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To Dispel Darkness Of Diabetes

DIET MANAGEMENT

EXERCISE

MEDICATION

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DIABETIC AUTONOMIC NEUROPATHY

*** Samina Burhanpurwala**

Diabetic Autonomic Neuropathy (DAN), a form of peripheral neuropathy, is one of the severe complications of diabetes that includes damage to sympathetic and parasympathetic nerves in the body that controls body systems, such as:

- Digestive system
- Heart and blood vessels
- Kidneys
- Urinary tract
- Sex Organs
- Eyes

DAN is often recognized very late and therefore can lead to severe consequences. There is symptomatic and asymptomatic phase in DAN. Hence, with the help of cardiovascular autonomic tests, autonomic neuropathy can be diagnosed early in an asymptomatic phase.

PATHOGENESIS:

The cause of DAN is complex and still unclear. But, its hyperglycemia which causes a number of vascular, metabolic, immune and neurotrophic changes which results in progressive damage. The hypothesis for the complications caused by hyperglycemia includes many, which can be summarized as:

- Activation of polyol pathway which leads to accumulation of sorbitol and fructose which increases oxidative stress & causes cell death
- Formation of ROS with the increase in oxidative stress resulting in vascular endothelium damage & reduced availability of nitric oxide
- Formation of advanced glycation end (AGE) products which disrupts the function of neurons
- Activation of protein kinase C (PKC) which reduces neuronal blood flow

All the above mentioned mechanisms may occur alone or act interdependently wherein the end result is deterioration of neurons and axons with the loss of nerve fibers and impairment in regeneration of nerve fibers.

MANIFESTATION:

As mentioned above, DAN can damage sympathetic and parasympathetic autonomic function; it can affect any organ from GI tract to the skin.

Hence, its advent can foretell a marked increase in mortality rate.

Cardiovascular System (CAN):

Cardiovascular autonomic neuropathy (CAN), clinically presents as exercise intolerance, resting tachycardia, diabetic cardiomyopathy, orthostatic hypotension. It is the most common manifestation of DAN. It is a serious and life threatening complication that may cause arrhythmias, MI & sudden death.

GI System:

- Dysfunction of esophagus
- Gastroparesis
- Constipation or Diarrhea
- Fecal incontinence

Genitourinary system:

- Erectile dysfunction
- Loss of vaginal lubrication
- Bladder dysfunction and
- Retrograde ejaculation

Respiratory system:

- Breathing dysregulation by CNS
- Bronchial reactivity

Neuroendocrine system:

- Unawareness of hypoglycemia
- Hypoglycemia associated autonomic failure

* Dietitian and Diabetes Educator at Dr.Chandalia's Diabetes Endocrine Nutrition Management & Research Centre

SCREENING AND DIAGNOSIS:

Screening for CAN should be done in T2DM patients at diagnosis and T1DM patients after 5 years of disease, especially those with a history of poor glycemic control (HbA1c >7%), or presence of one major cardiovascular risk factor or other complications.

Depending on the organic system to be tested, a series of tests can be done to confirm the diagnosis of DAN. Cardiovascular Autonomic Neuropathy is a common and well studied form of DAN. It is associated with very adverse outcomes. Also because of sensitivity, standardization, specificity and non-invasiveness, cardiovascular tests are used as gold standard method for diagnosis of DAN.

Based on the heart rate variation measurements, during resting, deep breathing, Valsalva maneuvering (an attempt to exhale air forcibly against closed air passages (glottis), affecting cardiac output, arterial pressure and heart rate) and active orthostatic test, test is conducted.

Conditions for the test are standardized:

- Patient is specifically asked to avoid smoking, black tea and coffee consumption for 3hrs prior to test.
- Testing should be performed in morning, fasting or at least 2hrs after a light breakfast

Following are the diagnostic tests for CAN:

1. **Resting heart rate:** >100 beats/minute is abnormal.
2. **Beat-to-beat heart rate variation:** When the patient lies supine and is at rest and breathes slowly, 6 times/ minute, a difference in HR of > 15 beats per minute is normal and < 10 beats per minute is abnormal. Also, expiration-to-inspiration R-R ratio of the R-R interval is determined and ratio > 1.17 is abnormal. This is an age dependent index and the ratio decreases with age.

AGE	E/I RATIO VALUE
20-24 years	1.17
25-29 years	1.15
30-34 years	1.13
35-39 years	1.12
40-44 years	1.10
45-49 years	1.08
50-54 years	1.07
55-59 years	1.06
60-64 years	1.04
65-69 years	1.03
70-75 years	1.02

3. **Heart rate response to standing:** R-R interval is measured during continuous ECG monitoring at beats 15 and 30 after the patient stands. The 30:15 ratio <1.03 is abnormal.
4. **Heart rate response to Valsalva maneuver:** During ECG monitoring, patient forcibly exhales into the mouthpiece of a manometer, exerting a pressure of 40mmHg for 15 seconds. In a normal subject, the heart rate slows with beginning of straining and increases during and after straining, which is succeeded by marked bradycardia. In patients with autonomic failure or advanced cardiac disease, these responses occur less or are absent.
5. **Systolic blood pressure response to standing:** Systolic blood pressure is measured when patient is in supine position and 2 minutes after standing. A fall of <10mmHg is normal response, a fall of 10-29 mmHg is borderline and a fall of >30mmHg is abnormal. This test mainly indicates parasympathetic activity. It is used as a tool to evaluate the condition of the heart.
6. **Systolic blood pressure response to isometric exercise:** The patient is asked to squeeze a handgrip dynamometer to set up his or her maximum. The patient then squeezes the grip at 30% maximum for 5 minutes. A rise of >16 mmHg in diastolic blood pressure in the other arm is normal response, a rise of <16 mmHg is abnormal.
7. **Electrocardiography:** A QT interval of >440 ms is abnormal. Depressed very-low frequency peak or low-frequency peak indicate sympathetic dysfunction. Depressed high-frequency peak indicates parasympathetic dysfunction. Lowered low-frequency/high-frequency ratio indicates

sympathetic imbalance.

8. **Neurovascular flow:** Noninvasive laser doppler measures peripheral sympathetic response to nociception (the ability to feel pain).

The test results of CAN could be graded as follows:

- Presence of one unusual finding indicates a possibility of CAN.
- At the minimum, 2 unusual finding are desired to confirm the diagnosis of CAN.
- Presence of orthostatic hypotension along with other unusual finding suggests advanced CAN.

Specific examination can be carried out depending on the symptoms and organ involved, if the CAN testing is abnormal:

SPECIFIC EXAMINATIONS IN DAN

Cardiac	Multigated angiography (MUGA), Thallium scan I^{123} metaiodobenzylguanidine (MIBG) scan
Orthostatic hypotension	Measure BP supine and standing Measure catecholamines (on clinical suspicion)
Gastrointestinal	Emptying study (solid & liquid component of meal is mixed with radioactive material, few hours after which the patient is scanned). Barium study , Endoscopy, Manometry Fasting serum Vaso-intestinal peptide, urinary 5HIAA (5- hydroxyindoleacetic acid) Foregut carcinoid markers: substance P and CGRP(calcitonin gene-related peptide)
Bladder	Cystometrogram Postvoiding sonography (Post-void Residual volume>150 ml indicates cystopathy)
Sexual Dysfunction	Penile-brachial pressure index(less than 0.7 indicates vascular cause) Penile Doppler Sonography (evaluates a venous leak manifested as vasodilator unresponisveness) Nocturnal penile tumescence (Normal study & intact morning erection: psychogenic) Testosterone, Prolactin assay (on clinical suspicion), Thyroid function test
Sudomotor	Sweat test, skin blood flow

TREATMENT:

For prevention of DAN, main strategy involves intensive glycemic control and treating the risk factors such as long-standing diabetes, hypertension, dyslipidemia, alcohol and smoking, obesity, nephropathy and retinopathy.

As mentioned above, based on the guidelines of American Neurological Society, screening for DAN should be done as soon as the diagnosis of type 2 diabetes is confirmed , 5 years after the diagnosis of type 1 diabetes, patients with increased risk due to poor glycemic control, with cardiovascular risk factors, and with risk of micro- and macro vascular complications. .

With the confirmation of DAN based on the symptoms, patients should be advised about simple behavioral and lifestyle modifications that can help alleviate the symptoms.

Basic measures

Orthostatic Hypotension

- When rising from supine position, patient should be advised to sit on the side of the bed for few minutes before standing up.

- Get up gradually in stages.
- Perform physical exercise like leg crossing, stooping and squatting.
- Wear elastic stockings that reach to the waist (help in attenuating BP reduction).
- Have adequate fluid intake and increase salt intake.
- Small frequent meals are advised to patients experiencing postprandial hypotension due to gastrointestinal and hepatic pooling.
- Reduce or exclude medications that cause orthostatic hypotension.e.g: thiazides, beta blockers, phenothiazine derivatives, tricyclic antidepressants, vasodilators, antihypertensives.
- Raise the head of the bed by 10-20º to stimulate renin-angiotensin aldosterone system.

Constipation

- Check for any other causes like hypothyroidism or any drug effect like calcium channel blockers.
- Increase intake of fiber rich foods
- Increase fluid intake
- Exercise regularly

Gastroparesis

- Have small, frequent meals.
- If required, have semi-liquid or liquid diet.
- Sit upright for 30 minutes after meals.
- Exclude drugs that slow gastric emptying such as GLP-1 analogs, calcium channel blockers and tricyclic antidepressants.
- Gastroparesis may interfere with nutrient delivery in the bowel, causing disruption in glucose absorption and synchronization with exogenous IV insulin administered. Hence, insulin timing and dosage should be carefully planned.

Bladder dysfunction

- Instruct the patients to try to urinate when the bladder is full. If unable to urinate, advise them to massage or press the abdomen, just above the pubic bone to start the flow.

Sexual dysfunction

- Lose weight if overweight/obese (or to be specific, lose body fat).
- Avoid smoking and alcohol.
- Cease the use of medication that can cause ED such as beta-blockers, thiazides, phenothiazines, tricyclic antidepressants, spironolactone, fibrates, and marijuana.

Pharmacotherapy

Usage of drugs becomes necessary when DAN moves to advanced, symptomatic stage, depending on the organ affected. There are currently no guidelines on this subject.

SYMPTOMS	DRUGS	TYPE & MECHANISM	DOSAGE
Orthostatic Hypotension	Midodrine	An α-adrenergic agonist The only FDA approved agent, used specifically for treatment of orthostatic hypotension. Works by inducing arterial & venous constriction.	Start with 2.5mg three times/day and gradually increase to 10mg three times/day
	Octreotide	A long-acting somatostatin analog. Inhibits the secretion of hormones involved in vasodialtion.	Recommended dosage ranges from 0.2-0.4 mcg/kg with a maximum of 1.6 mcg/kg.
	Clonidine	An α-2 receptor agonist. It stimulates α-1 receptors in peripheral vascular smooth muscle, resulting in vasoconstriction.	Daily recommended dosage is 0.1 to 0.5 mg at bedtime.

SYMPTOMS	DRUGS	TYPE & MECHANISM	DOSAGE
	Fludrocortisone	A synthetic mineralocorticoid. Small oral doses lead to increase in angiotensin activity causing sodium and fluid retention and increase in potassium excretion.	Dosage range from 0.05- 0.2 mg/day
Gastroparesis	Metoclopramide, Domperidone	It is a prokinetic. It stimulates gut motility by acting on different receptors in GI tract. It acts as anti-emetic by acting on vomiting center in CNS.	Recommended dosage is 5-10mg orally, 30 minutes before meals and at bedtime.
	Levosulpiride	It acts by increasing the release of acetylcholine which results in increased movement of stomach	Recommended dosage is 25 mg thrice a day.
Bladder dysfunction	Anticholinergics	It blocks the action of acetylcholine, which sends signals to the brain that triggers abnormal bladder contractions.	
	Doxazosin	It is an α-1 blocker. Relaxes the muscles around the bladder exit and prostate, which makes it easier to urinate by relaxing the sphincter.	Dosage range from 1-2 mg 2-3 times a day
Sexual dysfunction	Sildenafil	It is a phosphodiesterase inhibitor. It increases blood flow into the penis during sexual stimulation by relaxing its blood vessels.	Recommended dosage is 50 mg 2 hr before sexual activity, once a day.

DAN is one of the main aspects of diabetic neuropathy. The consequences of DAN can affect survival of diabetic patients by causing multiple system impairment in both T1DM and T2DM patients. This may lead to increased mortality rate from sudden cardiac arrest. Cardiac system is one of the most seriously involved systems.

Main etiology of DAN is persistent uncontrolled hyperglycemia resulting in increased oxidative stress and inflammation. There is no one particular therapy which will be able to reverse it, hence strict glycemic control with lifestyle modification and pharmacotherapy is the only prevention method.

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DIABETIC GASTROPARESIS

***Shambhavi Kamat**

Diabetic gastroparesis (DGP) is a complication of long-standing and uncontrolled diabetes found more commonly in Type 1 as opposed to Type 2 diabetics. It is defined by delayed gastric emptying (GE) in the absence of any mechanical obstruction, and presence of other GI symptoms for a period of more than 3 months. It is a manifestation of autonomic neuropathy where the functioning of the vagus nerve is affected. It presents with nausea, vomiting, early satiety and abdominal pain following meals.

Vagus nerve is responsible for motility and functioning of the GI tract and is a part of our body's parasympathetic nervous system. It innervates a variety of organs in the neck and abdomen region and performs a wide array of functions. It acts as a bridge between the enteric nervous system (ENS) and the central nervous system (CNS). The vagus nerve system is one of the largest nerve systems in our body, second only to the spinal nerves.

Prevalence of DGP

DGP is more common in females than in males. This may be attributed either to the fact that GE in females is slower than men on an average, or the fact as animal data have suggested that the enteric nervous system is more pronounced in females than in males.

Limited data is available on the prevalence of delayed gastric emptying or gastroparesis in diabetics, but many studies have evaluated the epidemiology of upper gastro-intestinal (GI) symptoms in diabetics. Many studies have shown that the prevalence of GI symptoms was not significantly higher in diabetics, compared to asymptomatic controls. In studies from tertiary care centers, delayed gastric emptying was reported in almost one-third of diabetic patients with an equal prevalence in type 1 and type 2 diabetes. At a population level, only 5% of Type 1 and 1% of Type 2 diabetics suffer from delayed GE along with typical symptoms of DGP. But

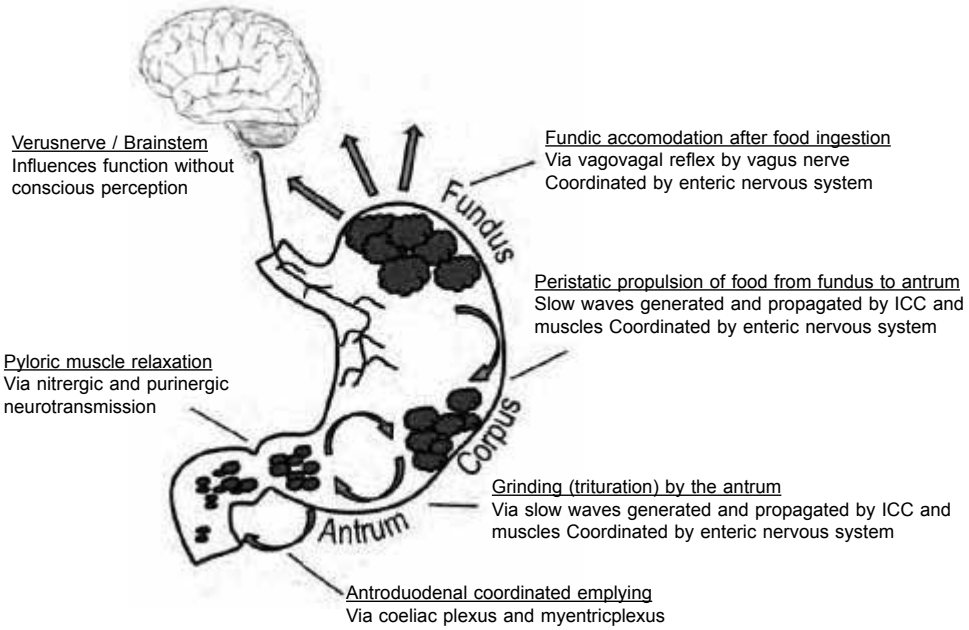

Figure 1: Gastric functioning in normal state

* Dietician and Diabetes Educator at Dr. Chandalia's Diabetes Endocrine Nutrition Management & Research Center

due to the massive increase in prevalence of Type 2 Diabetes, DGP is now being associated with Type 2 more than Type 1 Diabetes. It has been observed that DGP develops after > 10 years of Type 2 Diabetes, or when a type 1 Diabetic has developed the classic triopathy, a combination of retinopathy, neuropathy and nephropathy.

Normal mechanism of gastric motility

Gastric motility is the result of an extremely well-coordinated, controlled and balanced act between smooth muscle cells, interstitial cells of Cajal (ICC), enteric nerves and the vagus nerve. Figure 1 shows the normal functioning of the stomach contraction.

As ingested food reaches the stomach through the esophagus by peristalsis, the fundus relaxes to accommodate this food.

Filling of the stomach also activates mechanoreceptors in the gastric lining. Both these mechanisms are carried out via the vagus nerve. ICC network present at the border of fundus is activated upon ingestion of food and activates rhythmic electrical activity in adjoining cells to initiate a peristaltic wave. These rhythmic contractions push the food from fundus to the antrum, where it is ground into small pieces about 1-2 mm in size. At this stage, food is emptied into the duodenum where further digestion and absorption takes place.

The pyloric sphincter acts as a barrier and prevents food from passing undigested into the small intestine. This emptying is highly controlled as nutrients must be sent to the duodenum in ideal amount and rate so as to maximize utilization.

Pathophysiology of DGP

Although the exact mechanism of DGP is unknown, several etiological factors have been identified, such as:

- Hyperglycemia
- Vagal dysfunction
- Loss of neural nitric oxide synthase (nNOS) expression in mysenteric plexus
- ICC Network disturbance
- Oxidative stress

Hyperglycemia: An acute increase in the blood sugar (more than double of the normal level) will delay GE while an abnormal decrease (less than half the normal value) accelerates GE. A fluctuation in the nutrient delivery precipitates into abnormal blood sugar value further aggravating the GE, thus forming a vicious cycle. Hyperglycemia induces hypomotility in the antrum while hypoglycemia induces excitability in the vagus nerve. While optimal diabetes control is the best preventive measure, once GDP sets in, control of blood sugars does little to alleviate the symptoms.

Vagal dysfunction: The vagus nerve is responsible for muscle movements and release of chemical messengers in the digestive system. An under-active vagus leads to gastroparesis. The vagus nerves has numerous branches innervating organs of the digestive system. Ingestion of food leads to distention of stomach, release of polypeptides and other nutrients. The chemoreceptor ends of vagus nerve pick up the chemical substances while the mechanoreceptor endings pick up the distention of the stomach. They are relayed to the CNS, which causes an increase in the secretion of gastric acid, insulin and other digestive substances. All the above responses are impaired in the event of vagal dysfunction, thus causing indigestion, abdominal pain, early satiety and regurgitation.

Loss of neural nitric oxide synthase (nNOS) expression in mysenteric plexus: Myesenteric plexus is the network of nerves situated between the two muscles layers of the gut. It co-ordinates muscle movement by controlling the activity of excitatory and inhibitory neurons. Several classes of intraneurons and primary afferent neurons are involved in these activities too. Excitatory neurons, responsible for contraction of muscle,

release neurotransmitters like acteylcholine and susbtance P. Inhibitory neurons exert their relaxing action on muscles via release of nitric oxide, ATP and vasoactive intestinal peptide. A malfunction in the synthesis of these substances, especially the inhibitory neurons severely impair muscle tone and function. A known malfunction is the reduction in synthesis of the enzyme responsible for nitric oxide synthesis. Improper peristalsis results in delayed emptying and gastric dysrhythmia.

ICC Network disturbance: Loss of the ICC network has been reported in studies involving animal models as well as diabetic patients. ICC is a network present in the stomach whose function is to stimulate the adjoining cells electrically to initiate a peristaltic wave. Human studies have shown loss of ICC in the antrum of patients suffering from DGP along with loss of the inhibitory neurons positive for nitric oxide synthase. Under normal circumstances, the ICC network is maintained by balancing the harmful and healing processes of the body. But due to the oxidative stress, insulinopenia and reduced production of IGF-1 in a diabetic, the damaging pathways take a toll and the balance shifts towards damaging the ICC network rather than healing it.

Oxidative stress: Apart from excessive production of reactive oxygen secies (ROS), low levels of heme oxygenase-1 (HO-1), a known cytoprotective compound might cause increased oxidative stress in diabetics. The protective action of HO-1 is mediated by carbon monoxide, an opportunity to develop targeted therapies for DGP that may restore this enzyme's activity to its full capacity.

Symptoms & Clinical Features

Symptoms range from mild to severe based on the extent of autonomic neuropathy, dietary habits and weight status of a person. Severity of symptoms is usually correlated to a higher BMI. One may experience the following symptoms as a result of DGP:

- Nausea
- Vomiting (Especially in the morning, containing undigested food particles of food eaten last night).
- Early satiety
- Bloating
- Abdominal pain
- Anorexia

Some of the clinical features associated with DGP are as follows:

- Symptoms of peripheral and autonomic neuropathy (numbness or tingling in extremities, urinary incontinence, cardiac dysfunction, chronic diarrhea)
- Blood sugar fluctuations due to impaired gastric emptying rate. Patients taking insulin are at a higher risk of developing post-prandial hypoglycemia as the food fails to reach the intestine during the peak effect of the bolus dose.

Diagnosis & Assessment of DGP

If remnant food is found in an endoscopy after an overnight fast, this is indicative of ineffective antral interdigestive motility and gastroparesis, i.e. reduced capacity to empty the stomach of particles larger than 2 mm in size. Patients who are positive for gastric retention but are asymptomatic are said to have delayed GE and not DGP.

However, diagnosis of DGP in a patient is made only after exclusion of several other potential etiologies. Mechanical obstruction must be ruled out by endoscopy and radiological imaging. The non-specific and variable nature of GI symptoms calls for careful evaluation through use of validated techniques and diagnostic measures. The most widely used diagnostic test for DGP is "scintigraphic measurement of the emptying of solids" or "GE Scintigraphy"(GES). It is a non-invasive, quantitative assessment of GE. Alternate methods include stable-isotope GE

breath testing (GEBT), wireless motility capsule (WMC) and a functional ultrasonography.

GE Scintigraphy: Patient must discontinue all medications that alter motility (GLP Analogs, Opiates, Anticholinergics) for 2-3 days before the test. One must refrain from consuming alcohol or smoking on the day of the test. Fasting blood glucose must be under control as acute hyperglycemia (> 275 mg/dl) delays GE. After an overnight fast, the patient consumes a standardized test meal. The most commonly used meal is a 255 kcal low-fat, low-fiber solid meal labeled with a radioisotope. The meal is supposed to be eaten within 10 minutes. Standard imaging of the gastric area is performed at baseline, 1, 2 and 4 hours after meal ingestion, in a standing position. With the typical calorie load like the above, the increase in blood glucose to above 275 mg/dl is highly unlikely, if the fasting value was below 275 mg/dl and the patient is taking the routine anti-diabetic treatment.

Quantification of GE is done using computerized software. However, a major pitfall in the interpretation of the test data is unavailability of standard, sex-specific reference values. Females, on an average have a 15% slower GE rate compared to males.

Major limitations to widespread use of GES is lack of adherence to protocol by institutions, limited access to γ cameras (cameras for radiation imaging), and the questionable safety of radiation exposure.

All things considered, one must refrain from diagnosing a patient with DGP based solely on GES. A clinician must consider all facets of a patient's clinical profile before making a definitive diagnosis- like symptom severity, nutritional status, glycemic control and emergency hospitalizations due to severe symptoms.

GE Breath testing: This is a new alternative to GES and involves a ^{13}C labeled substrate (^{13}C-octanoate or ^{13}C-S. Platensis) incorporated into a solid meal. The rate of GE of the substrate is reflected by breath excretion of $^{13}CO_2$. While this method has been extensively used in research studies, it is not as popular in clinical practice. This is because tests results after using commercial ^{13}C-octanoate is of questionable validity and ^{13}C-S. Platensis is not approved for marketing. Experts recommend 6 hours of sampling scheme for accurate prediction of GE.

WMC: It is a single-use, orally ingested capsule that measures pH, pressure and temperature through the GI tract. This pill was developed in Israel and is available in the US and UK for clinical use. The pill transmits data to a recorder around the patient's neck. The GE time is recorded as the time taken for the pH to rise abruptly (stomach's acidic pH to duodenum's alkaline medium). However, the pill is 2 cm long and cannot possibly imitate the same effect as that of a mixed meal.

Dietary modifications

Dietary modification must be used as a first-line intervention for DGP. The most challenging part of dietary modification is controlling blood glucose levels. Since a large volume cannot be tolerated by patients, 5-6 small meals during the day are advised. If the patient is on intensive insulin therapy, s/he may be advised to take the bolus dose half hour after eating the meal, once s/he is sure that the meal will stay down. The following aspects of the patient's dietary habits may be modified:

(a) Consistency- Liquid meals require lesser mechanical processing compared to solid meals. They are emptied by gravity instead of peristaltic movement of the stomach, irrespective of the nutrient density. Thus, a semi-liquid diet may help patients who have mild to moderate symptoms. However, patients with severe GI symptoms may benefit greatly by full liquid diets. Consuming a predominantly liquid diet increases predictability of post-prandial glucose spikes and thus makes managing diabetes easier. If providing a full liquid diet,

one must take care that it is isotonic in nature i.e. it provides at least 1 kcal/ml of fluid prescribed.

(b) Volume- Increased volume reduces GE rate, lower oesophagial sphincter pressure and thus increased reflux. 5-6 small meals, with similar carbohydrate content must be provided instead of 3 large meals with a large carbohydrate load. This will help to attenuate very high post-prandial values.

(c) Fiber- Due to reduced gut motility, patients with DGP are at a higher risk of developing bezoars, a stony concretion of food particles. Foods known to cause bezoar formation in patients with impaired gut motility include figs, strawberries, tomato skin, potato skin, apple and corn. Bulking agents like psyllium, cellulose and inulin also must be avoided. A low-fiber, low-residue diet must be advised.

(d) Fat- Although it is normally restricted in patients with delayed GE, there is no reliable clinical evidence to prove this practice. Fat in liquids like milk, milkshakes, nutritional supplements, porridges are generally well-tolerated. Fat restriction must not be practiced especially if there is weight loss as fats are a valuable source of calories. Fat malabsorption may be present due to bacterial overgrowth in the small intestine. This can be treated with enteral antibiotics.

Enteral nutrition: Enteral nutrition may be considered if the patient is unable to gain weight and there is a concern regarding hydration and nutrient delivery. The nutrient delivery system can be nasojejunal (NJ), Percutaneous endoscopic gastrostomy- jejunostomy (PEG-J) with venting or jejunostomy (JT). A 48 hour trial for NJ Feeds may be done to check tolerance. In case of intractable nausea and vomiting, the tube may get dislodged or go back into the stomach. In such cases, a PEG-J or JT is preferred. NJ and PEG-J may respond well to bolus feeds whereas a JT feed calls for continuous drip method. A venting tube is used to decompress the stomach's content and prevent nausea and vomiting. A PEG-J provides nutrient delivery and venting via one insertion which is more convenient. However, there is need for clinical trials to demonstrate the efficacy of PEG-J tubes in gastroparesis. Nasogastric or NJ tubes with venting have proven to cause discomfort to the patient and thus are not widely used in clinical practice. Fiber can be provided through the enteral route if small intestine motility is not affected. An initial volume of 125-160 cc/hour is tolerated well by patients. Parenteral nutrition is not considered if the small and large bowel is functional as it predisposes a patient to life-threatening infections. Figure 2 shows placement of the enteral feeding routes.

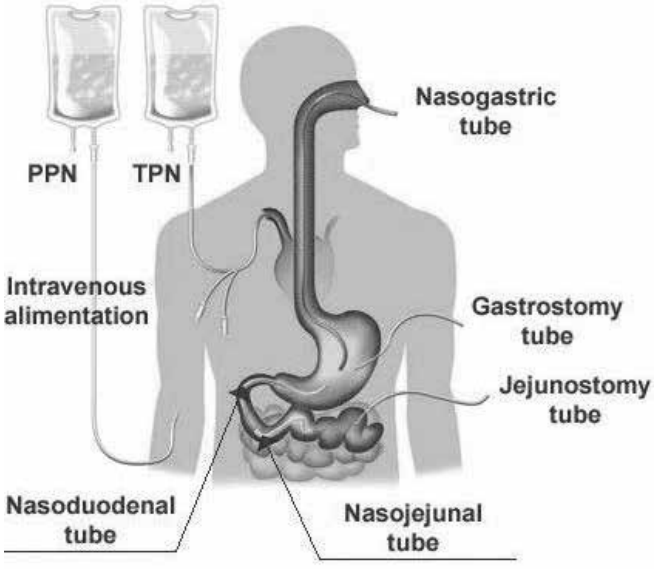

Figure 2: Placement of enteral feeding tubes

Medical Management Options

Antidopaminergic Prokinetics: These medications are Dopamine D_2 receptor antagonists. Dopamine reduces upper gut motility and reduces gastric emptying rate. Compounds like Domperidone, Metoclopramide, Levosulpiride and Itopride block the receptors of Dopamine and serve as prokinetics. Domperidone is the most widely used drug out of these as it has minimal side effects. Metoclopramide crosses the blood-brain barrier and causes neurological side effects. Levosulpiride is primarily an anti-

psychotic medication which also serves as a antidopaminergic agent. However, limited evidence is available to guarantee its safety in DGP. Insufficient evidence regarding safety and efficacy of Itopride prevents clinicians from using it regularly for managing DGP.

Serotoninergic Prokinetics: These medications are Serotonin 5HT4 Receptor agonists and they control peristaltic movements of the smooth muscle of GI Tract. Cisapride was the first and widely used compound but it resulted in fatal arrhythmias and prolonged QT intervals, and was thus discontinued. Other serotoninergic prokinetics include Prucalopride, Mosapride and Renzapride.

Motilin agonists: Motilin is a hormone that induces gastric emptying and peristalsis. Macrolide agonsist like Eryhtromycin and Azithromycin have shown promise in improvement of gastric motility. Erythromycin is not used as a first-line prokinetic and is prolongs QT interval and is associated with tachyphylaxis (reduced response to a specific drug). The use of azithromycin needs further critical evaluation till it comes to mainstream market.

Ghrelin agonists: Ghrelin is a gastric peptide which stimulates interdigestive and post-prandial motor activity. Currently, there are no FDA-approved medications for use in DGP but several oral, intravenous and subcutaneous drugs are under trial.

Antinauseants: All antinauseant medication have an anticholinergic action except D_2 antagonsists which counteract prokinetic action. However, their use in clinical practice is empiric due to lack of guidelines.

Pain modulators: Pain modulation in DGP remains a challenge that is not adequately addressed in clinical trials. Low-dose tricyclic antidepressants (TCA) may be used which are antagonistic to cholinergic, histamine, dopamine and serotonin receptors. Gabapentin or Pregabalin used for symptoms of peripheral neuropathy (PN) may also alleviate gastric pain, provided symptoms of PN exist along with DGP. Mild opiates like Tramadol may be prescribed in severe cases but are generally avoided as they inhibit gut motility.

Endoscopic or Surgical management: Gastric neurostimulation by a pulse generator is a novel approach to DGP but lacks reliable evidence in the form of blind, randomized clinical trials. In this procedure, the muscluaris layer of the antrum is stimulated intermittently by a device installed laparoscopically. Surgical resection of stomach (partial or complete) has shown symptomatic relief in vagotomy gastroparesis. However, its application in DGP is not well-researched. Currently, it is not recommended as a treatment option due to lack of evidence, invasive nature of the procedure and morbidity associated with diabetes itself.

Alternative therapies: Acupuncture has shown promising results in relieving symptoms of nausea and vomiting but is yet to be studied effectively and clinically.

Figure 3 shows management algorithm for management of DGP according to choice of treatment at every stage.

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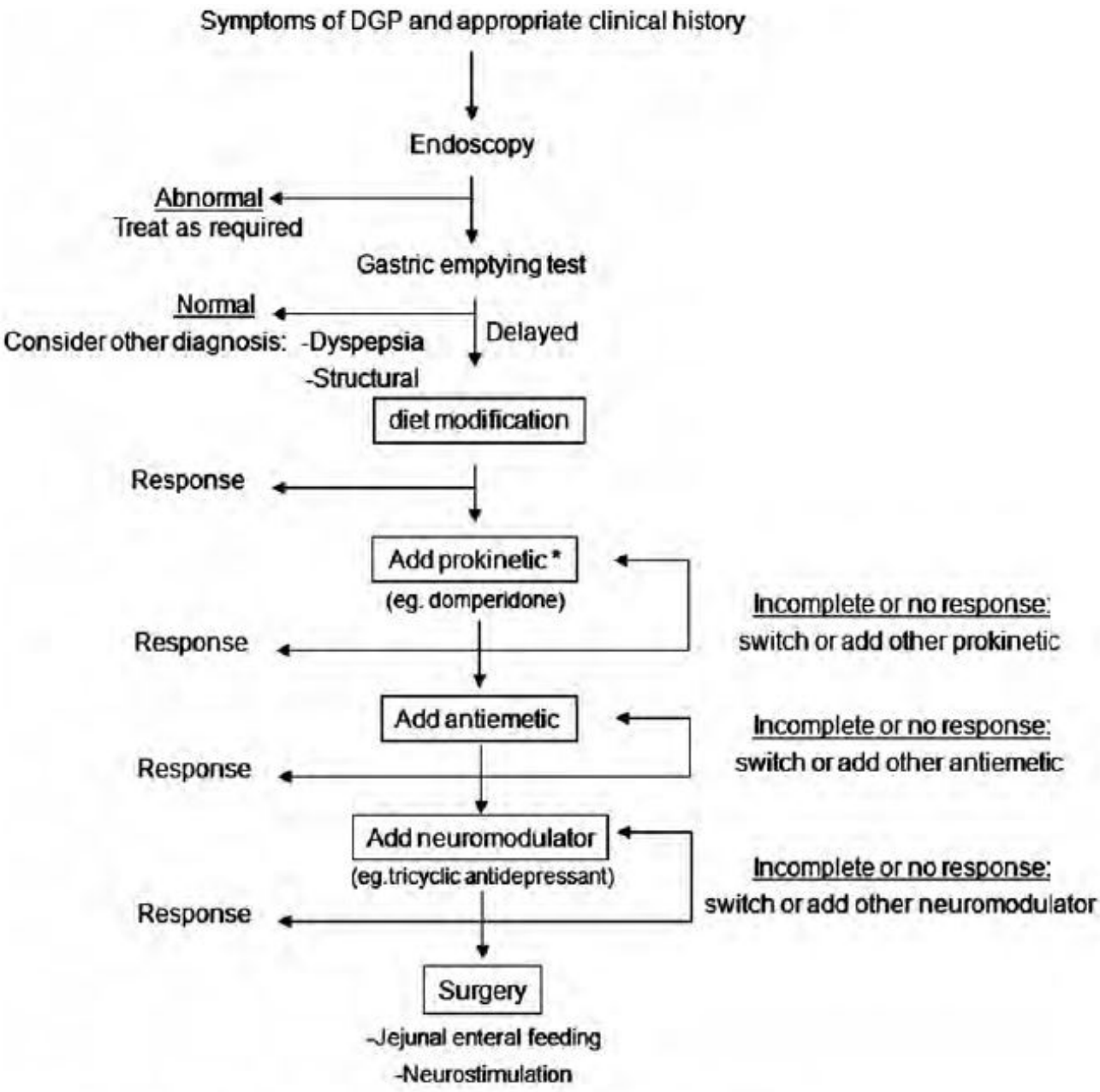

Figure 3: Algorithm for management of DGP

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QUESTION AND ANSWERS

Q) How are OHA doses manipulated in diabetic kidney disease?

Renal disease is associated with a reduced clearance of many OHAs and their metabolites. Let us have a look at OHAs which can be used safely, cautiously and which are to be completely avoided based on the eGFR and creatinine clearance.

Biguanides:

Use of metformin is contraindicated in patient with renal disease (Cr ≥ 1.4 mg/dl in females and ≥ 1.5 mg/dl in males) since they are at increased risk of lactic acidosis. For eGFR ≥ 60 mL/min, it can be used safely, but renal function has to be checked annually. In patients with eGFR 45 mL/min- 59 mL/min, dosage has to be reduced to a stable 1.5 gm per day and renal function to be checked every 3-6 months. With further decrease in eGFR < 45 mL/min, it is safe to omit metformin although some investigators have permitted its use with a reduced dose of < 1 gm daily.

Sulphonylureas:

Glyburide and Glimiperide are both metabolized by the liver and their active metabolites can accumulate in renal disease. Both can be used safely in patients with an eGFR > 60 mL/min. But with an eGFR 30-59 mL/min, a reduction in dosage of both these drugs is advised.

Gliclazide is metabolized to inactive metabolites by liver, which are then excreted via urine. Hence, it causes less hypoglycemia than other sulphonylureas. In patients with an eGFR ≥ 30 mL/min, gliclazide is considered to be safe. There is no data on its usage in patients with eGFR <30 mL/min, but according to its metabolism, a reduced dose can be given. In general though, use of both these drugs is better avoided in renal failure.

Glipizide is also metabolized by liver to inactive metabolites and its half-life is also short. Hence, this drug can be the choice of sulphonylureas in patients with diabetic kidney disease. But, in patients with eGFR < 30 mL/min, it has to be used with caution.

Non-sulphonylurea secretogogues, like repaglinide is metabolized in liver and excreted via bile into the feces, thereby reducing the risk of hypoglycemia. This drug is safely used in patients with up to stage 4 CKD with a dosage of upto 2 mg thrice a day. In patients with eGFR<15 mL/min, it has to be used with caution.

Thiazolidinediones:

Pioglitazone and Roziglitazone are exclusively metabolized by liver and hence have a lower risk of hypoglycemia and accumulation of these drugs in renal disease. However, a common side effect of this drug is fluid retention. Hence, to avoid the risk of fluid overload in renal patients with eGFR 30-59 mL/min it has to be advised cautiously and in patients with eGFR < 30mL/min, it is not advisable.

DPP-4 Inhibitors:

Linagliptin, Sitagliptin, Saxagliptin and Vildagliptin are commonly used in India. All of them are safely used in patients with eGFR ≥ 60 mL/min. Further decrease in eGFR leads to dose adjustments in these gliptins as follows:

<u>eGFR 30-59 mL/min:</u>

Linagliptin- 5 mg once a day

Sitagliptin & Vildagliptin-50 mg once a day

Saxagliptin- 2.5 mg once a day

<u>eGFR 15- 29 mL/min:</u>

Linagliptin- 5 mg once a day

Sitagliptin & Vildagliptin- 25 mg once a day

Saxagliptin- 2.5 mg once a day

eGFR< 15 mL/min:

Linagliptin- 5 mg once a day

Sitagliptin & Vildagliptin- 25 mg once a day

Saxagliptin- avoided

SGLT2 inhibitors:

SGLT 2 is a protein that is expressed in proximal tubule of kidneys, which has the ability to reabsorb 90% of glucose filtered through glomeruli. Thus, SGLT2 inhibitors lower plasma glucose concentration by promoting glycosuria and osmotic dieresis. This class of drug has been approved for patients with an eGFR ≥ 45 mL/min.

Alpha-glucosidase inhibitors:

These are drugs which delay rate of digestion and absorption of carbohydrates in intestine and hence cause decrease in postprandial glucose. Acarbose is almost completely metabolized in the GI tract and only less than 2% of its metabolite is recovered in urine. However, metabolites of acarbose can accumulate in kidney failure and cause liver toxicity. Miglitol and Voglibose are completely absorbed from intestine and excreted unchanged in the urine. Hence, both are considered safe with an eGFR upto 30 mL/min. Both are to be avoided with further decline in the eGFR.

SAMINA BURHANPURWALA

Q. What are the precautions that must be taken while using a glucometer?

Glucometers are often an integral part of diabetes management regimen. They are exceptionally useful tools especially for patients taking insulin or sulphonylurea drugs, as they are at a higher risk of having low blood sugars. Glucometer readings are usually ±15% of the laboratory value. Although glucometers are increasingly being used for monitoring and management of diabetes, one must keep a few things in mind while using a glucometer:

1. Temperature: Glucometers may show wrong readings in extremely hot or cold temperatures. Nowadays, however, most of the glucometers are equipped with a temperature sensor and report an error when it affects the functioning. It is advisable to keep the glucometer in a protective case, especially while travelling.
2. Contamination of meter: An unclean meter with dust particles or other contaminants on it may affect glucose readings. Care must be taken to keep it covered and clean at all times. One must avoid using glucometers at dinner tables or dressing tables as contaminants might enter the glucometer and affect its functioning.
3. Shelf life of strips: An expired strip may give inaccurate reading and affect the patient's management regimen. One must always check for the expiry date of the strips at the time of buying.
4. Calibration of meter: A glucometer may need calibration after recurrent use. One may get in touch with the company representative by calling their toll-free number, who may help with the calibration of the meter.
5. Using the appropriate test strips: One must make sure that one uses test strips that match the glucometer. This is because the chemical composition and sensitivity of every strip is different.
6. Keeping the skin clean: Rubbing the skin with an alcohol swab is essential before pricking the finger. This is because the presence of dust or food particles affects blood sugar readings. In case, an alcohol swab is not possible, one must wipe off the first drop of blood that oozes out after pricking, with a clean tissue and use the second drop of blood for testing blood sugars.
7. Keeping hands dry: The patient's hands must be kept dry while pricking as water may dilute the blood and give an improper reading.

8. Site of collection: Some modern glucometers allow blood samples from sites other than the fingertip (arms or thighs) as some patients are very sensitive to the pricking pain. However, the reliability of readings from these sites is questionable especially after meals, when the gradient of blood sugar between capillary and vein and center to periphery is more.
9. Pricking the fingertip: Pricking the finger tip at the right point and using minimum depth of prick can considerably decrease the pain associated with pricking. One must prick the sides of the fingertips instead of the pads. If one imagines a clock on their fingertip, the appropriate points to prick would be the position of the hour hand at 1, 2, 3, 9, 10, 11 and 12 o'clock. One must also practice site rotation- i.e. not pricking the same spot or finger consecutively.
10. Re-use of lancet: A lancet is always strong and sharp at the beginning. However, with recurrent and multiple use, the edge is blunted and it is no longer usable for capillary pricks. Although, ideally, a lancet must be replaced after every prick, it is usually recommended to change the lancet after 2-3 pricks as the needle becomes blunted and may contribute to pain while pricking.
11. Amount of blood: One should avoid excessive squeezing while testing as this may result in false low readings. To avoid multiple pricks, one must use the appropriate depth of prick and position the pricking device well. One must ensure that there is enough blood for the glucometer to perform the test. Doing this reduces the need for multiple pricks and brings in comfort and convenience in self monitoring.

SHAMBHAVI KAMAT

WHAT'S COOKING?

LAPSI- MOONG DAL KHICHDI

Ingredients:

- Lapsi (Broken wheat/dalia) 10gm
- Moong dal 10gm
- Onion (chopped) 50gm
- Vegetables of choice (chopped) 25gm
- Grated coconut - approx (optional) 5gm
- Oil 1 tbsp

Method:

1. Cook the lapsi separately in the pressure cooker with 1 cup water for 1 whistle. It should not become mushy.
2. Coarsely grind the green chilli, ginger and garlic cloves and keep aside. You can also chop it finely.
3. Heat the oil in a kadai, add the mustard seeds, cumin seeds, asafetida, broken red chilly and curry leaves.
4. Next add the chopped onions and saute till it is soft.
5. Add the ground mix and saute for few minutes.
6. Now add the chopped vegetables, salt, turmeric powder and sambhar powder. Saute the same till the time it is cooked. You can use any vegetables like carrot, beans, green peas etc. If you have some leftover sabzi, you can add it directly too.
7. Add the cooked dalia in it and mix well. Check the salt and if less can squeeze lemon while serving.
8. Switch off and garnish with coriander leaves/ drumstick leaves.

Serves- 1

Energy (Kcals)	Protein (gms)	Carbohydrates (gms)	Fats (gms)	GI
237	4.9	24	16.8	Low

GARLIC BROCCOLI SALAD

Ingredients

Ingredients

- Broccoli 50 g
- Butter/Olive Oil 10 g

Method:

1. Cut the broccoli crown into medium sized florets. Rinse the florets.
2. Put in into a ceramic or glass container. Mix in the olive oil, minced garlic, red pepper flakes and salt.
3. Microwave on high power for 2-3 minutes. The florets will turn dark green in color. It should retain its crispiness for best taste.

Serves- 1

Energy (Kcals)	Protein (gms)	Carbohydrates (gms)	Fats (gms)	GI
103	1	2.5	15.1	Low

MYTHS AND FACTS

Myth: Women with diabetes should not get pregnant.

Fact: Women with well controlled diabetes can have a normal pregnancy and give birth to a healthy baby.

Myth: Exercising when a person has diabetes only increases chances of hypoglycemia.

Fact: It's incorrect that just because someone has diabetes, they should avoid workout. Exercise is an integral part to controlling diabetes. If someone is on insulin or OHAs which increases insulin production in the body, they have to balance exercise, medication and diet.

Myth: Dairy products are fattening and unhealthy.

Fact: Dairy product is one of the important food groups as it provides protein as well as calcium. But dairy products made of whole milk are high in fat, which adds calories and hinders calcium absorption. Hence, diabetics can opt for low fat dairy products.

Myth: "Going vegetarian" will help lose weight and be healthier.

Fact: A vegetarian diet can be as unhealthy as a non-vegetarian diet. Avoidance of direct sugar, refined flour (e.g. Maida), heavy oil or butter intake and most importantly, portion size is the key. Whether the diet is vegetarian or non-vegetarian is immaterial. A badly planned non-vegetarian diet usually lacks vegetables and fruit - an essential ingredient of a healthy diet. Hence, the above myth.

Myth: Needing insulin in type 2 diabetes means it is the beginning of the end.

Fact: Taking insulin in type 2 diabetes is not a sign that patients are failing to take care of their diabetes. In this type of diabetes, the body becomes resistant to insulin; hence there is reduced uptake of glucose by the cells. Additionally, there is deficiency of insulin which increases with increased duration of diabetes. Over the time, when pancreas also stop producing sufficient amount of insulin, these drugs are not effective enough to keep blood glucose in check, so it may be necessary to take insulin usually along with OHAs.

HOW KNOWLEDGEABLE ARE YOU?

1. Insulin secretion is stimulated by glucose over the range:
   a) 1-5 μmol/l
   b) 1-5 mmol/l
   c) 5-15 μmol/l
   d) 5-15 mmol/l

2. Insulin secretion is regulated by:
   a) Circulating nutrients
   b) Incretin hormones
   c) Neurotransmitters
   d) All of the above

3. Beta cells respond to glucose primarily through:
   a) Cell surface receptors
   b) Increased metabolism
   c) Opening KATP channels
   d) Decreased intracellular calcium

4. Which of the following is not an incretin hormone?
   a) Cholecystokinin
   b) Glucagon like peptide-1
   c) Somatostatin
   d) Glucose-dependent insulinotropic peptide

5. Which drug causes hyperglycemia via β-cell destruction?
   a) Diazoxide
   b) Olanzapine
   c) Prednisolone
   d) Streptozocin

6. Which of the following antihypertensive drugs is a recognized cause of hyperglycemia?
   a) Doxazosin
   b) Indapamide
   c) Ramipril
   d) Spironolactone

7. The MODY subtype of diabetes is defined as:
   a) A form of type 1 diabetes in the young
   b) A syndromic form of diabetes with extrapancreatic features
   c) A form of early-onset familial non-autoimmune diabetes
   d) A ketogenic variety of diabetes affecting middle-aged people

8. Pheochromocytomas:
   a) Most commonly lie outside the adrenal medulla
   b) Characteristically secrete an excess of norepinephrine when in extra-adrenal sites
   c) Result from germline mutations in the majority of cases
   d) Should be prepared for surgical excision by beta-blockade followed by alpha-blockade

9. The primary mechanism underlying glucose intolerance and diabetes in acromegaly is:
   a) Insulin resistance
   b) Autoimmunity
   c) β-Cell proliferation
   d) Permanent, regardless of curative treatment of the acromegaly

10. Cushing syndrome is:
    a) Caused by excess circulating levels of glucocorticoid
    b) Caused by a corticotroph adenoma of the anterior pituitary
    c) More common in men than women when resulting from an endogenous cause
    d) None of the above

ANSWERS:

1) d 2) d 3) b
4) c 5) d 6) b
7) c 8) b 9) a
10) a

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BOOK REVIEW

RSSDI text book of Diabetes Mellitus; Editor-in-Chief: H B Chandalia, Executive Editor: G R Sridhar, Editors: A K Das, S V Madhu, V Mohan, P V Rao

Jaypee Brothers Medical Publishers; New Delhi; 2014; pages 1457; Price Rs 2995

The third edition of RSSDI Text Book of Diabetes Mellitus (D M) has been published six years after the second edition. It is authored and edited by those clinicians and professors who have been teaching and practising diabetes over many years within the country. A few chapters are contributed by Non-resident Indians. As pointed out by the editor-in-chief, this edition has undergone considerable revision. The material published both within the country and outside till the end of 2013 has been critically analysed and included. A few topics which are paid scant attention in other books, like-the complexity of insulin resistance, the criteria applicable to metabolic syndrome in Asians,challenges in the management of children and elderly with diabetes,musculoskeletal manifestation of diabetes, malnutrition modulated diabetes, Latent Autoimmune Diabetes in Adults (LADA), neonatal diabetes and the role of Yoga and relaxation techniques are unique to this book.

The flow chart on the management of diabetic ketoacidosis available in this book should be in possession of all ICUs. The colour pictures of retinopathy, foot lesions, skin diseases and musculoskeletal manifestation are well presented. The role of alternate therapy is extensively discussed. The guidelines for the beginner to organise a diabetic clinic and optimal health care for diabetes amidst diversity of social, economic and regional food habits is noteworthy. The limitation of stem cell therapy as of now is a good reminder. Some controversial issues are discussed in individual chapters. Much alike the chapter on A Glimpse in the Future, I wish a full chapter was devoted to controversies in diabetes. New chapters added in this edition are valuable and discuss important current issues. These include Sleep and Type 2 diabetes-mellitus, Early-onset Type 2 DM, Nutrient blockers and Bromocriptine, Insulin Pump Therapy, Glycemic Management in Hospitalized Patients, Continuous Glucose Monitoring System, Vitamin D and DM, HIV in Diabetes, Diabetes and Cancer.

The appendix is retained from the previous edition and gives a wealth of information applicable to Indian subjects like BMI and waist circumference and laboratory values in S I and conventional units.The index has attained perfection.The novel feature of this edition is mentioning the chapter number on the right edge of each page.

The book will prove to be valuable to students, physicians, diabetologists, endocrinologists and providers of diabetes care. It should be on the shelf of every medical library. The availability of this book has made the Western text books redundant. The single volume covering so many topics is bulky and heavy. I wish it was brought out in two volumes.

C. Munichoodappa. F.R.C.P.C.
Diplomate, American Board in Internal Medicine
Bangalore
Email id: dr.munichoodappa@gmail.com

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* Confirmed ⩽3.9 mmol/L (⩽70 mg/dL) or severe hypoglycaemic events (24 hours). ^ Better glycaemic control and less hypoglycaemia with insulin glargine 300 U/mL vs glargine 100 U/Ml. Ritzel R et al. Diabetes Obes Metab. 2017 Sep 1. (Epub ahead of print) 1. Bolli GB, et al. Diabetes Obes and Metab. 2015;17(4):386–394. 2. Becker RH, et al. Diabetes Care. 2015;38:637-643. 3. Toujeo™ prescribing information 4. Strong J et al. Curr Med Res Opin.2017 Apr;33(4):785-793

INSULIN GLARGINE INJECTION
TOUJEO® Solostar® **Abridged Prescribing Information**
COMPOSITION: Insulin glargine 300 U/ml. 1 ml contains 10.91 mg insulin glargine I.P., corresponding to 300 U of insulin glargine. **INDICATION:** For the treatment of diabetes mellitus in adults. **DOSAGE AND ADMINISTRATION:** Toujeo™ is given subcutaneously.Toujeo™ is administered once daily, at any time during the day, preferably at the same time every day. The recommended daily starting dose is 0.2 U/kg once daily followed by individual dosage adjustments. When needed, patients can administer their injections up to 3 hours before or after their usual time of administration. The desired blood glucose levels as well as the doses and timing of anti-hyperglycaemic medications must be determined and adjusted individually. Toujeo™ is not the insulin of choice for the treatment of diabetic ketoacidosis. Changing from once-daily basal insulin products to once-daily Toujeo™ can be done unit-to-unit based on the previous basal insulin dose. Changing from twice-daily basal insulin products to once-daily Toujeo™ , the recommended initial Toujeo™ dose is 80% of the total daily dose of the basal insulin that is being discontinued. Toujeo™ must not be mixed with any other insulin products. Toujeo™ must not be diluted. The safety and effectiveness of Toujeo™ has not been established in paediatric patients (under 18 years of age). Toujeo™ can be used in elderly patients, in patients with renal impairment and in patients with hepatic impairment. Close glucose monitoring is recommended. **SAFETY-RELATED INFORMATION Contraindications:**Toujeo™ must not be used in patients hypersensitive to insulin glargine or any of the excipients. **Warnings:** No Core Safety Information **Precautions: General** :Insulin treatment generally requires appropriate diabetes self-management skills including glucose monitoring, proper injection technique and hypo and hyperglycaemia management. Patients and their relatives must know what steps to take if hyperglycaemia or hypoglycaemia occurs or is suspected, and they must know when to inform a physician. Hypoglycemia: The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed. As with all insulins, particular caution should be exercised, and intensified blood glucose monitoring is advisable, in patients in whom sequelae of hypoglycaemic episodes might be of particular clinical relevance. The prolonged effect of subcutaneous Toujeo™ may delay recovery from hypoglycaemia. In patients with renal impairment or severe hepatic impairment, insulin requirements may be diminished. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements. Hypoglycaemia can generally be corrected by immediate carbohydrate intake. So that initial corrective action can be taken immediately, patients must carry a minimum of 20 grams of carbohydrates with them at all times. Intercurrent illness: Requires intensified metabolic monitoring. In many cases urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. **Medication errors prevention:** Insulin label must always be checked before each injection to avoid medication errors between Toujeo™ and other insulins. The patients must also be instructed to never use a syringe to remove Toujeo™ from the SoloStar pre-filled pen into a syringe and not to re-use the needles. **Pregnancy & Lactation:** It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycaemia. Toujeo can be used during pregnancy, if clinically needed. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly. Careful monitoring of glucose control, is essential in such patients. Patients with diabetes must inform their doctor if they are pregnant or are contemplating pregnancy. **Adverse Reactions:** Hypoglycaemia is most frequent and may occur if the insulin dose is too high in relation to the insulin requirement. A marked change in glycaemic control may cause temporary visual impairment. Lipodystrophy may occur at the injection site. Allergic reactions at the injection site includes redness, pain, itching, hives, swelling or inflammation. Immediate type allergic reactions are rare
For full prescribing information please write to Sanofi India Ltd., Sanofi House, CT Survey No 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai 400072
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For the use of a registered medical practitioner or a hospital or a laboratory only. SAIN.GLA.17.12.1565. 04/18

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My **NEW** Diabetes Therapy
helps me Control HbA1c & lose weight

NOVEL ß-CELL INDEPENDENT MOA[1]

UNSURPASSED EFFICACY
Compared to Glimepiride and Sitagliptin,
INVOKANA® 100mg is non-inferior[2,3]
INVOKANA® 300mg is superior[2,3]

SUSTAINED & SIGNIFICANT WEIGHT LOSS[3,4]

HYPOGLYCEMIA COMPARABLE TO PLACEBO[5]

Invokana®
canagliflozin tablets

A CLASS APART

References:

1. INVOKANA® India Prescribing Information (January 2014) **2.** Lavalle-González FJ et al. Diabetologia. 2013;56(12):2582-92 **3.** Cefalu WT et al. Lancet 2013;382(9896):941-50 **4.** Leiter LA et al. Diabetes Care. 2014. **5.** Stenlöf K et al. Diabetes Obes Metab. 2013;15(4):372-82.

For the use of a Registered Medical Practitioner or a Hospital or Laboratory Canagliflozin tablets 100mg / 300mg

INVOKANA®

Composition and Strength: Canagliflozin 100 mg / 300mg. Each 100 mg tablet contains 102 mg Canagliflozin hemihydrate, equivalent to 100 mg Canagliflozin. Each 300 mg tablet contains 306 mg Canagliflozin hemihydrate, equivalent to 300 mg of Canagliflozin. **Pharmaceutical form:** 100 mg - The tablet is yellow, capsule-shaped, immediate-release and film-coated, with "CFZ" on one side and "100" on the other side. 300 mg - The tablet is white, capsule-shaped, immediate-release and film-coated, with "CFZ" on one side and "300" on the other side. **Therapeutic Indications:** INVOKANA® is indicated as an adjunct to diet and exercises to improve glycemic control in adults with type 2 diabetes mellitus as monotherapy and combination therapy. **Dosage and Administration:** The recommended starting dose for adult > 18 years is 100 mg or 300 mg once daily orally preferably before the first meal of the day. A starting dose of 100 mg once daily should be used in patients on loop diuretics and patients ≥ 75 years of age. In patients with an eGFR 45 mL/min/1.73 m2 to < 60 mL/min/1.73 m2, the dose of INVOKANA® is limited to 100 mg once daily. The 300 mg dose may be considered for patients with an eGFR > 60 mL/min/1.73 m2, who need tighter glycemic control and who have a low risk of adverse reactions associated with reduced intravascular volume with INVOKANA® treatment. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** INVOKANA® has not been studied in pediatric patients (< 18 years), patients with type 1 diabetes and is therefore not recommended for use. INVOKANA® should not be used for the treatment of diabetic ketoacidosis or in patients with an eGFR < 45 mL/min/1.73 m2 [CrCl < 45 mL/min], as it would not be effective in these settings. In patients with evidence of reduced intravascular volume, correcting this condition prior to initiation of INVOKANA® is recommended. **Drug Interactions:** The metabolism of INVOKANA® is primarily via glucuronide conjugation mediated by UDP glucuronosyl transferase 1A9 (UGT1A9) and 2B4. If a combined inducer of these UGTs and drug transport systems (e.g., rifampicin, phenytoin, barbituates, phenobarbitol, ritonavir, carbamazepine, efavirenz) must be co-administered with INVOKANA®, monitor HbA1c in patients receiving INVOKANA® 100 mg once daily with consideration to increasing the dose to 300 mg once daily if additional glycemic control is needed. INVOKANA® neither inhibits cytochrome P450 CYP1A2, CYP2A6, CYP2C19, CYP2D6, or CYP2E1, CYP2B6, CYP2C8, CYP2C9, nor induces CYP1A2, CYP2C19, CYP2B6, CYP3A4 at higher than therapeutic concentrations. INVOKANA® is a P-glycoprotein (P-gp) substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Patients taking digoxin or other cardiac glycosides (e.g., digitoxin) should be monitored appropriately. **Pregnancy, Breast-feeding and Fertility:** There are no adequate and well-controlled studies in pregnant women. INVOKANA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known if INVOKANA® is excreted in human milk. A risk to the breast-fed child cannot be excluded. The effect of INVOKANA® on fertility in humans has not been studied. **Adverse reactions:** In clinical studies of INVOKANA® the most commonly reported adverse reactions during treatment (≥ 5%) were vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria. Other adverse reactions in clinical studies of INVOKANA® that occurred at a rate < 2% in placebo-controlled studies were adverse reactions related to reduced intravascular volume (postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope), skin rash, and urticaria. In the event of an overdose, it is reasonable to employ the usual supportive measures, including monitoring of vital signs and observation of clinical conditions. **Overdose:** Single doses up to 1600 mg of INVOKANA® in healthy subjects and INVOKANA® 300 mg twice daily for 12 weeks in patients with type 2 diabetes were generally well-tolerated. In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.
Storage: Store below 30°C and in dry place. Protect from light. Keep out of reach of children.

Warning: To be sold by retail on the prescription of Registered Medical Practitioner only. Version: CCDS 09 Jan 2014
For complete prescribing information, please contact: Johnson & Johnson Private Limited, Arena Space, Behind Majas Depot, Off J.V. Link Road, Jogeshwari (E), Mumbai 400060

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