting. This is a wrong approach. The actual dose may be less

Ms. Zankhana Shetty, PG Diploma (Nutrition), Advance Diploma in Nutrition & Dietetics, CDE, Fortis & Oak Hospital, Mumbai. Email Id: **zankhana.doshi@gmail.com**

but some insulin is necessary. Omission of insulin during illness raises the risk of developing DKA. Advise patients to never omit insulin. Infact, during sick days patients need to increase rapid or short acting insulin dose or even need to take an extra injection to reduce blood glucose and to get rid of ketones. Requirement of extra insulin may be needed for a few days, after the illness has passed.

Guidelines for Insulin adjustment

If blood glucose is higher than 240 mg/dl patients need to take extra rapid or short acting insulin. The sick day insulin dose adjustment is based on percentage of Total Daily Dose (TDD). Patients may require frequent doses of short acting or rapid acting insulin, if blood glucose is too high or ketones are present

The sick day adjustment will then be 10 %, 15 % or 20 % of TDD based on blood glucose and ketones level. Follow the below guidelines for sick day insulin adjustment. (Table 1)

For example, If a patient is usually taking regular insulin 12 U at breakfast, 10 U at lunch, 10 U at dinner and long acting 20 U insulin at night.

TDD is 52 Units.

10 % = 5 extra units

15 % = 8 extra units

20 % = 10.5 extra units

C:- IS FOR CARBOHYDRATES AND FLUIDS

If you are dealing with stomach pain, or flu, eating is likely the farthest thing from patients mind. But your body still needs nourishment. The stress of being SICK can raise your blood glucose even, if you are not able to eat or drink anything. Try to keep Carbohydrates intake as normal as possible. Encourage person with diabetes to maintain oral carbohydrate intake to reduce risk of hypoglycemia. Advise patients to take at least 45-50 gms carbohydrate every 3 to4 hours. If the patients are not able to eat normal food replace the normal food with semisolid or liquid fluids.

The food which contain approximately 15 gms of carbohydrates (1 serving)

- ½ cup apple juice
- 1 cup of sports drink
- 1 cup of milk
- 1 slice of toast with jam
- 1 cup of soup
- 1 cup of chicken broth
- 1 soft pudding
- 1 cup of fruit juice

Drinking enough fluids is very important. Patients can lose fluids due to fever or vomiting; diarrhea can cause dehydration and osmotic diuresis. It is very important to remember that because of osmotic diuresis even markedly dehydrated children can progress to more severe dehydration and this can make illness worse.

As rule of thumb patients should drink 1 glass of water every 1 hour. If blood glucose level is less than 180 mg/ dl advise liquid or semisolid food with sugar like green tea, caffeine free tea, soup, broth, milk, non- diet soda.

If patient's blood glucose is above 250 mg/ dl, give sugar free or calorie free liquid such as water, broth, sugar free soda, caffeine free tea, green tea.

K;- K is for KETONES

The presence of ketones in the urine becomes big concern for people with diabetes. Ketones are sign of insulin lack and burning too much of fat for energy. Having large amount of ketones and high blood glucose can lead to DKA. Ketostix is readily available to test ketone / acetone in the urine. This is a very cost effective way to test ketones in the urine. Blood

Table 1

Blood Glucose mg/dl	**>70 - 100**	**100-180**		**180-240**		**>400**
Urine ketones	No / Yes	No	Yes	No	Yes	
Change in rapid or short acting insulin	OMIT	No change	Give extra dose equal to 5% of TDD or 0.05 U / KG	Give extra dose equal to 10% of TDD or 0.05 – 0.1 U/kg	Give extra dose equal to 15% of TDD	Give extra dose equal to 20% of TDD
Changes in NPH/ Long acting	Decrease units by 20%	No change		No Change		No Change

ketones can also be tested on same blood glucose meters, by using a ketone-testing strip.

Test the ketones in the urine every 2 to 4 hours, when blood glucose is above 250 mg/ dl or any sign of illness is present.

Very occasionally patient's blood glucose level may fall during illness. If this is happens and blood glucose is below 60 mg/ dl treat with 15 gms of sugar and some snacks like sandwich and reduce insulin by 2-4 units.

When a patient is advised to call Doctor

- When the patients have been sick or had a fever for 2-3 days
- When patients have moderate to large amounts of ketones
- When patient's blood glucose is consistently higher than 250 mg/ dl despite having taken extra insulin
- When patients have been vomiting or having diarrhea for more than six hours
- When patients having any symptoms of DKA

PREVENTION

It is natural that patients will get sick once in awhile, but patients can keep themselves from getting sick more often. Sick day can be challenging for people with diabetes. Being prepared can make this time **less stressful.**

Some of the points need to remember to avoid or prevent any illness

- Wash your hand frequently, especially after coming into contact with sick people
- Getting yearly flu shot is very important, because having diabetes puts patients at an increased risk for developing complication of the flu, such as pneumonia
- Do regular checkups with health care professional
- Eating well and get enough sleep.

Role of Health care professional and Diabetes Educator

Studies in Germany and Scotland elegantly document the importance of emphasis on teaching sick day rules. Education and preparation is essential for successful sick day management. Education of the person with diabetes, prior to the occurence of a sick day, is essential. This should include the key areas of sick day management along with the preparation of a sick day care plan and a home sick day kit. Sick day education should be provided as part of the education process, after initial diagnosis, and regularly reviewed. Information should be tailored for the individual's situation, history, capacity and capabilities to self manage. Support people should be included in sick day education.

Cases:-

Case 1

In clinic / hospital you have seen a 6 year girl with diabetes with complaint of low grade fever, cold and malaise for 3-4 days. She is not vomiting.

Random blood glucose reading showing blood glucose level above 250 mg/dl for the last 2 days.

She appears mildly ill and a report indicates that she likely has a viral fever.

She is on basal / bolus therapy, 10 units of rapid acting insulin before each meal and 10 units of long acting insulin at night.

Treatment guidelines

Find out when insulin was last given

Check her blood glucose every 2 to 4 hrs and urine ketones when blood glucose is >250 mg/dl

Encourage to take solid food or liquid at least 1 cup in every hour.

Case 2

You are called by the mother of 12 year old boy with Type 1 Diabetes since age of 7 years of age. She reports that he has sore throat, headache and high grade fever (102°F). On his blood glucose meter read HI this morning. She didn't give insulin because he wouldn't eat food.

What do you want to know?

- His usual dose of insulin
- When it was last given
- Any ketones present in the urine?
- Is he able to drink fluids?

Patients takes

- 10 Units of Rapid acting insulin before breakfast and before lunch
- Mixtard 30 / 70 20 U at before dinner

Treatment guideline

Give morning dose of insulin 20 % of total daily dose i.e 4 Units extra

Check his blood glucose every 2 to 4 hours

Check his ketones 2 times /day and more frequently if blood glucose is persistently above 250 mg /dl

Encourage water intake.

Start some medication for sore throat

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Algorithm of Management of type 2 Diabetes

Mayur Patel

Abstract:

Type 2 diabetes mellitus (T2DM) is a global pandemic of our times. Its prevalence is increasing both in developing and developed countries. It is a major cause of cardiovascular morbidity and mortality. Many different therapeutic options are available for T2DM management. Comprehensive and complex guidelines and algorithms from various international bodies are also available, which may confuse a practicing physician. The present review evaluates some commonly used guidelines and algorithms in T2DM management. There are many similarities and differences between these algorithms. Targets of glycemic control have been more relaxed and adjustable to risk factors of individual patients. Strict glycemic control is not expected in all diabetic patients. Metformin, an age old drug still remains first choice due to its safety and cardio-protective effects despite availability of many newer oral anti-diabetic drugs (OADs). Most guidelines suggest use of OADs instead of insulin unless there is symptomatic hyperglycemia. There is increasing use of incretin based therapies in combination with other agents. Knowledge of these algorithms will help physicians to optimize the therapy for T2DM patients. Algorithms based on Indian data is a desirable and expected in the future.

Introduction

Because of the ageing population, and partly due to changes in lifestyle and the resulting epidemic of obesity, there is an increasing percentage of people with type 2 diabetes mellitus (T2DM) in the general population. The current worldwide prevalence is estimated to be approximately 366 million and is expected to reach 552 million by 2030[1]. As per an ICMR study, there were 62.4 million people with diabetes and 77.2 million people with prediabetes in India in 2011.[2] The worldwide costs of diabetes in 2011 were approximately $465 billion and are likely to be $595 billion by 2030.[1]

Many patients with T2DM have a variety of cardiovascular (CV) risk factors, including hypertension, dyslipidemia, and overweight/obesity, that contribute to the development of complications [3]. It is imperative that a comprehensive assessment and treatment plan consider all these comorbidities. Because primary care providers treat the majority of patients with T2DM in developing countries like India, they are faced with complex decisions in the pharmacologic management of these patients and their associated conditions.

Why treatment algorithms are required for management of T2DM?

The development of new classes of blood glucose–lowering medications [incretin based therapies, SGLT 2 (Sodium Glucose Transporter) inhibitors,] to supplement the older therapies, such as lifestyle-directed interventions, insulin, sulfonylureas, and metformin, has increased the number of treatment options available for management of type 2 diabetes. Most of T2DM patients require multi drug therapy including antiplatelets, ACE inhibitors and statins. Whether used alone or in combination with other blood glucose–lowering interventions, the increased number of choices available to practitioners and patients has heightened uncertainty regarding the most appropriate means of treating this widespread disease.[4] Although numerous reviews and practice guidelines on the management of type 2 diabetes have been published in recent years, practitioners are often left without a clear pathway of therapy to follow for their diabetic patients.

Moreover, use of a single guideline may not be optimal for T2DM patients all over the world. In a recent study in Brazil,[5] 90 T2DM patients were treated as per ADA (American Diabetes Association) guidelines for T2DM for one year. No significant improvement was noticed in HbA1c or percentage of patients achieving target HbA1c in spite of use of more than 3 oral antidiabetic drugs (OAD) per patient.

Dr Mayur Patel, MD, Ph.D, MNAMS, FIAMS, Chairman and Chief Diabetologist, All India Institute of Diabetes & Research, Swasthya Diabetes Care, Ahmedabad. Email Id: **mayur@swasthyaindia.com**

This suggests that individualization of treatment as per geographical, racial and cultural differences is required for proper management of T2DM patients.

The purpose of this review is to evaluate current treatment recommendations for the management of patients with T2DM and determine if any recommended treatment algorithms address the patho-physiologic defects underlying T2DM.

Recent guidelines and algorithms for management of type 2 diabetes

1. ADA and EASD (European Association for the Study of Diabetes) consensus statement 2009[6]

This statement was based on the evaluation of the clinical trials and clinical experience and judgment of the writing committee. The choice of specific anti-hyperglycemic agents is predicated on their effectiveness in lowering glucose, extraglycemic effects that may reduce long-term complications, safety profiles, tolerability, ease of use and expense.

According to this consensus statement, HbA1c levels should be < 7.0%, but even lower levels should be sought (in young patients, newly diagnosed T2DM, without any CV complications) if it is possible to do so without the risk of hypoglycemia. The recommendation is that all patients be treated with metformin and lifestyle modifications at diagnosis. Lifestyle interventions to improve glucose, blood pressure, and lipid levels, and to promote weight loss or at least avoid weight gain, should remain an underlying theme throughout the management of type 2 diabetes, even after medications are used. Metformin should be initiated at 500 mg once or twice per day with meals (breakfast, dinner, or both) or 850 mg once per day. If gastrointestinal side effects have not occurred after 5 to 7 days, the dose can be advanced to 850 to 1000 mg twice per day (before breakfast and dinner). If gastrointestinal side effects subsequently occur, the dose should be decreased to 500 mg twice per day. Further attempts to advance the dose can be made at a later time.

If the patient cannot tolerate the drug at any dose, other options should be considered, such as a sulfonylurea, basal insulin, glucagon-like peptide-1 (GLP-1) mimetic, or a dipeptidyl peptidase-4 (DPP-4) inhibitor, which can improve both postprandial blood glucose and fasting blood glucose. If HbA1c remains at 7% or higher after 3 months, the ADA recommends two alternate therapies. These therapy options are listed as Tier 1, the well-validated core therapies, and Tier 2, the less well-validated therapies (Fig. 1).

* Tier 1 treatment continues lifestyle adjustments (including exercise, high fibre diet and food stuffs with lower glycemic index) and metformin and adds a sulfonylurea (except glybenclamide or chlorpropamide) or basal insulin if not at glycemic goal. Both Sulfonylurea and basal insulin are relatively cheap therapies, but have some risk of adverse effects like weight gain and hypoglycemia. Effect of sulfonylureas on cardiovascular outcome is still unclear.
* Tier 2 also continues lifestyle changes and metformin therapy, but it adds a GLP-1 agonist or a thiazolidinedione as add-on therapy. As GLP-1 agonists are very expensive and administered by injection (affecting patient compliance), they are less preferred by the physicians as well as patients specially in the developing countries. Another possible choice can be the addition of a DPP-4 inhibitor. Most patients will eventually need three or four medications to achieve glycemic goals. Potential side effects of Tier 2 therapies are nausea (GLP-1 agonist), edema, increased risk for fractures, and weight gain (thiazolidinedione). Long term pioglitazone therapy may be associated with increased risk of urinary bladder cancer.

Special recommendations are given in this statement for patients presenting with severe hyperglycemia from the beginning. In the setting of severely uncontrolled diabetes with catabolism, defined as fasting plasma glucose levels > 250 mg/dl, random glucose levels consistently > 300 mg/dl, HbA1C > 10%, or the presence of ketonuria, or as symptomatic diabetes with polyuria, polydipsia and weight loss, insulin therapy in combination with lifestyle intervention is the treatment of choice.

2. American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) algorithm 2009 [7]

The AACE and ACE algorithm gives more importance to the clinical safety and efficacy of the treatment as compared to the cost of therapy. They have recommended the choices of medications according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost of medications.

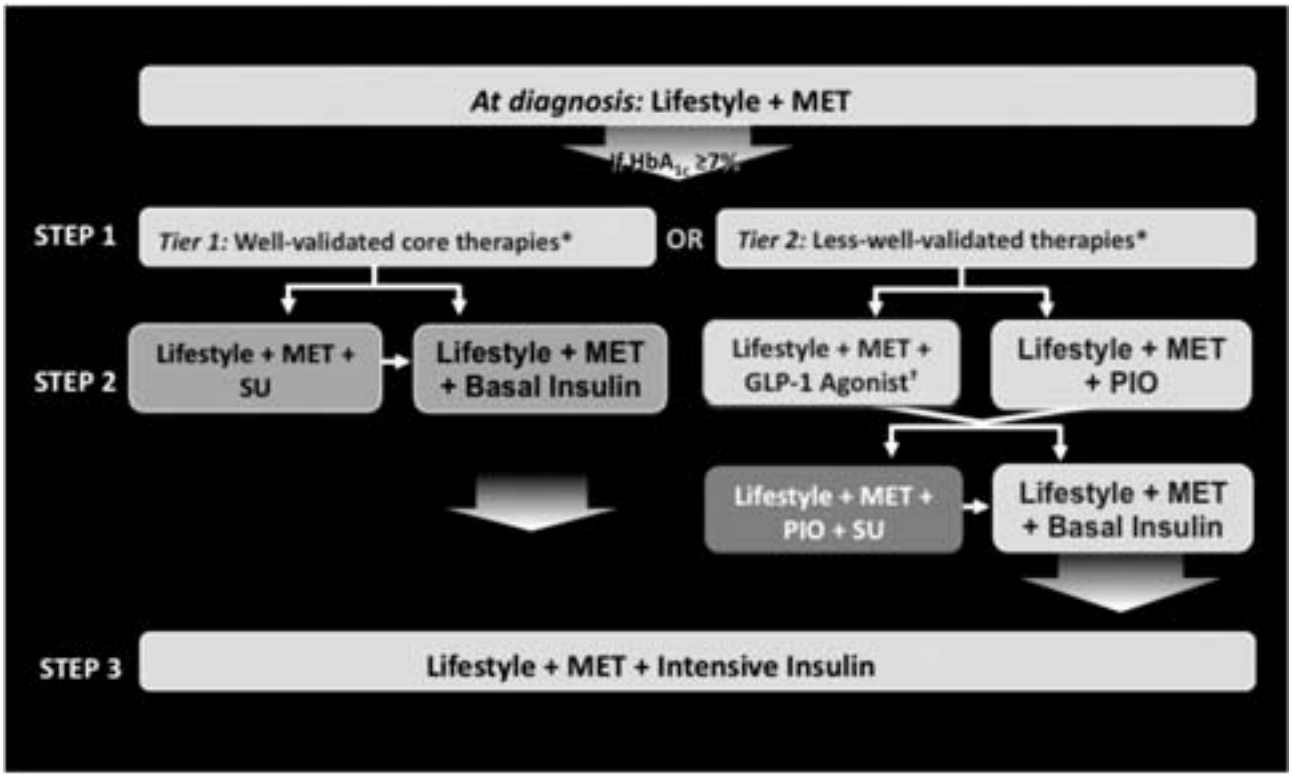

Figure 1: ADA/EASD consensus statement algorithm for medical management of type 2 diabetes. (MET, metformin; PIO, pioglitazone; SU, sulfonylurea)

As per this algorithm, HbA1c goal for type 2 diabetes patients should be < 6.5%. This goal must be customized for the individual patient, with consideration of numerous factors such as co-morbid conditions, duration of diabetes, history of hypoglycemia, hypoglycemia unawareness, patient education, motivation, adherence, age, limited life expectancy, and use of other medications. Lifestyle modification is recommended for all patients. (Figure 2) They recommend the therapy based on baseline HbA1c levels as follows.

* 6.5% to 7.5% – Monotherapy is the first line of therapy. Metformin, TZDs, DPP-4 inhibitors, and a-glucosidase inhibitors (AGIs) are recommended. Metformin is considered most appropriate agent to start monotherapy in the absence of contra-indications. If the HbA1c goal is not achieved safely, dual therapy can be initiated after 2 to 3 months. One of the drugs in dual therapy should be insulin sensitizer (metformin or pioglitazone).
* 7.6% to 9% – Treatment should begin with dual therapy and is followed by triple therapy and insulin during the following 4 to 6 months if HbA1c goals are not met.
* Higher than 9.0% – If the patient is asymptomatic, one might begin with double/ triple drug therapy. 8 different alternatives are suggested:

    1. Metformin + GLP-1 agonist
    2. Metformin + GLP-1 agonist + sulfonylurea
    3. Metformin + DPP-4 inhibitor
    4. Metformin + DPP-4 inhibitor + sulfonylurea
    5. Metformin + TZD
    6. Metformin + TZD + sulfonylurea
    7. Metformin + GLP-1 + TZD
    8. Metformin + DPP-4 inhibitor + TZD

If, however, the patient is symptomatic, or therapy with similar medications has failed, it is appropriate to initiate insulin therapy, either with or without additional orally administered agents.

The basis for therapeutic choice was driven by a tier approach. Tier 1 included well-validated core therapies, such as metformin, sulfonylureas, and basal insulin, and Tier 2 included less well-validated core therapies, such as TZDs and GLP-1 agonists. At the time of publication, there was not enough exposure of DPP-4 inhibitors to place it in this algorithm.

In this algorithm, the initiation of therapy with metformin is recommended unless the patient cannot tolerate the agent because of gastrointestinal problems. If that patient has a HbA1c > 8.5% at baseline, therapy may be initiated with two medications; however, HbA1c levels are unlikely to decrease by 2% without dual therapy unless the patient can make lifestyle changes. HbA1c levels should be monitored in patients with diabetes every 3 to 4 months, and if not improved, therapy should be progressed, as specified in the algorithm.

As per this algorithm, newer insulins like insulin detemir and glargine are recommended over regular and NPH insulin. They have mentioned that rapid-acting insulin analogues are superior to "regular human insulin" and provide a better, safer alternative. Four possible alternatives are described for insulin therapy:

* Long acting basal insulin once daily
* Premixed insulins, using a rapid-acting analogue and protamine usually given twice daily with breakfast and dinner but occasionally used only with the largest meal;
* Basal-bolus insulin or multiple daily injections, using rapid-acting insulin analogues; aspart, lispro, glulisine with a long-acting insulin glargine or detemir;
* A "prandial" regimen, involving rapid-acting insulin analogues, but without a basal or long-acting insulin. This is done if patient is being treated with an insulin sensitizer (metformin) that provides adequate control of fasting plasma glucose.

3. IDF (International Diabetes Federation) guidelines and algorithm for T2DM management 2012[8]

IDF has divided diabetes care in 3 parts:

* **Recommended care:** is evidence-based care which is cost-effective in most nations with a well

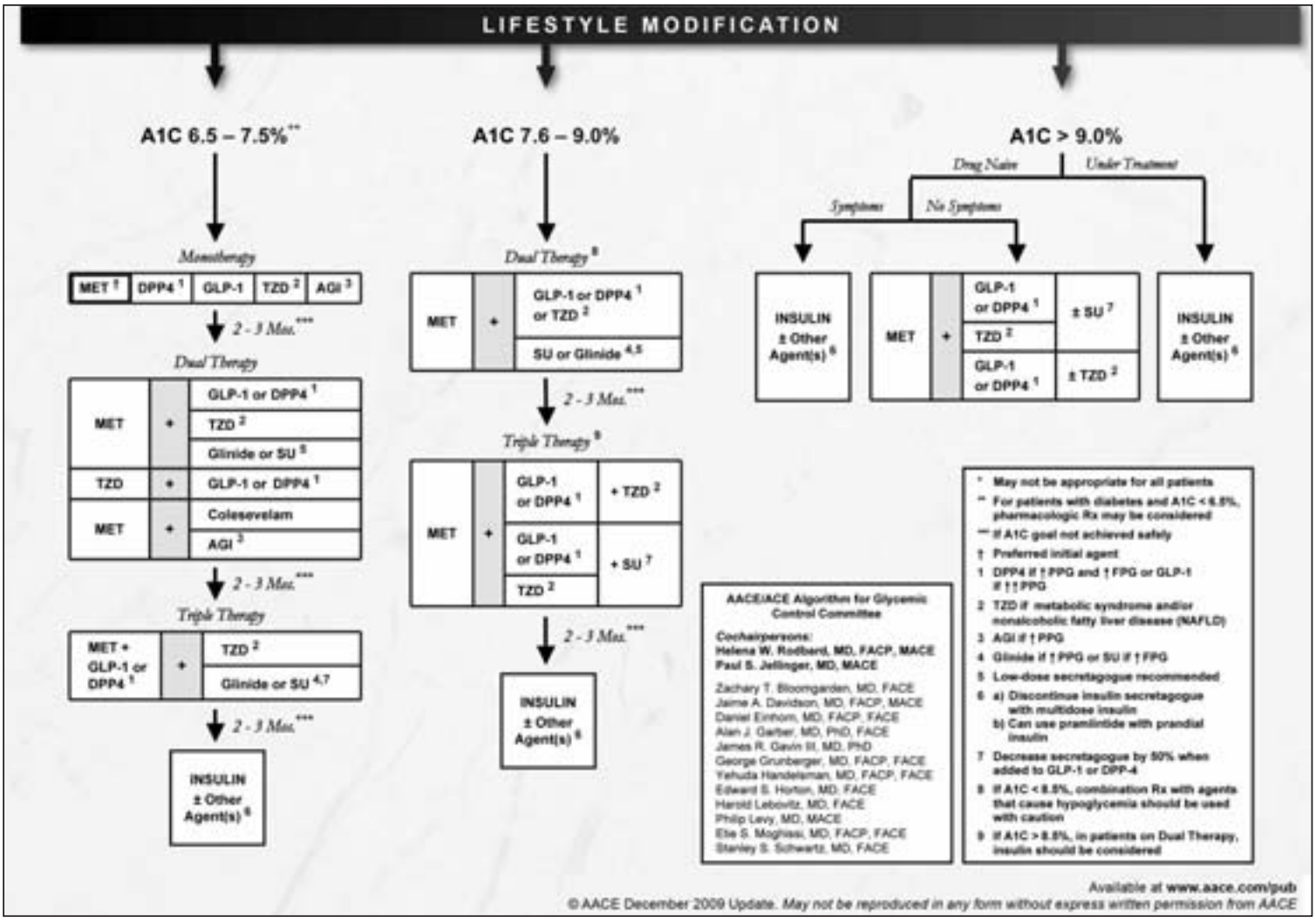

Figure 2: AACE and ACE algorithm for management of T2DM (2009)

developed service base, and with health-care funding systems consuming a significant part of national wealth. Recommended care should be available to all people with diabetes and the aim of any health-care system should be to achieve this level of care. However, in recognition of the considerable variations in resources throughout the world, other levels of care are described which acknowledge low and high resource situations.

* **Limited care** is the lowest level of care that anyone with diabetes should receive. It acknowledges that standard medical resources and fully-trained health professionals are often unavailable in poorly funded health-care systems. Nevertheless this level of care aims to achieve with limited and cost-effective resources a high proportion of what can be achieved by Recommended care. Only low cost or high cost-effectiveness interventions are included at this level.
* **Comprehensive care** includes the most up-to-date and complete range of health technologies that can be offered to people with diabetes, with the aim of achieving best possible outcomes. However the evidence-base supporting the use of some of these expensive or new technologies is relatively weak.

IDF has advised a target HbA1c < 7% for management of T2DM. A higher HbA1c target may be considered for people with co-morbidities or when previous attempts to optimise control have been associated with unacceptable hypoglycemia. An individual's HbA1c target should be regularly reviewed taking into account benefits, safety and tolerability to individual patients. Treatment should be reviewed and modified if HbA1c level is above the agreed target on two consecutive occasions.

IDF has also recommended capillary plasma glucose levels which can be considered equivalent to HbA1c < 7%. So, Fasting plasma glucose target is < 115 mg/dl and post prandial blood glucose target is < 160 mg/dl. They have recommended four lines of management in their treatment algorithm (Fig. 3):

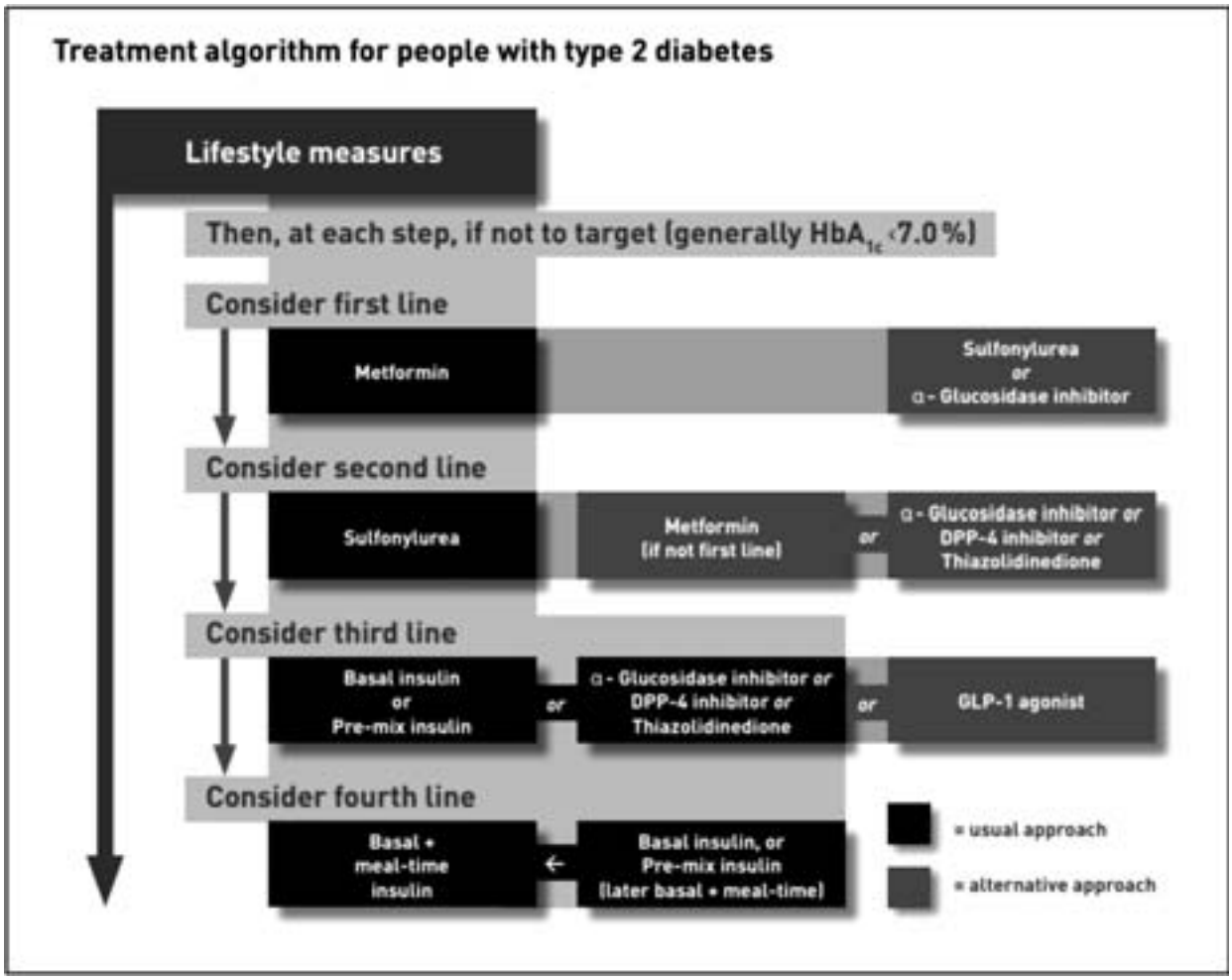

Figure 3: IDF 2012 algorithm for T2DM

1st line therapy: As per other international guidelines, metformin is the 1st line therapy unless there is renal impairment or other contraindication. Monitor renal function carefully during metformin therapy if estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2. Other options include a sulfonylurea (or glinide) or a-glucosidase inhibitors; these agents can also be used initially where metformin cannot.

2nd Line therapy: If glycemic targets are not achieved, add a sulfonylurea. Other options include adding metformin (if not used as first-line, an a-glucosidase inhibitor, a DPP-4 inhibitor or a thiazolidinedione. A rapid-acting insulin secretagogue is an alternative option to sulfonylureas

3rd line therapy: Start insulin or add a third oral agent. If starting insulin, add basal insulin or use premix insulin. If adding a third oral agent options include an alpha glucosidase inhibitor, a DPP-4 inhibitor or a thiazolidinedione. Another option is to add a GLP-1 analogue.

4th line therapy: Begin insulin therapy if OADs cannot achieve glycemic targets. Neutral

Protamine Hagedorn (NPH) insulin, insulin glargine or insulin determir can be used to begin insulin therapy. Intensify insulin therapy, if already using insulin

Participation of patient for decision making for the therapy selection and patient education for the glycemic control is also stressed in IDF guidelines. Self-monitoring of blood glucose (SMBG) is recommended for patients who have the knowledge, skills and willingness to actively adjust treatment, enhance understanding of diabetes and assess the effectiveness of the management plan on glycaemic control. SMBG is specially more important for patients using insulin therapy.

4. ADA/EASD 2012 position statement for management of hyperglycemia in T2DM[9]

In their most recent recommendations, ADA and EASD has realized need of patient centered approach for the management of T2DM. So, glycemic targets and drug therapy should be variable according to individual patients. Moreover, there should be greater active involvement of patient for decision making for selecting a particular therapy

Following criteria are used to decide T2 DM therapy:

* Efficacy for blood glucose lowering,
* Risk of hypoglycemia,
* Effect on body weight,
* Other adverse events and
* Cost of therapy

Stringent HbA1c levels (6-6.5%) can be targeted for young, newly diagnosed, highly motivated patients without other cardiovascular risk factors if this can be achieved without significant hypoglycemia or other adverse effects of treatment (Figure 4).

Less stringent HbA1c goals e.g., 7.5–8.0% or slightly higher are appropriate for patients with history of severe hypoglycemia, limited life expectancy, advanced complications, extensive co-morbid conditions and those in whom the target is difficult to attain despite effective doses of multiple glucose-lowering agents, including insulin.

As per this statement, in most patients; begin with lifestyle changes (healthy eating practices, weight control and minimum 150 min exercise/week), metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the HbA1c target is not achieved after around 3 months, consider one of the five treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin.

Patients with a high baseline HbA1c (e.g., > 9.0%) have a low probability of achieving a near normal target with monotherapy. It may therefore be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations (e.g. >300–350 mg/dL) or HbA1c (e.g., 10.0–12.0%), insulin therapy should be strongly considered from the outset. Such treatment is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.

Some other drugs not mentioned in algorithm (a-glucosidase inhibitors, colesevelam, dopamine agonists, pramlintide) may be used in selected patients, but have modest efficacy and/or limiting side effects (Fig. 5).

Summary

There are visible similarities and differences between the international guidelines and therapy algorithms for diabetes management. All recommend lifestyle changes as cornerstone of management in every

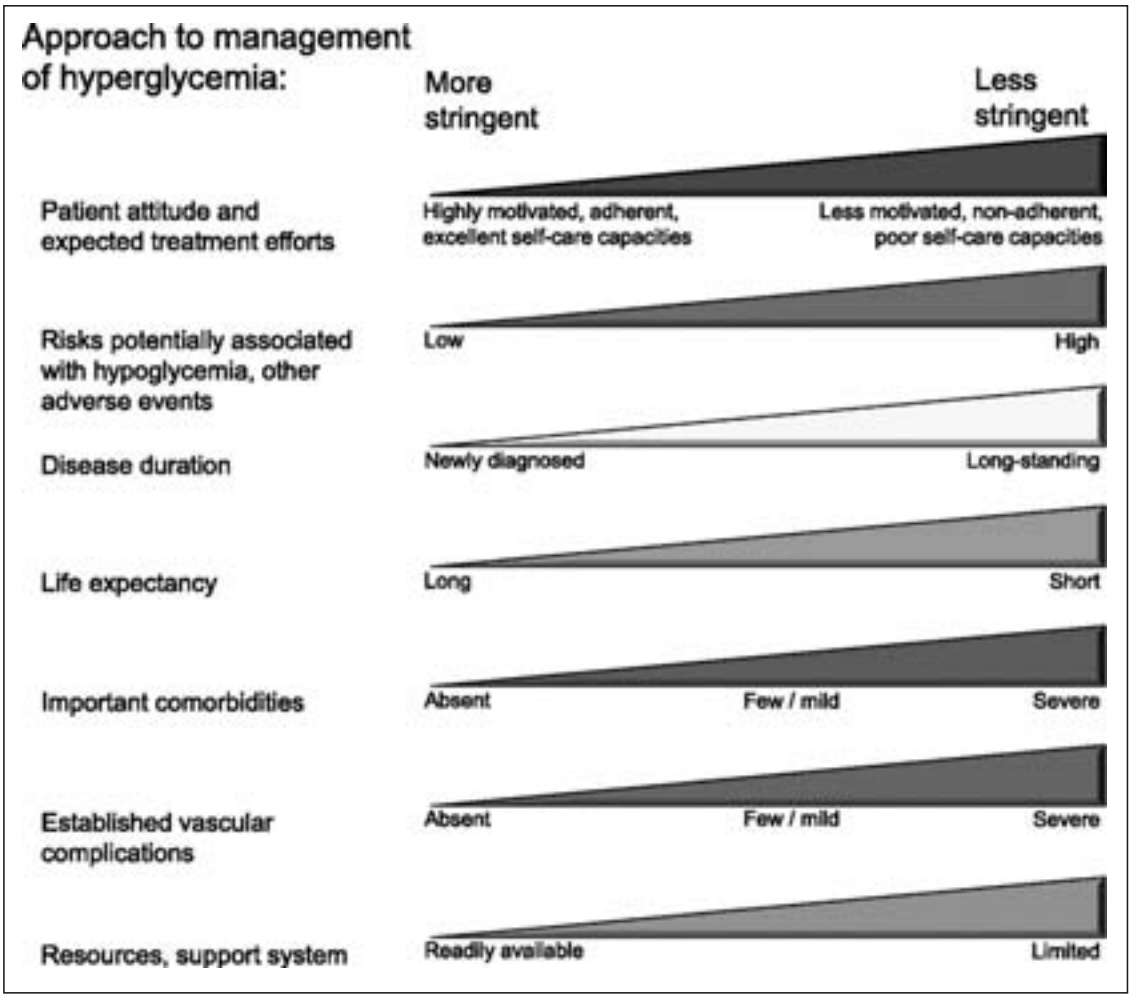

Figure 4: Factors affecting individual target for glycemic control

Source: Inzucchi SE, Bergenstal RM, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the study of Diabetes (EASD). Diabetes Care 2012;35:1364-79.

diabetic patient. Due to its safety and efficacy to reduce cardiovascular complications [10], metformin remains the first choice for T2DM management. AACE has recommended TZDs, AGIs and DPP-IV inhibitors as possible alternatives for monotherapy. AACE has recommended glycemic management based on initial HbA1c levels. Double/triple drug therapies are used based on their efficacy, safety and convenience to the patient. Insulin should be added when oral agents cannot achieve glycemic control even in combinations. For patients presenting with symptomatic hyperglycemia, insulin can be used from beginning to achieve faster glycemic control.

Lately, there is increasing emphasis to involve patient in selection of drug therapy and SMBG. Fixed HbA1c goals are outdated and most guidelines recommend flexible glycemic goal depending on individual patient characteristics. IDF has also recommended capillary glucose levels which can be considered equivalent to HbA1c targets.

We can expect that with availability of all these algorithms, a physician will be more comfortable to select a particular therapy for his T2DM patients. Still, we require Indian guidelines and algorithms based on Indian data.

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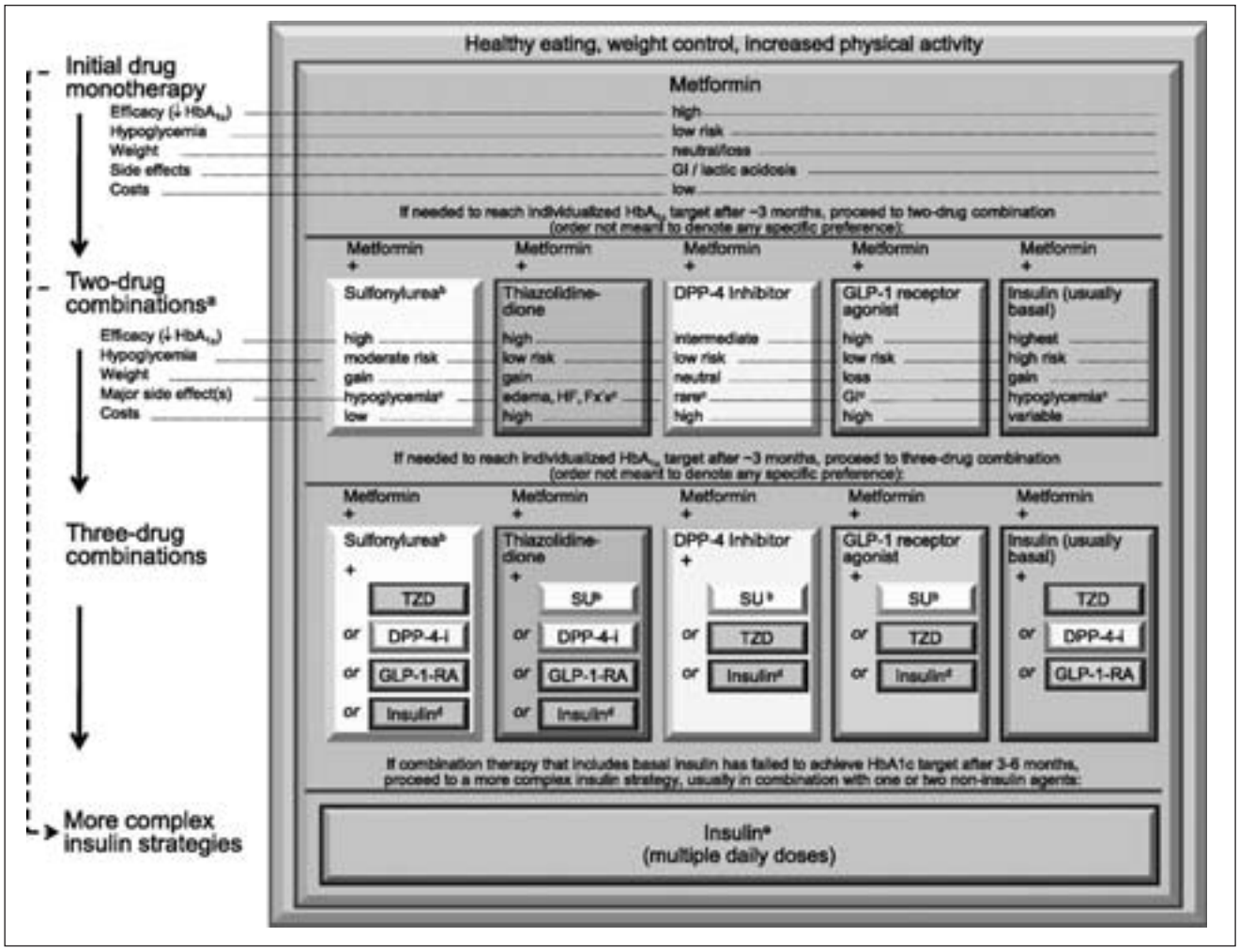

Figure 5: ADA/EASD algorithm for management of hyperglycemia in T2DM

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Insulin Injection Technique

Paulami Choudhury

Introduction:

Insulin is used in the treatment of patients with diabetes of all types. Insulin is necessary for normal carbohydrate, protein, and fat metabolism. The need for insulin depends upon the balance between insulin secretion and insulin resistance. All patients with type 1 diabetes need insulin treatment permanently, unless they receive an islet or whole organ pancreas transplant; many patients with type 2 diabetes will require insulin as their beta cell function declines over time.

An insulin regimen is often required in the treatment of gestational diabetes.

This paper addresses issues regarding the use of conventional insulin administration (i.e., via syringe or pen with needle and cartridge) in the self-care of the individual with diabetes.

Insulin

Insulin used to be obtained from pork pancreas but present, most insulin is made chemically identical to human insulin by recombinant DNA technology. Insulin analogs have been developed by modifying the amino acid sequence of the insulin molecule.

Insulin is available in rapid-, short-, intermediate-, and long-acting types that may be injected separately or mixed in the same syringe.

Storage

1. Insulin should not be frozen. (Frozen insulin should be thrown away.)
2. Never use insulin beyond the expiration date stamped on the vial, pen, or cartridge that is supplied from the drug manufacturer.
3. Never expose insulin to direct heat or light.
4. Inspect insulin prior to each use. Any insulin that has clumps or solid white particles should not be used. Insulin that is supposed to be clear should not have any cloudy appearance.
5. Check storage guidelines specific to the insulin formulation. This is usually in the product package insert.
6. Unopened, not-in-use insulin should be stored in a refrigerator at a temperature of 2 – 8°C.
7. Opened, in-use insulin should be stored at room temperature below 30°C.
8. Opened vials can be used for maximum 28 days & as per the instruction from manufacturer.
9. Insulin pen to be stored in the room temperature at 25 – 30°C.
10. Avoid keeping insulin pen with needle in the fridge.

Mixing insulins

Administration of mixtures of rapid- or short- and intermediate- or long-acting insulin will produce an improved control in some patients than use of single insulin. Therefore, mixing of insulin is often required. In order to mix insulins, follow these guidelines:

1. Patients who are well controlled on a particular mixed-insulin regimen should maintain their standard procedure for preparing their insulin doses.
2. No other medication or diluents should be mixed with any insulin product unless approved by the prescribing physician.
3. Insulin glargine should not be mixed with other forms of insulin due to its low pH.
4. When rapid-acting insulin is mixed with either an intermediate- or long-acting insulin, the mixture should be injected within 15 min before a meal.
5. Phosphate-buffered insulins (e.g., NPH insulin) should not be mixed with lente insulins. Zinc phosphate may precipitate, and the longer-acting insulin will convert to a short-acting insulin to an unpredictable extent.
6. Insulin formulations may change; therefore, the manufacturer should be consulted in cases where its recommendations appear to conflict with the guidelines.

Ms. Paulami Choudhury, BSc (Nursing), CDE, PG Diploma (Hospital & Health Care Management), Kolkata. Email Id: **pou@rediffmail.com**

Syringes

U-40

U-100

A U-100 insulin has 100 units of active insulin in each mL of liquid.

A U-40 insulin has 40 units of insulin in each milliliter (mL) of liquid.

This means that the same volume (liquid amount) of a U-100 insulin has 2.5 times more insulin in it than a U-40 insulin. Or, the U-100 insulin is 2.5 times stronger than the U-40 insulin.

It is extremely important that

U-40 insulin is administered in U – 40 syringe

U-100 insulin is administered in U – 100 syringe

Disposal

Regulations in some states require the destruction of used insulin syringes and needles after burning it. Recapping, bending, or breaking a needle increases the risk of needle-stick injury. Unless the syringe will be reused, it should be placed in a puncture-resistant disposal container or needle-clipping device, which retains the clipped needle in an inaccessible compartment

Needle reuse

Manufacturers of disposable syringes and pen needle is recommend that they only be used once. As per the FIT guidelines also reusing needles to be avoided. One potential issue, which arises with the reuse of syringes or needles, is the inability to guarantee sterility. Most insulin preparations have bacteriostatic additives that inhibit growth of bacteria commonly found on the skin.. Patients with poor personal hygiene, an acute concurrent illness, open wounds on the hands, or decreased resistance to infection for any reason should not reuse a syringe or pen needle.

Another issue has arisen with the advent of newer, smaller (31 and 32 gauge, 4mm length) needles. Even with one injection, the needle tip can become bent to form a hook which can lacerate tissue or break off to leave needle fragments within the skin. The medical consequences of these findings are unknown but may increase lipodystrophy or have other adverse effects.

Some patients find it practical to reuse needles. Certainly, a needle should be discarded if it is noticeably dull or deformed or if it has come into contact with any surface other than skin. If needle reuse is planned, the needle must be recapped after each use. Patients reusing needles should inspect injection sites for redness or swelling and should consult their healthcare provider before initiating the practice especially if signs of skin inflammation are detected.

Before syringe reuse is considered, it should be determined that the patient is capable of safely recapping a syringe. Proper recapping requires adequate vision, manual dexterity, and no obvious tremor. The patient should be instructed in a recapping technique that supports the syringe in the hand and replaces the cap with a straight motion of the thumb and forefinger. The technique of guiding both the needle and cap to meet in midair should be discouraged, because this frequently results in needle-stick injury.

Cleansing the needle with alcohol should not be done, because it may remove the silicon coating that makes. The process of injection smooth and virtually painless.

Injection procedures

"Appropriate injection technique is thus an indispensable part of diabetes management. The FIT (Forum for Injection Techniques) India guidelines have been developed based on these facts. (see www.fit4diabetes.com/India) for detailed guidelines.

Insulin injection recommendations:

Needle length

For children and adolescents, a 4 mm needle should be used.

Adults, including obese patients, can use 4, 5, and 6 mm needle length.

In general, 4mm needle length is sufficient for all people. When needle is short, pricking the skin or pricking up a skin fold is not required.

Site rotation

An easy-to-follow rotation scheme should be taught to the patients from the onset of injection therapy.

Lipohypertrophy

Injection sites should be inspected at every visit. Patients should be taught to inspect their own sites and should also be given training on how to detect lipohypertrophy.

The best current strategies to prevent and treat lipohypertrophy are to rotate the injection sites with each injection, using larger injecting zones and non-reuse of needles.

Safety issues

Safety needles should be recommended whenever there is a risk for a contaminated needle-stick injury.

Several factors, including the method of administration, dosing, compliance, selection of injection site, depth of the injection, time lapse before withdrawing the needle and misconceptions about insulin therapy, influence the success of insulin injection therapy

Injections are given into the subcutaneous tissue. Most individuals are able to lightly grasp a fold of skin and inject at a 90° angle. Thin individuals or children can use short needles or may need to pinch the skin and inject at a 45° angle to avoid intramuscular injection, especially in the thigh area.

Steps :

1. Syringe & Vial Preparation

   Get Supplies

   – Insulin (Verify)
   – Syringe
   – Alcohol wipe
   – Disposable gloves
   – Sharps container
2. Wash hands; apply gloves
3. Clean the insulin vial
4. Select injection site.
5. Check the insulin dose
6. Remove the cap from syringe.
7. Pull the plunger down to number of units to be administered.
8. Inject air into bottle.
9. Draw out prescribed number of units of insulin .
10. Pinch up the skin.
11. Push needle into skin at 90°.
12. Release pinch.
13. Push the plunger in.
14. Count to “10”.
15. Dispose of syringe.

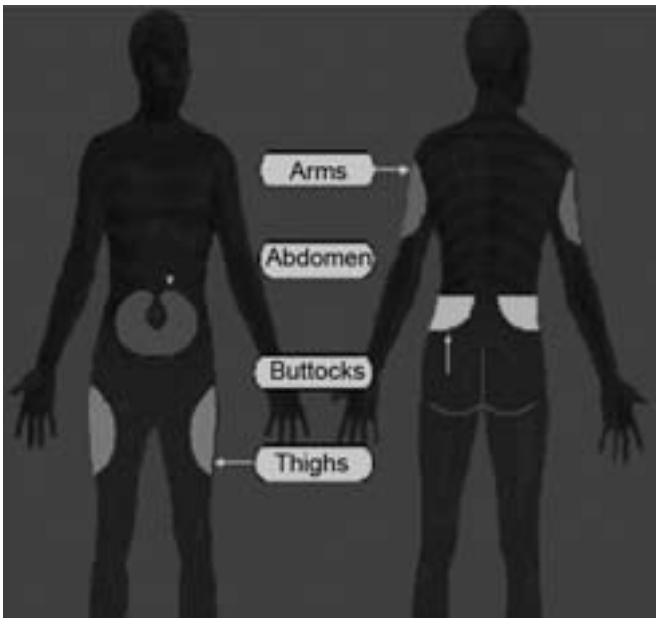
Painful injections may be minimized by the following:

1. Injecting insulin at room temperature.
2. Using needles of shorter length & smaller diameter.
3. Insert the needle in quick smooth movement.
4. Making sure no air bubbles remain in the syringe before injection.
5. Keeping muscles in the injection area relaxed, not tense, when injecting.
6. Penetrating the skin quickly.
7. Not changing direction of the needle during insertion or withdrawal.
8. Not reusing needles.

Injection site

Injection should be given at a clean site with clean hands.

Prior to the injection, the site has to be palpated for lipohypertrophy and inspected for wounds, bruises, or blisters. If the injection site shows any signs of these, then a different site should be selected until the problem has been resolved.



Insulin may be injected into the subcutaneous tissue of the upper arm and the anterior and lateral aspects of the thigh, buttocks, and abdomen (with the exception of a circle with a 2-inch radius around the navel). Rotation of the injection site is important to prevent lipohypertrophy or lipoatrophy. Rotating within one area is recommended (e.g., rotating injections systematically within the abdomen) rather than rotating to a different area with each injection. This practice may decrease variability in absorption from day to day. Site selection should take into consideration the variable absorption between sites. The abdomen has the fastest rate of absorption, followed by the arms, thighs, and buttocks. Exercise increases the rate of absorption from injection sites, probably by increasing blood flow to the skin and perhaps also by local actions. Areas of lipohypertrophy usually show slower absorption. The rate of absorption also differs between subcutaneous and intramuscular sites. The latter is faster and, although not recommended for routine use, can be given under other circumstances (e.g., diabetic ketoacidosis or dehydration).

Other considerations

Mostly insulin should be self-administered by the patient. In the case of children, the proper age for initiating this depends on the individual developmental level of the child as well as family and social circumstances. Usually, 8 year old child can be trained to self inject insulin.

Syringe alternatives

An insulin pen is used to inject insulin for the treatment of diabetes. It is composed of an insulin cartridge (integrated or bought separately) and a dial to measure the dose, and is used with disposable pen needles to deliver the dose

There are two pen systems: durable (re-usable) and prefilled:

- A durable pen uses a replaceable insulin cartridge. When the insulin cartridge is empty, it is disposed off and a new one is inserted in the pen.
- A prefilled pen is entirely disposable. The pen comes pre-filled with insulin, and when the insulin cartridge or reservoir is empty, the entire unit is discarded.

Global Patient Uptake

Insulin pens are used by 95% of insulin-treated patients in Europe, Asia, with excellent results.

Insulin pens offer several significant advantages over insulin syringes, mainly of handling and accuracy. They are more discreet to use.

To use an insulin pen

- Screw or click on a new pen needle
- Prime the pen to remove any air from the needle
- Turn the knob on the end of the pen (or "dial") to the number of units needed
- Insert the needle into the skin
- Press the button on the end of the pen to deliver the dose
- Count to ten
- Remove.

Advantages

Insulin pens have a number of advantages:

- More convenient and easier to transport than traditional vial and syringe
- More accurate dosages

- Less injection pain (as polished and coated needles are not dulled by insertion into a vial of insulin before a second insertion into the skin)

Disadvantages

Unlike with the traditional syringe two different insulins cannot be mixed by the user in an insulin pen. On the other hand, some of the newest types of insulin. (e.g. Glargine). cannot be mixed at all. In addition, using pens and pen needles is usually more expensive than using the traditional vial and syringe method;.

Patients should be aware that air bubbles in an insulin pen can reduce the rate of insulin flow from the pen; inadequate delivery of insulin can occur when air bubbles are present, even if the needle remains under the skin for as long as 10 seconds after depressing the plunger. Air can enter the insulin pen reservoir during either manufacture or filling especially if the needle is left on the pen between injections. To prevent this potential problem, avoid leaving a needle on a pen between injections and prime the needle with 2 units of insulin before injection.

Patient Management

Self-monitoring

Whenever possible, insulin-using patients should practice self-monitoring of blood glucose (SMBG). Insulin dosage adjustments should be based on blood glucose measurements. SMBG is extremely valuable in patients who take insulin because they experience day-to-day variability in blood glucose levels. This variability is influenced by differences in insulin absorption rates, insulin sensitivity, exercise, stress, rates of food absorption, and hormonal changes (e.g., puberty, the menstrual cycle, menopause, and pregnancy). Illness, traveling, and any change in routine (e.g., increased exercise and a different diet during vacation) may require more frequent SMBG under the guidance of a physician. Travel through three or more time zones requires special advice regarding insulin administration. During illness, it is important that insulin be continued even if the patient is unable to eat or is vomiting. When accompanied by hyperglycemia, a positive urine or blood test for ketones during illness indicates a need for extra, not less, insulin. Health professionals should obtain information regarding blood glucose values whenever patients need assistance in handling illness or stress.

SUMMARY

The injection of insulin is essential for management of patients with type 1 diabetes and may be needed by patients with type 2 diabetes for intermittent or continuous glycemic control. The species and dosage of insulin used should be consistent, and the patient's injection technique should be reviewed periodically with the diabetes care team. The effective use of insulin to obtain the best metabolic control requires an understanding of the duration of action of the various types of insulin and the relationship of blood glucose levels to exercise, food intake, intercurrent illness, certain medications, and stress; SMBG; and learning to adjust insulin dosage to achieve the individualized target goals established between the patient, family, and diabetes care team.

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Artificial Sweeteners

Sonal Modi

The sensory properties of food highly influence the selection and consumption of food in man. Taste, smell, texture and appearance of the food plays a crucial role in the regulation of human appetite and nutrient intake. When a wide variety of food is offered, food intake increases, thus adding to an increase in energy intake. The perception of taste is extremely important in determining appetite regulation. There are four primary taste sensations. They are sour, salty, bitter and sweet. Physiologically, the tip of the tongue is highly sensitive to sweet and salty substances. It has been also studied that the T1r3 gene is linked with sweet tasting ability. Thus the ability for sweet taste varies genetically. As a result, there are varying levels at which the perception of sweet taste occurs in different individuals and in certain diseases.

A person with diabetes would not like to miss this sweet taste and cut out twenty-five percent of his eating pleasure. The main problem that a person with diabetes faces is an increase in the threshold level of sweetness compared to non-diabetics. Therefore a person with diabetes needs sweeter food than a person without diabetes to appreciate the same taste. This is supported by certain studies done in the past decade. One such study showed that the perception of sweet taste is significantly impaired in patients with type 2 diabetes but not in those with type 1 diabetes. This evidence is corroborated by the fact that there is a raised threshold level for blood glucose sensing in the beta cells of the pancreas. The villain of the piece is sucrose. Sucrose or 'cane sugar' is the direct table sugar that one uses daily. It is a disaccharide made up of glucose and fructose and it provides four calories per gram. Hence, sweeteners are very important as they provide fewer calories than sugar. A sweetener is a food additive which duplicates the effect of sugar on taste. Therefore they are also called 'sugar substitutes'. There are two types of sweeteners, nutritive and non- nutritive.

NUTRITIVE SWEETENERS

The nutritive sweeteners provide same or fewer calories than sugar. Examples are fructose; maltose; lactose; honey; polyols like sorbitol, xylitol, lactitol, mannitol, erythritol, isomalt, maltodextrin, polydextrose, hydrogenated starch hydrolysate.

Fructose

It is a monosaccharide component of sucrose present in fruits as fruit sugar (laevulose). It is used in beverages, fruit juices, pulps. It provides similar amount of energy as sucrose. Fructose is termed a 'slow sugar' as it is metabolized slower than sucrose. In a well-controlled diabetic, the fructose metabolic pathway demonstrates a positive flux towards formation of glycogen from fructose i.e. glycogenesis. Further the breakdown of glycogen to glucose i.e. glycogenolysis occurs as and when required in a slow and steady pace.

On the other hand, in an uncontrolled diabetic glycogenesis occurs at the same pace, but glycogenolysis occurs rapidly. This causes a brisk rise in the blood glucose levels in these patients. In either case the metabolism of fructose is slower than that of sucrose. The utilization of fructose follows an insulin independent p a thway . Fructose is metabolized even in the absence of insulin which is important in a diabetic. Hence, it causes an overall slower rise in blood glucose levels than glucose. An increased intake of fructose may cause hypertriglyceridemia, especially in patients with uncontrolled diabetes. Consumption of fructose up to 50 – 60 gm per day is seen to have no adverse effect on bloodglucose, glycosylated hemoglobin and serum lipids. The recommendation of 2 to 3 servings of fruit per day holds good in a well-controlled diabetic.

Polyols

These are alcohol derivatives of sugar and provide fewer calories than sucrose. It is synthesized from

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Ms. Sonal Modi, Chief Nutritionist & Diabetes Educator, Dr. Chandalia's Diabetes Endocrine Nutrition Management and Research Centre (DENMARC), Mumbai. Email Id: **modisonalv@hotmail.com**

dextrose on a commercial scale. Polyols are stable up to 160°C. They are absorbed by passive diffusion and metabolized slowly. They produce a low glycemic response. Intake of large amounts of polyols exerts a laxative effect causing abdominal cramps and diarrhea. Erythritol has the best tolerance level among all Polyols. Polyols also prevent dental caries when used a substitute for sugar in different products. It is popularly used a bulking agent in the food industry to improve the taste, mouth-feel and texture of the food.

NON-NUTRITIVE SWEETENERS

These provide negligible calories. They are also known as high-intensity sweeteners as they are required in minute quantities to provide the same sweetness as sugar. Examples are saccharin, aspartame, sucralose, acesulfame-K, stevioside, cyclamate.

Saccharin

It is one the oldest non-nutritive sweeteners. It is over 125 years old and has had a history with great vicissitudes. It was banned in 1977 as it was incriminated in the causation of bladder cancer in rats. This ban was revoked in 1991 after much review and scrutiny . Till late, a warning label was required for products containing saccharin. It has been recently removed from the carcinogen list. It is a sulfonamide produced from a compound found in coal tar. It has a bitter, metallic aftertaste and is unstable at high temperatures. It may cause urticaria and eczema in some people. Intake of saccharin is restricted in pregnant women as it is avidly concentrated in the placenta. In India, it is widely used in the cosmetic, pharmaceutical, food and beverage industry.

Aspartame

Aspartame is one sweetener that many people love to hate. It has been one of the most controversial sweeteners till date. Aspartame is extensively used all over the globe and is slowly replacing saccharin in India too. It is a high intensity sweetener dipeptide in nature. It is made up of two amino acids, aspartic acid and methyl ester of phenylalanine. It is unstable at high temperatures and is added in the end-cycle of cooking. The specific byproducts of aspartame i.e. methanol, formaldehyde and phenylalanine have been studied individually. They are said to cause an array of side-effects, including allergic reactions in some people. It has also been linked to neuropsychiatric disorders like migrainous headaches in sensitive individuals, panic attacks, mood changes, epileptic seizures. People who are sensitive to monosodium glutamate may also experience side effects with aspartame. All this data is a lot of hype and jargon from deterrents of aspartame and do not hold much ground. It is a known fact that amino acids and methyl esters are found naturally in foods like milk, meat, fruits and vegetables. When digested the body handles the amino acids in aspartame in the same manner as those in our daily food. eg an 8 oz glass of milk has six times more phenylalanine and thirteen times more aspartic acid than an equivalent amount of soda sweetened with aspartame sweetener. An 8 oz glass of tomato juice or fruit juice contains 3 to 5 times more methanol than an equivalent amount of soda sweetened by aspartame sweetener. This dispels this misconception. Hence, aspartame is relatively safe to use.

Acesulfame-K

It is a high intensity sweetener which is a potassium salt of dimethyl-oxathiozine dioxide in nature. It is not metabolized and excreted unchanged in the body. It can withstand high temperature cooking and baking. Acesulfame-K has a grittier texture than direct sugar but it has a slight bitter aftertaste. This sweetener needs long-term study from the carcinogenicity and genotoxicity angle to confirm its safety. Caution is required in individuals on potassium restricted diet or having sulfa antibiotic based allergy. Abroad, it is being used increasingly along with aspartame in many foods and beverages and is second in popularity to aspartame.

Sucralose

Sucralose is an extremely versatile and interesting high intensity sweetener. It is simply a modification of the sucrose molecule ie. a chlorinated version known as trichlorogalactosucrose. It is not absorbed and gets excreted unchanged in the body. Sucralose retains its sweetness over wide range of temperatures. It does not cause any rise in blood glucose levels. It goes by the brand name Splenda abroad. It has recently been marketed in India under the brand name Sugar free Natura and Sweet ‘n’ Healthy. There have been some reports on the side-effects and adverse reactions of sucralose, e.g. it causes shrinkage of the thymus gland, enlargement of the liver and kidney. A theoretical possibility always

exists, but for all practical purposes these side effects are inconsequential .

NEWER ARTIFICIAL SWEETENERS

Alitame and Neotame

These non-nutritive sweeteners are awaiting approval from the FDA. They are structurally similar to aspartame. Alitame is 2,000 times sweeter than sucrose whereas neotame is 8,000 times sweeter than sucrose. Both are already in use in beverages and soy-based, nutritionally fortified products, respectively. Their carcinogenicity and reproductive toxicity reports are yet to be scrutinized.

Fructofibres

Fructofibres are essentially fructanes or fructo-oligosaccharides. They contain inulin and oligo-fructose both of which are inert polysaccharides. It goes through unabsorbed in the body. Fructofibres provide added benefit as it gives the bulk to the diet and help prevent constipation. It lowers blood glucose levels and serum lipids. These effects exerted by fructofibres may be insignificant as they are used in very small quantities in sweeteners.

Stevioside

Stevia rebaudiana is a naturally, sweet herbal plant native to South America, mainly Paraguay and Brazil. The leaf extract has the main constituents comprising of glycosides, namely, stevioside and rebaudiside. These glycosides are not metabolized and pass out unabsorbed from the body. It is heat stable up to

200° c. It can be used in cooking, baking and frying. It has shown no teratogenic, carcinogenic activity in rats. It is approved as a 'dietary supplement by the FDA. It is used widely in the South Americas and the Orient. It is popular in Japan, China and Korea and has been used there for more than three decades. It is marketed in India by the brand name 'Stugar'.

OTHER PROPERTIES OF ARTIFICIAL SWEETENERS

It is also important to look into the other properties of artificial sweeteners as a group. A comparison of the degree of sweetness is crucial to know in order to use them more efficiently. The nutritive sweeteners are only marginally sweeter than sucrose. Whereas the non-nutritive sweeteners are more than hundred folds sweeter than sucrose. Hence, they are called high intensity sweeteners as very minute quantities are required to manifest the same level of sweetness.

The commercial availability of sweeteners is of practical importance. In India, aspartame and saccharin are widely used. Aspartame is available in tablet as well as powder form in sachets. The tablet provides 18 mg of aspartame and is equivalent to one teaspoon of sugar. The sachet contains 35 mg of aspartame and is equivalent to two teaspoons of sugar. Saccharin is available in tablet form and contains 12 mg per sachet. It is equivalent to two teaspoons of sugar.

The artificial sweeteners have to be classified according to the concept of safety levels. Generally, they are designated as food additives which are expressed as accepted daily intake (ADI). This reflects an amount hundred times less than the maximum level at which observed adverse effects occur in animal or human studies. Accepted daily intake is usually expressed as mg per kg body weight per day.

High intensity sweeteners e.g. saccharin, aspartame, acesulfame-K, sucralose are usually promoted a s food additives .Other nutritive sweeteners are usually classified as generally recognized as safe substances (GRAS) substances. Stevioside is approved by FDA as a 'dietary supplement'.

The side-effects and contraindications of the artificial sweeteners have to be looked into to determine their use. Large amounts of fructose when ingested may cause hyperglycemia and have a laxative effect (70 to 100 gm /day). Large amounts of sorbitol (30 to 50 gm/day) may also result in diarrhea. Consumption of more than 15 to 30 gms/ day of honey may cause hyperglycemia due to its glucose content. Apsartame has been implicated in causing migrainous headaches. It is not recommended for growing children, phenylketonuric children and pregnant women with hyperphenylalaninemia. The blood–brain barrier in children is not fully developed and both the amino acids contained in aspartame are easily absorbed across this border. Thus elevated levels of these substances which seemingly act as a neurotransmitter alters the behavior pattern in children. Phenylketonuria is a genetically transmitted disease. In this condition, an enzyme called phenylalanine hydroxylase is dysfunctional thus resulting in accumulation of phenylalanine. A high level of this amino acid is neurotoxic to the individual. Hence,in pregnant women with

hyperphenylalaninemia, aspartame is restricted as the mother may not be able to metabolize phenylalanine which is toxic to the fetus. The warning of restriction of aspartame in pregnancy was present earlier, but has now been revoked. Therefore, use of aspartame in pregnancy is allowed (about 20 mg/ kg body weight /day). This should still be used with caution. Saccharin is restricted in pregnancy as it is avidly concentrated by the placenta. Sucralose does not seem to show any specific side effects and is considered relatively safe in all conditions and across all age groups.

COMMERCIAL USE OF ARTIFICIAL SWEETENERS

Artificial sweeteners are used widely in various industries. They are used as tabletop sweeteners, in the food industry in baked goods, confections, convenience foods, diet foods. They are used extensively in the beverage industry in both hot and cold beverages. Other than these, artificial sweeteners have created their own niche in other consumer products such as the cosmetic industry, pharmaceutical industry. Presently, the trend is to blend high intensity sweeteners so as to increase their potency.

Fructose and other non-nutritive sweeteners like saccharin, aspartame, sucralose, acesulfame-K, stevioside are used as tabletop sweeteners. Sorbitol, sucralose, acesulfame-K are used in baked products as they can withstand high temperature cooking.

Confections, candy, lozenges and chewing gum mainly contain polyols like sorbitol, xylitol, lactitol and erythritol. They may also use sucralose as a sweetening agent. Saccharin and aspartame are mainly used in cold beverages, as they cannot withstand high temperatures. Whereas other sweeteners like sucralose, fructose, polyols and stevioside are used in a variety of beverages, both hot and cold.

Diabetic foods mainly contain sorbitol, sucralose and saccharin. Polyols and fructofibres essentially are used a bulking agents or diluents with many sweeteners.

The cosmetic industry uses saccharin in various flavored cosmetic products. The pharmaceutical industry uses mainly saccharin, sorbitol and sucralose in a variety of medicines e.g. inadvertently a patient maybe prescribed a cough syrup which contains sorbitol in large amounts which may act as a laxative. Many hygiene products such as toothpaste, mouthwashes contain polyols and sucralose as sweeteners.

USE OF ARTIFICIAL SWEETENERS IN VARIOUS CONDITIONS

Dental Health

It has been established that the between-meal consumption of high-sugar foods promotes dental caries. Foods containing polyols especially sorbitol, mannitol, xylitol and other non-nutritive sweeteners are non-cariogenic, thus help prevent tooth decay and cavities.

Behavioral Disorders

There exists a paradox of sorts. It is inferred that excessive consumption of sugar in growing children causes extreme hyperactivity, restlessness and leads to attention deficit disorder (ADD). On the other hand, carbohydrate – rich foods are recommended to alleviate negative moods and a depressive state of mind. Unfortunately, there is no clear evidence and carbohydrate-rich foods are loosely linked to both these conditions. Hence, artificial sweeteners would be of tremendous help in preventing these situations. Aspartame has been indicated to cause mood alteration and headaches in sensitive individuals and has to be used with caution in these conditions .

Children

Children show the highest intake of sweeteners because of high food and beverage consumption. Sweetened drinks, fruit drinks have high fructose and sorbitol content and may cause non-specific diarrhea in children. Aspartame is restricted in children as this compound diffuses easily across the blood-brain barrier and high levels of this neurotransmitter causes alteration in brain activity. We should consider the consumption of diet drinks by youngsters by a practical example. A youngster, weighing 60 kg decides to lose weight and replaces regular colas with diet colas. He may raise the daily consumption to 10 to 12 cans per day. Each 12 ounce can of cola contains 54 mgs of aspartame. Hence, the total consumption may be to the tune of 540 to 600 mg of aspartame daily. Yet, this falls well below the ADI of

40 to 50 mg/kg body weight/ day i.e. 2000 mg/day. However, this does not mean that one encourages the consumption of these beverages. Sucralose, apparently has no adverse effect and is considered safe.

Pregnancy

Generally recognized (GRAS) as safe sweeteners are accepted in pregnancy. Saccharin is restricted in pregnancy as the placenta actively concentrates it (17). Aspartame was found to have no adverse effect on fetal exposure but it is restricted in pregnant women with hyperphenylalaninemia. Sucralose is found in low levels in the placenta. It is safe in pregnancy. Acesulfame-K and stevioside need more studies to ascertain their safety in pregnancy.

Diabetes Mellitus

Nutritive sweeteners like sucrose, lactose, maltose, fructose, sorbitol are used extensively in diabetes. Monosaccharides and disaccharides have to be avoided if they cause hyperglycemia in diabetics. As an alternative, use polysaccharides. In type 2 obese diabetics, non-nutritive sweeteners are recommended. Use of these would increase adherence to the diet regime.

Obesity

The role of sugar in the etiology of obesity is not very well established and no direct correlation is seen. On the whole, non-nutritive sweeteners play a crucial role in weight management strategies. It is a Herculean task cutting down 500 calories in a weight reduction diet. A reduction of direct sugar i.e. about

100 calories from the diet by replacing it with an artificial sweetener is one-fourth the battle won. If this is done daily for about 2 months, one has lost approximately 1 kg in weight. It further helps in improving the adherence to the diet program. Hence, the artificial sweeteners play a very important role in obesity as well as diabetes.

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Glitazones: Current Controversies

Shaival Chandalia

Type 2 diabetes is a disease of insulin resistance. Insulin resistance is a condition characterized by resistance to the action of insulin at the cellular level. Insulin exerts its multifarous effects on various tissues in the body like liver, adipose tissue and skeletal muscle. It promotes the uptake of glucose by the muscle tissues. Thus insulin is like a key that opens the lock of the cell and allows glucose to enter the cell. If the key is not working properly, glucose and other nutrients cannot enter the cell and diabetes results from the high glucose levels in the blood. Insulin resistance is responsible for the malfunction of the key.

How do you measure insulin resistance?

Insulin resistance can be measured in the laboratory by a sophisticated method called a euglycemic clamp. For all practical purposes, insulin resistance can be inferred by measuring insulin levels in the blood. If insulin resistance exists, the pancreas secretes more insulin in an attempt to overcome the insulin resistance and the insulin levels rise. So high insulin levels are a surrogate marker for insulin resistance and various population-based studies use this parameter to measure insulin resistance.

Glitazones: origins and mechanism of action

In the 1990's, a new class of drugs became available called thiazolidinedinones or glitazones. Their origins can be traced back to the biological discovery of the century, the discovery of deoxyribonucleic acid or DNA. DNA is the chemical that makes our genes. Genes are the elements of heredity that are responsible for transmitting hereditary traits from generation to generation. The discovery of the chemical structure of genes (DNA, RNA) by Watson and Crick opened the doors to a world of opportunity for possible controlled manipulation of genes and their products, in order to treat patients. The next hundred years is therefore, rightfully called the century of the gene.

Glitazones emerged in the 1990's in the background of increased understanding of the mechanisms of insulin resistance at the molecular and cellular level. Glitazones reduce insulin resistance by acting on some genes (made up of DNA). They alter the activity of these genes and hence of their protein products, thus reducing insulin resistance at the molecular level. This is just one example of how the discovery of the constituents of our heredity (DNA) placed medical science on the path of discovery of glitazones years later.

Glitazones from laboratory to clinical science

In type 2 diabetes, insulin resistance precedes the development of hyperglycemia (high glucose levels in the blood). By the time, diabetes is detected by a high blood glucose level, the beta cells of the pancreas which make more insulin initially in the face of insulin resistance start failing and get burnt out. Thus insulin levels drop and glucose levels go up as a result. Intervention at this stage reduces the insulin resistance and allows the beta cells to produce enough insulin to overcome insulin resistance without getting exhausted. The result is a reduction in blood glucose and protection from the complications associated with a high glucose level. The glitazones are remarkably effective in controlling blood sugars. They reduce the HbA1c (hemoglobin A1c-average blood glucose over 2 months) by 1.5 to 2%. Thus they are remarkably effective. Also they do this without producing much hypoglycemia. Similar to metformin in producing minimal hypoglycemia, they are classified as anti hyperglycemic agents rather than oral hypoglycemic agents.

Controversies and adverse reactions

The two glitazones available in the market are pioglitazone and rosiglitazone. Use of both the glitazones is associated with weight gain. This is due to fluid retention and deposition of fat under the

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Dr Shaival H Chandalia, Endocrinologist & Diabetologist at Dr. Chandalia's Diabetes Endocrine Nutrition, Management and Research Center (DENMARC) & Jaslok and Bhatia Hospitals and Research Centre, Mumbai. Email Id: **shaivalc@hotmail.com**

skin. This weight gain can be a significant problem with some patients gaining 10-15 kgs. Obviously, overweight patients are not candidates for glitazones in spite of their remarkable effectiveness in lowering blood sugars. Similarly, the glitazones are not to be used in heart failure, liver disease or kidney failure as the conditions are associated with fluid retention and any further fluid retention can be dangerous.

Another side effect is an increased incidence of fractures especially in the hands and feet. This unusual side effect has caused physicians to be cautious in prescribing glitazones in patients with osteoporosis and low bone density.

But the biggest controversy that erupted around rosiglitazone was in 2007. Stephen Nissen and colleagues found that rosiglitazone in spite of reducing the blood glucose may actually be increasing the risk of heart problems (like heart attacks) in the long term. This ignited a firestorm of a controversy, which has not subsided till today and reduced rosiglitazone sales drastically. The consensus was that pioglitazone being available as a viable alternative, should be used (rather than rosiglitazone) because it is safer. The differential effects of rosi and pioglitazone in affecting cardiovascular risk (like future heart attacks) may be due to their differential effects on lipids (like cholesterol) with pioglitazone affecting cholesterol favorably and rosi unfavorably.

To complicate the matters further, use of pioglitazone has been described to be associated with an increase in the incidence of urinary bladder cancer. This is a recent findings which requires critical appraisal.

Who should get a glitazone?

To summarize, since pioglitazone is a viable alternate to rosiglitazone (which is still shrouded in controversy) we would recommend using pioglitazone rather than rosi. It may be used initially when a diabetic has just been diagnosed with diabetes. It can also be used in combination with metformin or a sulfonylurea. Weight gain should be watched out for especially in patients who are overweight to begin with. Also it should be used cautiously in patients with osteoporosis or low bone density. When used carefully within its limitations, pioglitazone is a remarkably effective drug.

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