GRCP InfoApex

Half yearly news letter

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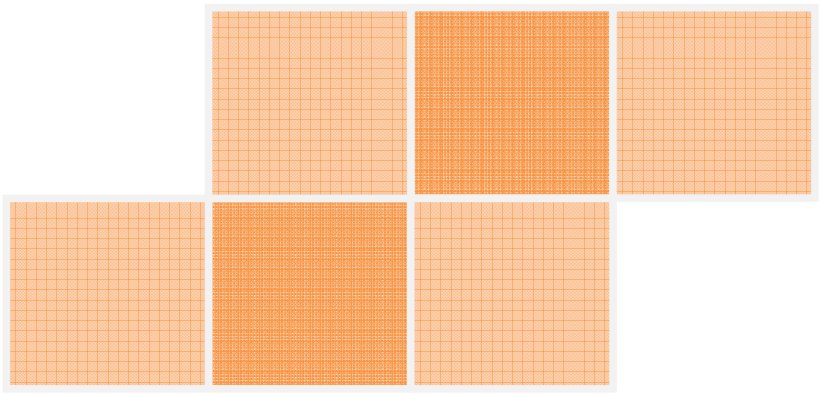

Gokaraju Rangaraju College of Pharmacy

Imparts Pharmaceutical Education of International Standards

Bachupally, Hyderabad-90. Andhrapradesh, India

Contents

Motto of this Journal
1. To provide scientific, technical and social welfare updates
2. To promote scientific drafting among staff and students
3. To circulate institutional updates
4. To build flat form to serve the community
5. To identify and appreciate potential achievements

What you need to know about diabetes?

Mrs. V. Pavani

Diabetes is a metabolic disorder that prevents the body from utilizing glucose completely or partially. The normal fasting blood sugar is 80-120 mg/dL; this can go up to a level of 160 mg/dL two hours after meals.

There are basically two types of diabetes

1. Type 1 diabetes mellitus (insulin-dependent diabetes)

2. Type 2 diabetes mellitus (non-insulin-dependent diabetes)

Type 1 diabetes

1. The body doesn't produce enough insulin to keep blood sugar at normal levels.
2. Type 1 diabetes usually occurs in childhood or adolescence but can develop at any age. These patients need insulin everyday.

Type 2 diabetes

1. The cells do not properly respond to the insulin. It is common among adults, especially those who are overweight and over age 40.
2. These people are able to control their blood sugar levels through weight control, regular exercise and a well-balanced diet.

Diabetes is on the rise, yet most cases of diabetes are preventable with healthy lifestyle changes. Some can even be reversed. The bottom line is that you have more control over your health than you think.

If you're concerned about diabetes, you can make a difference by eating a healthy diet, keeping your weight in check, and getting exercise.

What you need to know about diet?

- You do not need to eat special foods, but instead simply emphasize vegetables, fruits, and whole grains.
- A diabetes diet is simply a healthy eating plan that is high in nutrients, low in fat, and moderate in calories.

It is a healthy diet for anyone!

Eating right for diabetes helps overcoming problems associated:

What you eat?

1. Your diet makes a huge difference
2. You should eat mostly plant foods
3. Cut back on refined carbs and sugary drinks
4. Choose healthy fats over unhealthy fats

When you eat?

Diet is part of it, but keeping regular meal and snack times also affects your blood sugar levels and will help to keep them more constant.

How much you eat

Portion sizes matter. Even if you eat very healthy meals, if you eat too much you will gain weight, which is a factor in diabetes.

Symptoms of Diabetes Mellitus

- Increased thirst
- Frequent urination
- Increase in appetite
- Weakness or loss of strength
- Weight loss in type 1 diabetes
- Decreased healing capacity
- Skin irritation or infection
- Erection problems
- Obesity in type 2 diabetes

Causes of Diabetes

- Hereditary factors
- Excess intake of carbohydrate foods like chocolates, rice etc
- Insulin deficiency
- Insulin resistance
- High blood pressure
- High cholesterol
- Stressful and over burdened life
- Lack of exercise or physical activities
- Excess eating habits

Diabetes Complications

If diabetes is poorly controlled or left untreated, it may lead to

1. Hardening of the arteries (atherosclerosis): Myocardial infarction, stroke
2. Eye problem: Blindness
3. Kidney problems
4. Nerve damage
5. Limb amputation
6. Coma

Early diagnosis and treatment, the chances of living a long and productive life are higher than if the disease creeps along until irreversible damage occurs.

Natural Home Remedies for Diabetes

1. Drink a watery juice of small bitter gourd (remove seeds) every morning.
2. Add 3 table spoon of cinnamon to 1 litre of boiling water, simmer for 20 min in a low flame and then strain the mixture. Daily intake of Drinking this mixture cure diabetes.
3. Eat tender curry leaves (fresh) twice daily.
4. A teaspoonful of amla (Indian gooseberry) juice mixed with a cup of bitter gourd juice daily reduces blood glucose level.
5. (Will awaken the islets of Langerhans, that secrete the hormone insulin in the pancreatic gland and decreases the blood sugar in diabetes)
6. An infusion of mango leaves is prepared by soaking 15 gm of restorative leaves in 250 ml of water nightlong, and squeezing them well in the water. This filtrate should be consumed each morning to manage beginning diabetes.
7. Equally, as an alternative, the leaves should be dehydrated in the shade, fine-grained and preserved for use in case of necessity. Half a teaspoon of this powder had better be taken two times daily.

AVOID THESE FOODS

Avoid Dairy as Diabetes Alternative Treatment

- Cow's milk and all milk products are the cause of childhood or type 1 diabetes.
  1. Milk causes an auto-immune response in the body with acts to direct antibodies to the child's pancreas. The immune system then attacks the cells of the pancreas destroying it.
  2. Unable to produce insulin, type 1 diabetes is the result.
  3. Once the cells of the pancreas have been destroyed, they will not grow back.
- Sugar and artificial sweeteners, including honey. The only allowed sweetener is stevia.

- Sweets and chocolates, including so-called sugar-free types. (If you want a chocolate treat, say once a week, then eat Continental dark chocolate with 70% or more cocoa solids, not the British stuff where sugar is the first named ingredient.)

- Foods which contain significant proportions of things whose ingredients end in -ol or -ose as these are sugars (the only exception is cellulose, which is a form of dietary fibre)

- Grains and foods made from them: wheat, rye, barley, corn, rice, bread, pasta, pastry, cakes, biscuits, pies, tarts, breakfast cereals, et cetera.

- Starchy vegetables: potatoes and parsnips in particular; and go easy with beet, carrots, peas, beans, et cetera and packets

of mixed vegetables which might contain them

- Beans with the exception of runner beans

- Beware of commercially packaged foods such as TV dinners, "lean" or "light" in particular, and fast foods, snack foods and "health foods".

- Fruit juices, as these are much higher in carbs than fresh fruit. (If you like fruit juices as a drink, dilute about 1 part fruit juice with 2-4 parts water.)

These are foods you can eat:

- All meat — lamb, beef, pork, bacon, etc, include the organ meats: liver, kidneys, heart, as these contain the widest range of the vitamins and minerals your body needs (liver has 4 times as much Vitamin C as apples and pears)
- All poultry: chicken (with the skin on), goose, duck, turkey, etc. But be aware that turkey is very low in fat, so fat needs to be added.
- Continental sausage (beware of British sausage which usually has a high cereal content.)
- All animal and meat fats – without restriction – never cut the fat off meat.
- Fish and seafood of all types
- Eggs (no limit, but avoid "omega-3 eggs" as these have been artificially fed which upsets the natural fatty acid profile)
- All cheeses (except cottage cheese as this has a high carb content and very little fat)
- Butter and cream (put butter on cooked veges instead of gravy; use cream in hot drinks in place of milk)
- Plain, natural full-fat yogurt
- Vegetables and fruits as allowed by carb content.
- Condiments: pepper, salt, mustard, herbs and spices.

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Type 2 Diabetes mellitus (T2DM) is characterized by an increase in blood glucose concentration due to resistance of insulin action. High blood glucose (hyperglycemia) is the main pathogenic factor for the development of diabetic complications including coronary heart disease, retinopathy, nephropathy, and neuropathy In addition, chronic hyperglycemia leads to progressive impairment of insulin secretion and to insulin resistance of peripheral tissues which is known as glucose toxicity

Treatment of diabetes has been mainly focused on maintaining normal blood glucose levels by using either insulin or oral hypoglycemic agents (OHAs).The mechanism of action of the anti-diabetic agents used for the treatment of type 2 diabetes, include increasing insulin release, increasing insulin sensitivity, controlling hepatic glucose release or inhibiting intestinal glucose absorption.

Often, therapy with insulin and OHAs become less effective in controlling hyperglycemia, particularly as a result of weight gain, worsening insulin resistance and progressive failure of insulin secretion due to glucose toxicity. Insulin therapy alone or with hypoglycemic agents can produce weight gain due to reducing glucose excretion.

Among commonly used OHAs, thiazolidinediones and sulphonylurea contribute to weight gain, whereas metformin causes weight loss and dipeptidyl peptidase-4 inhibitors are weight neutral. Overall, there is a need for novel agents which can effectively control blood sugar level without producing weight gain or hypoglycemia. A number of new targets have indicated promise for the treatment of T2DM, including sodium glucose transport inhibition, glucokinase activation, glucagon receptor antagonism, fibroblast growth factor-21 receptor activation, 11β-hydroxysteroid dehydrogenase type 1 inhibition, and others.

Rationale for SGLT inhibition in Diabetes treatment:

SGLT2 is a molecular target to directly induce glucose excretion and to safely normalize plasma glucose in the treatment of type 2 diabetes. SGLT2 inhibitors increase the glucose excretion and control the blood sugar level without any risk of hypoglycemia and weight gain. Currently the upcoming molecule of this class is in phase 3 development.

Physiology and pathology of glucose transport:

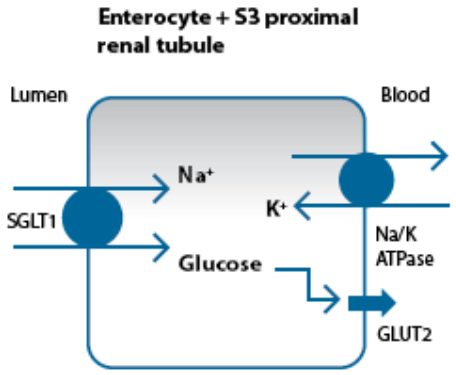
The kidney plays an important role for the body's energy control. Glucose filtered from the blood in the glomerulus is reabsorbed mainly in the S1 segment of the kidney's proximal tubule, but when the capacity for glucose reabsorption reaches saturation, excess glucose is excreted in the urine.Approximately 180 g of glucose is filtered on a daily basis, with 90% reabsorbed in the convoluted segment of the proximal tubule, and the remaining 10% in the distal straight segment of the proximal tubule.

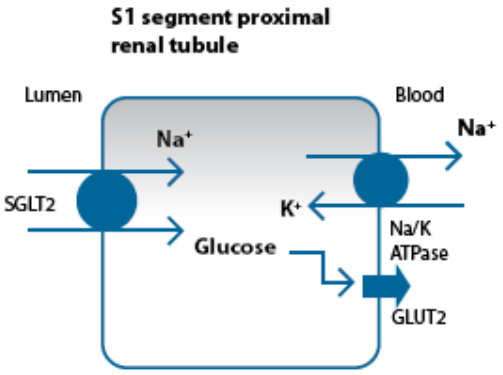
In healthy persons, glucose present in the plasma is filtered by the kidneys, but all of it is reabsorbed, such that less than 1% of glucose is excreted in urine due to not reaching to threshold value for glucose excretion.

In patients with diabetes, however, hyperglycemia can lead to hyperfiltration, and the increased luminal glucose exceeds the maximal reabsorption rate, resulting in glucosuria. As well, maximal renal glucose reabsorption can further contribute to high

plasma glucose levels. The inhibition of renal glucose reabsorption may result in decreased plasma glucose levels.

Glucose transportation in the body is mainly mediated by two types of transporters: sodium glucose linked transporters (SGLT) and facilitative glucose transporters (GLUTs). SGLT are the members of sodium substrate co-transporters .Two sodium-glucose co-transporters are responsible for glucose reabsorption: SGLT1 and SGLT2. SGLT1, which is also found in the gut and other tissues, accounts for about 10% of reabsorption.Genetic mutations in the SGLT1 gene leading to a functional defect are responsible for glucose/galactose malabsorption. The low affinity sodium glucose Cotransporter SGLT2, expressed exclusively in the S1 segment of the proximal tubule, accounts for about 90% of reabsorption .





Mode of action of SGLT1 and SGLT2

Glucose Homeostasis and Imbalance in Patients with Diabetes:

Cell membranes, which contain lipid, are impermeable to a polar compound such as glucose. Thus, carrier proteins aid in transporting glucose across the cell membrane. Once plasma glucose has been filtered by the renal glomeruli, it is reabsorbed by the SGLTs across the apical or luminal membranes of the epithelial cells of the proximal tubule, coupling the transport of sodium with that of glucose.

Cellular glucose and sodium uptake occurs in a 1:1 ratio. The sodium:potassium adenosine triphosphatase (ATP) pump transports sodium across the basolateral surface into the intracellular fluid, maintaining the physiological levels of sodium in the cell. The inward sodium concentration gradient drives the 'uphill' glucose reabsorption (a secondary active transport mechanism). Cellular glucose concentrations are maintained by facilitative glucose outflow through transporters in the basolateral membrane of the cell. After binding intracellular glucose the transporters undergo a conformational change that subsequently moderates the movement of glucose (down its concentration gradient) back into the blood.

SGLT2 mediates glucose reabsorption in the kidney. SGLT2 catalyzes the active transport of glucose (against a concentration gradient)

across the luminal membrane by coupling it with the downhill transport of Na+. The inward Na+ gradient across the luminal epithelium is maintained by active extrusion of Na+ (driven by ATP) across the basolateral surface into the intercellular fluid, which is in equilibrium with the blood. Glucose passively diffuses of the cell down a concentration gradient via

basolateral facilitative transporters, GLUT2 (and GLUT1).

Early SGLT2 Inhibitors

Phlorizin

Phlorizin, originally isolated from the bark of apple treesthe glucosuric effect of phlorizin. It could induce glucosuria in humans by inhibiting renal glucose reabsorption. Secondary effects include reversal of secondary insulin resistance due to amelioration of glucose toxicity.

Mechanism of action: Phlorizin is a competitive inhibitor of both SGLT1 and SGLT2. The glucoside moiety of phlorizin binds to SGLT2 transporters and the '*O*'-linked phenolic distal ring is responsible for its inhibitory properties.

Disadvantage: Phlorizin inhibits intestinal glucose-galactose absorption which results in glucose-galactose malabsorption. It is poorly absorbed from the gastrointestinal (GI) tract due to easily hydrolyzed by lactase-phlorizin hydrolase. Because of these demerits it has not been developed further as a medication for the treatment of diabetes, but it has been a useful tool that has been used to study the potential effects of blocking renal glucose reabsorption in the treatment of diabetes.

Phlorizin derivative T-1095

It is a prodrug of the active molecule T-1095A was developed with improved oral bioavailability. However, this compound also had significant activity against the SGLT1 transporter, and may be a nonspecific SGLT inhibitor.

Agents Currently Under Development

Dapagliflozin

Dapagliflozin is a highly selective SGLT2 inhibitor. It is more potent than phlorizin against human SGLT2 and 4-fold less potent than phlorizin against human SGLT1. Dapagliflozin stimulates significant excretion of glucose in the urine in both normal nondiabetic rats, as well as in rats that were already glucosuric because of diabetes.

Sergliflozin

It has been shown 7-fold selectivity for human SGLT2 Vs human SGLT1 in cell culture system. It induces glucosuria in healthy mice, rats and dogs., and also lower postprandial blood glucose in diabetic rats independently of insulin secretion. Minor adverse events like headache, sore throat in healthy subjects and headache, dyspepsia in diabetic patients

Remogliflozin etabonate

Remogliflozin etabonate is a prodrug based on benzylpyrazole glucoside and is metabolized to its active form, remogliflozin, in the body. remogliflozin etabonate increases urinary glucose excretion in a dose-dependent manner in both mice and rats. In normal rats, remogliflozin etabonate inhibits the increasing plasma glucose level after glucose infusion without increasing insulin secretion.

Advantages: There are many advantages of SGLT2 inhibitors to treat diabetes by increasing excretion of glucose in urine: 1) Weight loss or weight maintenance, a key target for any type 2 diabetes treatment. 2) No hypoglycemia because SGLT2 inhibitors do not induce insulin secretion or inhibit hepatic glucose production. 3) Improve insulin sensitivity and indirectly preserve β-cells by depletion of toxic glucose concentration in blood. 4) SGLT2 inhibitors also produce osmotic diuretic effect which may be advantageous in patients with hypertension and CHF.

Disadvantages: Apart from above advantages, SGLT2 inhibitors may have some disadvantages. There may be a risk of negative effect of glucosuria on the kidneys, polyuria and increased thirst, but the lack of such evidences in patients with familial renal glucosuria provides some reassurance. Another theoretical problem in relation to the genitourinary tract is increased risk for either bacterial or fungal infection, but only long term clinical trial can answer about this risk. The final concern that may be directly related to the mechanism of action of SGLT2 inhibitors is

whether some patients would experience salt-wasting.

Conclusion: Inhibition of SGLT2 represents a novel approach in diabetes treatment. SGLT2 inhibitors have significant potential in the treatment of type 2 diabetes as a class of drugs that can effectively lower blood glucose without the risk of hypoglycemia. Additionally SGLT2 inhibitors improve both fasting and post prandial serum glucose level and produce weight loss. Due to such a remarkable profile, SGLT2 inhibitors can be used to treat co morbidities like hypertension, obesity and dyslipidemia. SGLT2 inhibitors would be expected to be beneficial in treatment of T2DM either as a monotherapy or in combination with insulin or other OHAs. The results of longer-term clinical trials of safety and efficacy will ultimately determine whether SGLT2 inhibition can be added to the list of drugs that have a place in the management of T2DM.

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