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Mini Review

A glucose-centric perspective of hyperglycemia

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Digestion of food in the intestines converts the compacted storage carbohydrates, starch and glycogen, to glucose. After each meal, a flux of glucose (>200 g) passes through the blood pool (4-6 g) in a short period of 2 h, keeping its concentration ideally in the range of 80-120 mg/100 mL. Tissue-specific glucose transporters (GLUTs) aid in the distribution of glucose to all tissues. The balance glucose after meeting the immediate energy needs is converted into glycogen and stored in liver (up to 100 g) and skeletal muscle (up to 300 g) for later use. High blood glucose gives the signal for increased release of insulin from pancreas. Insulin binds to insulin receptor on the plasma membrane and activates its autophosphorylation. This initiates the post-insulin-receptor signal cascade that accelerates synthesis of glycogen and triglyceride. Parallel control by phos-dephos and redox regulation of proteins exists for some of these steps. A major action of insulin is to inhibit gluconeogensis in the liver decreasing glucose output into blood. Cases with failed control of blood glucose have alarmingly increased since 1960 coinciding with changed life-styles and large scale food processing. Many of these turned out to be resistant to insulin, usually accompanied by dysfunctional glycogen storage. Glucose has an extended stay in blood at 8 mM and above and then indiscriminately adds on to surface protein-amino groups. Fructose in common sugar is 10-fold more active. This random glycation process interferes with the functions of many proteins (e.g., hemoglobin, eye lens proteins) and causes progressive damage to heart, kidneys, eyes and nerves.

Some compounds are known to act as insulin mimics. Vanadium-peroxide complexes act at post-receptor level but are toxic. The fungus-derived 2,5-dihydroxybenzoquinone derivative is the first one known to act on the insulin receptor. The safe herbal products in use for centuries for glucose control have multiple active principles and targets. Some are effective in slowing formation of glucose in intestines by inhibiting α–glucosidases (e.g., salacia/saptarangi). Knowledge gained from French lilac on active guanidine group helped developing Metformin (1,1-dimethylbiguanide) one of the popular drugs in use. One strategy of keeping sugar content in diets in check is to use artificial sweeteners with no calories, no glucose or fructose and no effect on blood glucose (e.g., steviol, erythrytol). However, the three commonly used non-caloric artificial sweeteners, saccharin, sucralose and aspartame later developed glucose intolerance, the very condition they are expected to evade. Ideal way of keeping blood glucose under 6 mM and HbA1c, the glycation marker of hemoglobin, under 7% in blood is to correct the defects in signals that allow glucose flow into glycogen, still a difficult task with drugs and diets.

Keywords: Diabetes, Dysfunctional glycogen storage, Gluconeogenesis, Glucose intolerance, GLUTs, Herbals in glucose control, Insulin mimics, Post-insulin-receptor signal cascade, Random glycation, Tissue-specific glucose transporters

Introduction

Defective utilization of diet-derived glucose and of pancreatic insulin are generally known to cause hyperglycemia[1]. The crux of the problem in hyperglycemia is the progressive failure of storing the load of glucose that arrives in blood after each meal as glycogen in muscle and liver. If left untreated, glucose is retained in blood for a long period at a high level. The undesirable consequence is indiscriminate addition of glucose units on the surface of proteins obstructing their functions and cause irreversible damage to heart, kidneys, eyes and nerves. This perspective article is centred on glucose in the overall chain of its formation from food in digestion, dynamics in blood, transport to tissues and storage, as well as some aspects of metabolic disturbances, of substitution with artificial sweeteners and of beneficial effects of some herbal preparations.

Glucose and Glycogen as energy sources

Nature chose glucose, a water soluble 6-carbon sugar ($C_6H_{12}O_6$), among the many naturally-occurring sugars as the calorie source for delivery to tissues. Its metabolism through several steps of glycolysis, tricarboxylic acid cycle and mitochondrial oxidation yields 'energy currencies' in the form of ATP and

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NAD(P)H, and also provides carbon skeletons of other metabolites of cell components. Through glycosidic linkages large number of molecules of glucose can be compacted by specific synthase enzymes into polymeric forms of starch (plants) and glycogen (animals) as water-insoluble granules that conserve on osmolarity and storage space in cells. A distinctive advantage is thus provided to store and retrieve the required energy whenever needed. Carbohydrates, fats and proteins are derived in varying proportions from natural food material usually in two big meals in a day. These are the main sources of energy in the human body utilized in that order and contribute to the glucose pool.

During digestion of food in gastrointestinal tract, a process initiated by saliva in the mouth, the complex polysaccharides, starch and glycogen, are hydrolyzed by enzymes, α-amylase and α-glucosidase, in small intestines. Glucose thus formed appears in blood within minutes and passes through to the receiving tissues. Usually within few hours after each meal in an adult, a large amount of glucose (up to 200 g) passes through blood on the way to be distributed to all tissues it perfuses. Most of it is cleared within about 2 h and transferred to muscle and liver to be stored in the form of glycogen. This avoids prolonged elevated blood glucose. On carbohydrate-limiting diets, other digestion products from fats by lipases and amino acids from proteins by proteases are diverted to liver to form new glucose by gluconeogenesis which then joins the blood pool. Flow chart of glucose in the body is given in Fig. 1.

Hyperglycemia occurs when glucose is stranded in blood on arrival after each meal consequent to failed storage as glycogen in muscle and liver.

Distribution of glucose to tissues

Blood, a liquid tissue of about 5 L in an adult connected with all tissues in the body to supply vital nutrients, is the hub for glucose transfers. A pool of 4-6 g. of glucose is circulating blood in a normal healthy adult at the normal blood glucose concentration in the range of 80 mg/100 ml (4.4 mM) to 120 mg/100 mL (6.6 mM). Maintained even while fasting, this high millimolar concentration range is obviously necessary to ensure a gradient to facilitate its passage by diffusion into most cells, and by glucose transporters with or without insulin intervention. The demand for glucose by all tissues put together amounts to about 20 g/h (based on 2000 calories per day at 4 calories/g). It is impractical to keep exogenous supply of such amounts continuously (like in glucose drip).

Liver has a high glucose concentration ranging 5-10 mM or sometimes more, invariably higher than that of blood (about 5 mM). Liver takes up glucose from blood and converts into storage glycogen (up to 100-120 g). Liver reconverts this stored glycogen by glycogen phosphorylase and glucose-6-phosphatase to glucose to replenish blood glucose essentially to supply it to other tissues. The high liver glucose fits with outflow indicating its inherent supply role. Strangely for its own fuel, liver uses amino acid-derived α-keto acids.

Liver also forms new glucose from lactate from muscle, glycerol from adipose tissue, and glucogenic amino acids from the diet into glucose by gluconeogenesis. Indeed this process becomes the sustaining source of glucose in starvation. Glucose is

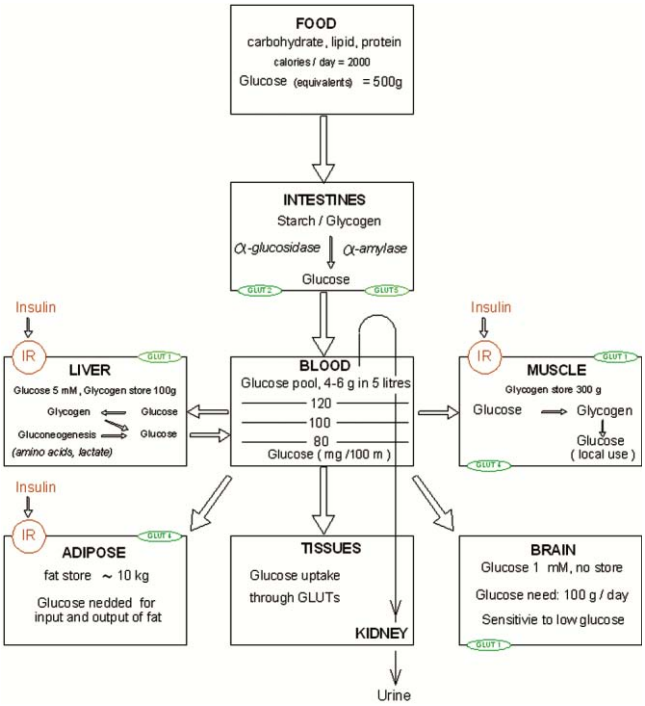


Fig. 1—Flow chart of glucose derived from starch and glycogen in food on digestion in intestines by α-amylase and α-glucosidase. The glucose load after each meal passes through blood in about 2 h giving a brief surge to the normal levels of 80-120 mg/100 ml. Glucose is drawn from the blood by tissues using specific glucose transporters (GLUTs). Insulin activates the insulin-receptor (IR) on the membrane and accelerates the conversion of glucose into storage forms in the insulin-responsive tissues, as glycogen in liver and muscle, and as triglycerides in adipose. Excess glucose will be siphoned out through kidneys into urine.

drawn at the required rate by the cells from the blood. The concentration of blood glucose is regulated by the liver from its stores or gluconeogenesis as a continuous process, enhanced by glucagon and suppressed by insulin. This reversible storing and supplying glucose to blood is a core function selective to the altruistic liver. Therefore, liver becomes the focus of attention in glucose management.

Skeletal muscle has a large store of glycogen of up to 300-500 g, almost three-fourths of all the glycogen in the body. All this is used by muscle cells after converting to glucose as energy source for bursts of muscular activity. Skeletal muscle does not export glucose.. Note significant glucose transport in this major storage tissue occurs independent of insulin. Heart muscle and smooth muscle have little or no glycogen store and directly source glucose from blood

Adipose, the fat tissue, stores enormous amount of triglyceride of about 12 kg in an adult, almost 20% of body weight. Made in liver from glucose, triglycerides are transported via blood VLDL to adipose where insulin-stimulated lipase hydrolyzes them to free fatty acids which are reconverted to triglycerides in adipocytes. Glucose is required for this, as well as for determining how much of these are returned to blood.

Brain with only about 2% of body weight is a large consumer of glucose, about 100 g daily, a little over 25% of total consumption! Glucose is maintained at 1 mM concentration in brain and has to be replenished on a continuing basis.

On depletion of glycogen store blood glucose drops to low levels (<4 mM) but is never totally lost even in fasting conditions. Supply of glucose to the tissues is inadequate at this low level. When this falls below as in the condition of hypoglycemia, the limiting glucose supply cannot meet the energy requirements, particularly that of brain and the person can become unconscious.

Glucose transporters

Selected materials are allowed passage into cells by membrane-based channels and transporters. Glucose transporter (GLUT) facilitates glucose transfer across membranes[2]. They are family of membrane integral proteins containing 12 membrane-spanning helices, with differences in rates, specificities and tissue location. Twelve isoforms (GLUT 01-12) are so far discovered in different cells. The glucose transporters basically identify glucose in circulation, utilize the diffusion gradient of glucose and transfer it across plasma membranes into the cells. Generally, density of GLUTs in membranes increases in response to decreased blood glucose to draw more glucose into the cell. (Fig. 1)

GLUT1, a ubiquitous glucose transporter, is responsible for basal and adequate uptake of glucose in muscle[3]. A highly glycosylated form of GLUT1 takes glucose across blood-brain barrier. Glucose transport into skeletal muscle utilizes both glucose transporter proteins GLUT1 and the insulin-responsive GLUT4. The amount of GLUT1 is orders of magnitude higher than GLUT4 and 'insulin treatment resulted in a modest, but significant increase in glucose uptake'[4].

GLUT2 is present in liver, kidney, small intestines carrying large glucose fluxes, and also pancreas, and serves as a two-way transporter[5]. GLUT3 is present in neurons in brain and in placenta which have a high demand for glucose. It is a high-affinity form able to pick up glucose even from low concentration.

GLUT4 in adipose tissues and skeletal muscle is the insulin-responsive glucose transporter. Insulin-mediated translocation of the transporter-containing vesicles from cytosol to the plasma membrane is unique for GLUT4. An immediate 10 to 20-fold increase in glucose transport occurs into the cell. This action rapidly removes glucose from blood into these storage tissues. It is responsible for controlling postprandial rise in plasma glucose. It is also found in brain and heart. Note liver, the other insulin-responsive tissue, does not have GLUT4.

Adipose tissue and skeletal muscle express GLUT1 as the constitutive transporter for basal glucose transport, and GLUT4 as the specialized insulin-responsive transporter for rapid disposing of glucose following a meal[6].

Information on the newly discovered glucose transporters, GLUT5-13 is now emerging. They carry out selective transport functions in some tissues and may also be used to transport other sugars. Some of the newly discovered glucose transporters are distributed in different tissues: GLUT5 in small intestine, testes and kidneys, GLUT11 in liver, lung and brain, and GLUT12 in heart, small intestine, prostate and insulin-sensitive tissues. It is commonly seen that more than one GLUT occur in a tissue.

Glucose load and tolerance

Glucose load produced in the intestines after each meal is nearly 20-fold larger than the glucose pool in blood. In a short time of few hours, this new glucose passes through blood with its level surging to a peak usually in 30 min. On completion of transfer and the

crucial rapid storage, mostly by liver (about 100 g.) and muscle (about 300 g.), blood glucose reverts to normal level in about 2 h, and is retained for about 8-12 h till the next meal. In a healthy person, the peak at 30 min will be small (about 2-fold) and it drops to a value near normal at 2 h. When the crucial mechanisms of glucose storage in liver and muscle are dysfunctional, blood glucose can rise to 4-fold or higher, and stay high for several hours beyond 2 h before returning to normal (Fig. 2). This is tested by giving a bolus of 75 g glucose orally and measuring blood glucose after 2 h, known as glucose tolerance test. The extended postprandial hyperglycemia is a characteristic of disturbed glucose homeostasis and a person having blood glucose levels of "140-199 mg/100 ml (7.8-11.0 mM)" has impaired glucose tolerance indicative of risk, according to the World Health Organization and the American Diabetes Association.

Glucose does not overshoot in blood because of inability of tissues to withdraw glucose. Some glucose enters cells all the time. Even as glucose is backing up in blood, sign of glucose intolerance, cells are not starving, and indeed there is more glucose inside some cells. Glucose transporters are apparent "regulatory inlet valves" but their under-performance does not explain failure of clearance of blood glucose. Coming through blood, the large flux of glucose is deposited, within about 4 h, as glycogen in storage tissues, muscle and liver. Under conditions of hyperglycemia some of these critical steps of glycogen storage appear to have been affected. Glucose is then retained for several hours in blood at 2-4 fold higher levels while clearing the 'flood' of glucose coming from intestines. Recently, hexane extract of *Annona squamosa* Linn. has been shown to increase insulin level and also inhibit intestinal α-glucosidase activity, and thereby help regulating postprandial hyperglycemia, a major cause for diabetic complications[7].

Insulin, the acclaimed glucose modulator

Massive influx of glucose into blood after a meal needs to be directed for storing in liver and muscle as polysaccharides or in adipose as fat, and this rapid action needs assisted transfer. Insulin is summoned by high blood glucose for this task. Insulin has a critical role in controlling glucose and lipid metabolism, and also in cell growth (Fig. 2).

Insulin secretion decreases on damage to pancreatic cells. Insufficient insulin affects hemorheological properties of blood. Insufficient insulin, for example,

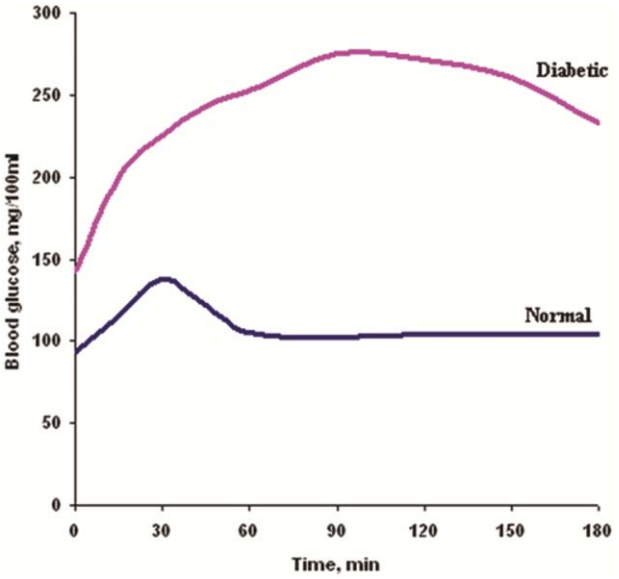
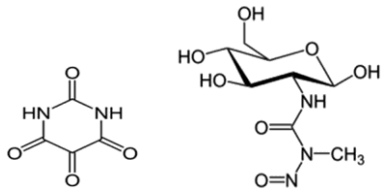


Fig. 2—Stylized diagram of typical progressive changes of blood glucose after a meal in normal healthy (●) and type 2 diabetic subjects (●). Glucose concentration 100 mg/100 ml is about 5.5 mM.



Alloxan Strepozotocin

affects hemorheological properties of blood[1]. Such damages can be produced in experimental animals by giving compounds that generate reactive oxygen (alloxan)[8-10] and nitrogen (streptozotocin)[7,11-13] species implicating these radicals as causative agents. These treatments indeed gave animal models for experimental work on diabetes. The resultant hyperglycemia, corrected by supplying exogenous source of insulin, is known as insulin-dependent-diabetes mellitus (IDDM) or type-1 diabetes[14]. Insulin therapy had phenomenal success in the early decades after its introduction in 1920's and gave the impression that this disease is under control.

Cases of hyperglycemia that fail to respond to insulin are now increasing at an alarming rate. Distressingly, resistance to insulin in the non-insulin dependent diabetes mellitus (NIDDM) or type-2 diabetes is now a worldwide epidemic according to International Diabetes Foundation. Dramatic increase in numbers of type-2 diabetes and obesity are recorded after 1960 possibly due to shift to diets with more processed food items, enriched in the nutrients but deprived of some unknown beneficial components. During large scale

processing of food items other chemicals are added inadvertently which have adverse effects. An example is the appearance of alloxan, an oxygen radical generating inducer of type-1 diabetes, in wheat flour, a common food item used for preparing white bread and rotis. It is formed during chlorine-bleaching for whitening the flour (http://community.diabetes.org/t5/ating-Right-with-Diabetes/Alloxan-in-white-bread/td-p/99829). Normally produced, as well as supplemented insulin, are less effective in controlling postprandial blood glucose under this condition. Known as 'insulin resistance', insulin receptor in target tissues is desensitized. Excess dietary calorie intake induces hyperinsulinemia, but not elevation of fasting blood glucose[15]. Increased consumption of sugar that overloads fructose is one of the causes. Indeed an easy way to produce experimental type-2 diabetes in animals is to feed a fructose-rich food. The possibility of inactivation of some critical proteins in glycogen synthesis by glycation is thereby indicated.

Insulin resistance accompanies glucocorticoid treatment

Glucocorticoid therapy is beneficial in autoimmune diseases as well as compromising immune response in saving organ transplant from rejection, and is excellent in suppressing pain and inhibiting inflammatory cytokines and inducing anti-inflammatory cytokines. Its extensive use is constrained by serious side-effects of "increased susceptibility to infection, weight gain, glucose intolerance, increased skin fragility, muscle breakdown, negative calcium balance and osteoporosis, cataracts, and CNS effects". As side-effects, glucocorticoid treatment precipitates hyperglycemia and insulin resistance as well as enhanced fat accumulation and gluconeogenesis in liver. Intracellular changes that accompany include decreased transcription of insulin receptor substrate, increased transcription of protein tyrosine phosphatase 1B (PTP1B) and of p38 mitogen-activated protein kinase (p38MAPK) in skeletal muscle, decreased insulin receptor substrate level in fat tissue, and decreased insulin receptor and of phosphorylation of insulin receptor substrate in liver, and others. Together they seem to present the same picture of hyperglycemia and dysfunctional glucose metabolism similar to type-2 diabetes[16,17].

Insulin receptor and signaling pathways

Action of insulin involves a cascade of signals in target tissues that regulates multiple metabolic events within the cells. These changes enhance uptake of glucose and its conversion and storage as glycogen in liver and muscle, and as triglycerides in adipose. Enormous information is now available describing the complex network of signals of phos-dephos, and also of redox, impacting an expanding number of proteins and activities[18]. A brief description of the events that occur on binding insulin to the insulin receptor is as follows:

1 The first crucial step in insulin action is its binding on the extracellular side to the alpha-subunit of the insulin receptor (IR), a plasma membrane-located trans-membrane protein.
2 Protein tyrosine kinase (PTK) of its intracellular beta-subunit is activated by self-phosphorylation.
3 PTK phosphorylates some tyrosine residues of the insulin receptor substrate-1 (IRS-1), a cytosolic signal transduction protein**.**
4 The activated IRS-1 protein serves as a docking base for many proteins including phosphatidylinositol-3-kinase (PI3K) and protein tyrosine phosphatase (PTP).
5 The activated IRS-1 also forms a complex with other adaptor proteins and then activates Ras, mitogen activated protein kinase (MAPK), and protein phosphatase-l-G (PP1-G).
6 Two independent and parallel signaling cascades of PI3K activated Akt (also known as protein kinase B, PKB) and of IR-PTK- mediated phosphorylation of protooncogene Cb1-associated protein (CAP) are involved in translocation of glucose transporter-4 (GLUT4) from cytosol to plasma membrane to bring glucose into the cells in liver and muscle.
7 MAP kinase and Akt inhibit glycogen synthase kinase-3 (GSK-3) known to negatively regulate glycogen synthase (GS), and thereby enhance glycogen synthesis.
8 Activation of Ras/MAPK and Akt pathways show growth and mitogenic effects.
9 Akt inhibits gluconeogenesis through disruption of a complex of the critical signaling protein-CBP to regulate glucose output in the liver.
10 PI3K-PDK-PKC pathway promotes fatty acid synthesis through activation of sterol regulatory element binding factor (SREBP-1C), a key transcription factor that regulates genes in the *de novo* lipogenesis and glycolytic pathways, and increases liver and serum triglycerides.
11 NADPH oxidase assembled on the plasma membrane that generates H_2O_2 is known to be

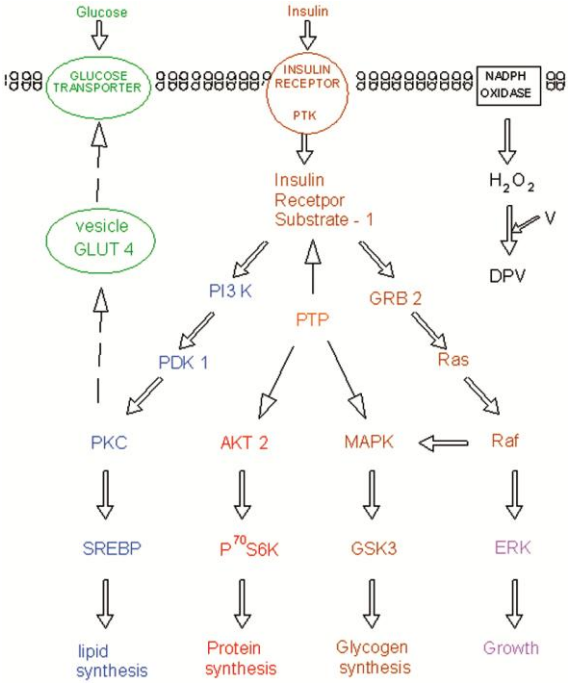


Fig. 3—A simplified scheme of insulin action in insulin-responsive tissues. Insulin binds to the insulin receptor on the outside and activates receptor protein tyrosine kinase on the inside that phosphorylates the insulin receptor substrate-1, a docking protein, and initiates the cascade of reactions including enhanced synthesis of glycogen and transfer of glucose transporter vesicles to the membrane. Insulin is known to activate H_2O_2-generating NADPH oxidase. H_2O_2 complexes with vanadate to form stable diperoxovanadate and all these three are known insulin mimics possibly by inactivating phosphatases and by activating kinases in the cascade. Abbreviations: PTK (protein tyrosine kinase), V (vanadate), DPV (diperoxovanadate), PI3K (phosphatidylinositol -3-kinase), PTP (phosphotyrosine phosphatase), GRB2 (growth factor receptor bound protein), PDK1 (phosphoinositide-dependent kinase), Ras (signal transducing small GTPases), PKC (protein kinase C), AKT2 (RAC-beta ser/thr protein kinase, also known as protein kinase B), MAPK (mitogen-activated protein kinase), Raf (RAF protooncogene ser/thr protein kinase), SREBP (sterol regulatory element binding factor), $P^{70}S6K$(S6 ribosomal protein ser/thr kinase), GSK3 (glycogen synthase kinase-3), ERK (extra cellular signal regulated kinase), GLUT4 (glucose transporter 4).

activated by insulin action. H_2O_2 and vanadate form the complex, diperoxovanadate (DPV). DPV is stable at physiological pH, catalase-resistant and substitutes H_2O_2 in peroxidation reactions.

12. H_2O_2, vanadate and DPV are known to be insulin-mimetic. Vanadate inhibits phosphate hydrolysis in general and also PTP. H_2O_2 and DPV activate some of the kinases in the cascades.

A simplified scheme of reaction pathways is given in Fig. 3.

The broad purpose of the insulin cascade is to rapidly deposit the absorbed glucose resource in the form of glycogen in liver and muscle and triglycerides in adipose that can be retrieved on demand by tissues. Revelation of the multiple steps, enzymes and proteins implicated in the overall process of glucose homeostasis leaves one in wonder why such complex system is necessary and why it fails in some instances. Embedded in this broad potential are the possibilities of endogenous as well as exogenous compounds acting as insulin mimics by targeting any one of these intracellular steps. Indeed, success of a few of these cases provides hope to control this epidemic.

It is hard to believe that insulin has marginal effect on most tissues. The insulin-responding tissues are liver, muscle and adipose. Most of concepts of insulin action are built on studies with adipocytes, and not all are applicable to other cells.

It is normal to have increase in glucose in blood after each meal. Insulin and its receptor, evolved for smooth management of blood glucose, ensure that it is transferred to the storage tissues, liver, muscle and adipose. The trouble starts when insulin receptor loses this ability progressively over a period of years. The insulin receptor is modified and desensitized and the poor response to insulin is not overcome even with extra insulin summoned. In its wake other metabolic problems crop up as the higher glucose, now retained for several hours imparts its slow damage. Selective diets and regular exercise continue to be of help.

Some beliefs on insulin and its action need rethinking**.** It is hard to believe that insulin has marginal effect on most tissues. The true insulin-responding tissues are liver, adipose and muscle. Most of concepts of insulin action are built on studies with adipocytes. And not all are applicable to other cells. Located in intracellular vesicles insulin-responsive glucose transporter, GLUT4, is known to migrate to plasma membrane in response to insulin to hasten otherwise slow glucose entry. This is established only in adipose. Glucose uptake is not insulin dependent in most tissues. It is not true that tissues and cells cannot take up glucose without insulin. Concentration gradient across the cell membrane is a determining factor for glucose uptake in peripheral tissues that use different GLUTs. It appears that a majority of glucose uptake is normally insulin independent. The significant action of insulin in liver is its inhibition of gluconeogenesis and glucose production thereby

controlling postprandial blood glucose. Insulin is necessary but alone will not suffice in glucose control.

Post-receptor intracellular insulin mimics

Chromium

Chromium mimics some effects of insulin on blood glucose and lipids. Chromium was identified as the active 'glucose tolerance factor' found in brewer yeast that decreased blood glucose. Chromium increases translocation of GLUT to the plasma membrane independent of insulin signaling. As a complex with a small 1500 kD oligopeptide composed of glycine, cysteine, glutamic acid and aspartic acid, chromium binds to insulin-bound insulin receptor and enhances its protein tyrosine kinase (PTK) activity. By inhibiting phosphotyrosine phosphatase (PTP), it retains the phosphorylation status of insulin receptor and increased insulin sensitivity[19]. Chromium picolinate is used to correct some of the diabetes symptoms in patients, albeit the extended claims are under debate. Trivalent chromium, present in common food items, is an essential nutrient, now routinely added to total parenteral nutrition (TPN) solutions and to vitamin and mineral supplements (450 μg or more per tablet).

Vanadium

Vanadium, a trace transition element, with versatile redox properties, mimics effects of insulin signaling cascade[20]**.** Insulin-like effects were obtained with vanadate in adipocytes depleted of insulin receptors indicating post-receptor action. Vanadate activates two cytosolic protein kinases, mitogen activated protein kinase (MAPK) and non-receptor protein tyrosine kinase (PTK), known to influence glucose metabolism. The most significant end-effect of vanadate is to improve and retain the phosphorylation status of proteins involved in the downstream signal cascade of insulin[21]. This is because it is a powerful inhibitor of hydrolysis of phosphate esters, first discovered with ATP[22]. For the same reason, its salts are toxic and therefore, must be used with due caution. Reducing toxicity of vanadium by complexing it with organic ligands is actively being pursued. At low sub-toxic doses metavanadate (anionic pentavalent vanadium) and vanadyl sulfate (cationic teteravalent vanadium) do show clear effect of decreasing glucose and triglycerides, and on long treatment improved the secondary damages to kidney and eye[23].

Metavanadate is added to multivitamin and minerals tablets (Equate, 100 μg per tablet) and to iodized-protein hydrolysate tonic (neogadine, 440 μg per 10 mL dose) formulated in France a century back. It is included in homoeopathic *Materia medica* for some chronic diseases. Thus, sub-toxic doses of vanadium and chromium, as present in multivitamin and mineral tablets, could be useful in glucose management.

Hydrogen peroxide

Mukherjee and coworkers[24] found that insulin added to adipocytes in culture stimulated plasma membrane based activity of H_2O_2-generating NADPH oxidation, in addition to other insulin-responsive actions. This gave the clue that endogenous H_2O_2 may act as an intermediate in insulin actions, possibly by phos-dephos reactions and by oxidizing reactive sulfhydryl groups known to regulate glucose transport[25]. Added membrane-permeable hydrogen peroxide (H_2O_2) in cell culture studies elicits post-receptor insulin actions: increased protein tyrosine phosphorylation and decreased of protein tyrosine phosphate hydrolysis, enhanced glucose transport, increased glycogen synthesis, and stimulated lipogenesis. H_2O_2 also stimulates these post-insulin receptor reactions. Increasing generation of endogenous H_2O_2 in the cells will be able to mimic insulin actions. Insulin itself stimulates plasma membrane-based NADPH oxidation and generates H_2O_2 in adipocytes[24]. Thus, H_2O_2 fulfills the necessary criteria of an endogenous insulin mimic[26].

Vanadium peroxides

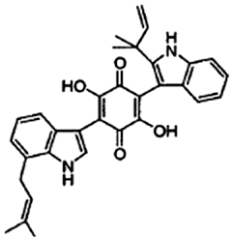
It is a coincidence that both H_2O_2 and vanadate have similar insulin mimic actions. How can the small amounts of H_2O_2 be effective in presence of abundant cellular catalase? This can be achieved by the complex diperoxovanadate (2 H_2O_2 + V), stable at physiological pH, refractory to catalase, and 10- to 100-fold more effective[27]. H_2O_2, vanadate and diperoxovanadate have strikingly similar effects of enhanced glucose transport, glucose oxidation, lipogenesis, glycogen synthase, and protein tyrosine kinase (PTK), and also inhibition of lipolysis, protein tyrosine phosphatase (PTP). H_2O_2 as diperoxo-vanadate at much lower concentration can regulate the post-insulin receptor cascade by redox operation in parallel with phos-dephos reactions. H_2O_2 and vanadate, both toxic to cells, occur mercifully in very

VO_3^-	VO^{2+}	$^-OV(O\text{-}O)_2$
Metavanadate-V^V	Vanadyl-V^{IV}	Diperoxonanadate-V^V

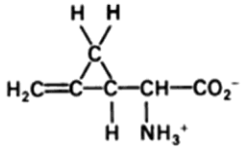
small amounts, and apparently are physiologically functional owing to the vastly enhanced activity of their complex.

New insulin mimic at receptor level

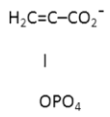
Insulin, an endogenous oligopeptide, is known all these years to regulate glucose in the few significant insulin-receptor sensitive tissues. Insulin mimics known so far target intracellular events after the membrane-located insulin receptor is activated. Now this field is open to non-peptide, exogenous small molecules. Merck laboratories (NJ, USA) discovered in 1999 that a fungal metabolite (3,6-substituted-2,5-dihydroxy-benzoquinone) isolated from *Psuedomassaria* sp. acts as insulin mimic in several insulin-specific assays and also lowers blood glucose[28]. Its selectivity of insulin receptor tyrosine kinase, and not others, is remarkable. Oral administration of the compound to db/db mice corrected hyperglycemia and hyperinsulinemia. Information is awaited on the new dihydroxyquinone with respect to its toxicity, redox activity and response under conditions of insulin resistance.



2,5-Dihydroxy-1,4-benzoquinone (3- and 6- substituted)



Leucine derivative



Phosphoenolpyruvate

A plant toxin mimicking insulin action of inhibiting gluconeogenesis

An unusual amino acid, α-(methylenecyclopropyl) glycine[29], was isolated from litchi seeds as early as 1962. This compound was effective in lowering blood glucose in animals. It is a derivative of leucine with cyclopropyl ring and a methylene group. The litchi compound might inhibit the key gluconeogenic enzyme, pyruvate caboxylase, as the methylene group (H_2C=C–) in its structure is common with the critical intermediate, phosphoenolpyruvate.

An episode in Muzaffarpur area in Bihar, India in 2013 around the month of June linked consumption of litchis and undernourishment to neurological responses. "Children under the age of 15 are jolted awake in the middle of the night with seizures, mental confusion and memory loss" reported Priyanka Pulla[30]. After a systematic elimination of inflammation and pesticide toxicity in the brain, investigators have focused on litchi fruit, abundant at that time of the year, consumed by these children. Similar episodes of neurotoxicity are reported from Bangladesh, Vietnam and other places where litchis or related fruits are consumed. Unusually, low blood glucose, as low as 48 mg/100 mL, in these patients was uncovered in routine clinical examination. This surprising finding gave the vital clue that a litchi toxin might be causing severe hypoglycemia[31]. Brain, a large consumer of glucose without a store, depends on continuous supply from blood and is extremely sensitive to glucose starvation. The response symptoms very much like insulin shock were found in these children. The attacks occurred at night by which time their apparently inadequate glycogen stores in livers would have been exhausted. Then, new glucose synthesized by gluconeogenesis in liver should have become the alternative source to blood which must have failed. The toxin possibly blocked it allowing the blood glucose to dip below danger mark. Oral supplement of fast absorbing dextrose (glucose) indeed saved some of these patients.

Why is high glucose harmful?

Glucose is one of the abundant chemicals in cells. Sweetness is incidental to its recognition in the mouth by sweet buds (only "tongue deep") with no relevance beyond. How can such a nice, sweet and useful natural constituent be harmful? It is because of its tendency to randomly react with amino groups of surface-exposed lysine and arginine residues in proteins[32]. Unstoppable chemical addition of glucose units to proteins follows. This is a slow non-enzymatic chemical reaction and its rate depends on glucose concentration. The process is known as glycation[33]. This protein glycation is slow and small but the products accumulate over the years and interfere with cellular functions almost in all body tissues.

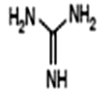
This is in contrast to the enzyme-catalyzed glycosylation that adds glucose units at specific defined positions on proteins to make them functional. Glycation is initiated by forming Schiff's base followed by rearrangement and cross-linking reactions.

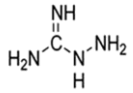
High blood glucose is harmful because glucose units are added randomly to several proteins (eg. skeletal collagen, blood hemoglobin, neuronal myelin, eye lens crystalline) progressively interfering with their functions.

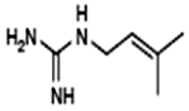
The glycated proteins and advanced glycation endproducts (AGE) accumulate.in cells At normal glucose levels in blood (4-6 mM), some glycation occurs in all body proteins and these pose little problem. But at persistent high postprandial glucose (PPG) random increase in glycation interferes with functions of some proteins. Some examples are: skeletal structures collagen, endothelium proteins, blood fibrinogen, nerve cells myelin, brain amyloid precursor proteins, eye lens crystallins and red blood cells hemoglobin. Increase in glycation decreases functional ability of these proteins. Accumulation of such proteins over extended period of several years progressively causes multiple damages. The effects are severe on the long lasting proteins and in long-lived cells in age-dependent chronic diseases. The preferred option therefore is to keep the blood glucose low in normal limits. Recently, phlorotannins (100 µL) from brown algae *Padina pavonica*, *Sargassum polycystum* and *Turbinaria ornata* have been shown to have protective effects against AGE formation[34].

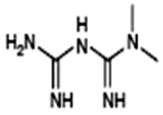
It follows that keeping protein glycation within limits will have long term benefits. Glycated hemoglobin, HbAlc, is a marker for protein glycation over a 3-month period, the normal life-span of red blood cells. In normal healthy people HbAlc is in the range of 4.0-5.9 %. It will go beyond 8.0% in severe diabetes cases. The existing recommendation to keep HbAlc below 7.0%, indicative of good management, is now considered excessive, especially in patients aged and in poor health. The required intense medication for achieving the target increases risk of consequent hypoglycemic responses such as ‘confusion, coma, falls, and fractures.

Competing amino-compounds can protect lysine/arginine from glycation. Arginine itself is an efficient inhibitor of glycation and AGE formation tested *in vitro*[35]. Free lysine and arginine occur in low amounts but sustaining them at higher levels is impractical. Aminoguanidine, having guanidine group similar to arginine, is capable of preventing protein glycation *in vivo*[36]. Similarly, phlorotannins too exhibit protective effect against AGE formation *in vivo*[34].


Guanidine


Aminoguanidine


Galagene


Metformin

Requirement of unacceptable high concentrations coupled to its other pharmacological actions such as inhibition of nitric oxide synthase and diamine oxidase makes aminoguanidine unsuitable as a drug. The commonly used drug Metformin (glucoformin) is methyl-biguanide.

Some extracts of culinary herbs and spices, correlating with their total phenolic content, prevent fructose- and glucose-mediated protein glycation of serum albumin[37]. Typically, isoferulic acid, a common plant phenolate, is highly efficient in blocking protein glycation[38]. The plant products show many biological activities in test systems *in vitro* but only those that overcome the barrier of intestinal absorption and reach the tissue sites will be effective.

The preferred option, therefore, is to keep the blood glucose low in normal limits. For achieving this, the factors that slow down formation of glucose during digestion and absorption and limiting consumption of high-starch foods and sugar assume importance. Some sugar substitutes have come into use as artificial sweeteners.

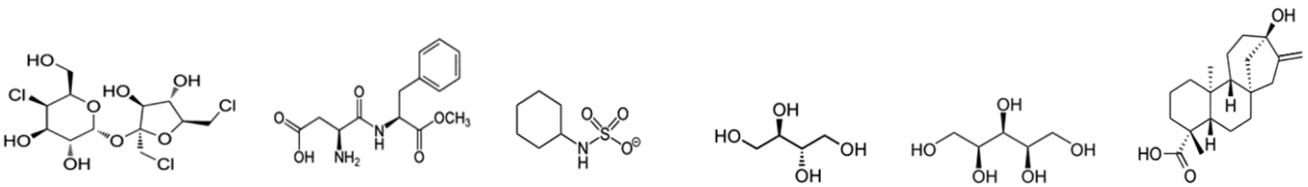
Sugar substitutes

Common sugar, sucrose (1:2 linked glucose and fructose), is an energy source. With increasing fondness of sweet food items, the share of sucrose and syrups in the diets is increasing with a consequent spurt in fructose, a glycating sugar 10-fold more active than glucose. Awareness of the danger of high blood glucose forced drastic reduction of sugar consumption. Being unable to give up the sweet taste, replacement with sugar substitutes— artificial sweeteners, has been widely practiced over several decades. Some of them in common use are listed in table 1.

Some natural food items or those used in traditional medicine for health benefits and are generally regarded as safe are now replacing the synthetic chemicals. Invariably, these are mixtures of sweet

Table 1— Some common sugar substitutes/artificial sweeteners and their properties

Sugar substitutes/ artificial sweeteners	Properties
Saccharin (ortho-sulphobenzamide)	Oldest chemical product in use for a long time, is about 300 times as sweet as sucrose, but has a metallic aftertaste. It slips through the human digestive system without gas formation and is generally regarded as safe
Sucralose (trichlorosucrose)	Chlorinated product of sucrose, is not metabolized, therefore non-caloric. It is about 500 times as sweet as sucrose
Aspartame (methyl L-α-aspartyl-L-phenylalanine)	Dipeptide, is about 200 times sweeter than sucrose
Cyclamate (sodium N-cyclohexylsulfamate)	Synthetic chemical, about 30 times sweeter than sucrose. It is banned because it is procarcinogenic.
Erythrytol (butane-1,2,3,4-tetraol)	Non-caloric 4-carbon sugar alcohol, and has no effect on blood glucose. It is absorbed into the bloodstream and excreted in urine and feces, and therefore no gastric side effects. It is about 60% as sweet as sucrose
Xylitol (pentane-1,2,3,4,5-pentol)	Sugar alcohol, with low calories and glycemic index and has laxative effect common with sugar alcohols. It is as sweet as sugar with virtually no aftertaste
Stevia (C_{20}-diterpenoid compounds)	From extract of South American stevia plant, contains glycosides of steviol (rebaudioside A) that do not ferment, therefore zero calories. It provides health benefits of regulating blood sugar and blood pressure but side-effects on long term use are not known. It is up to 300 times sweeter than sugar with little aftertaste[39]
Levulose (fructose)	Used as a safe sugar substitute. Has same calories as glucose and sugar but sweeter. It has lower glycemic index and does not increase blood glucose or insulin, considered virtues. Fructose consumption actually causes insulin resistance, increases blood pressure, triglycerides and cholesterol. Fructose selectively induces its own transporter GLUT5 to enter liver where it is phosphorylated by a specific fructokinase and then enters metabolism. In fact fructose is a major driver of type 2 diabetes[40]
Honey (a mixture of sugars)	Used sometimes in place of sugar. Contains typically fructose (38%), glucose (31%), maltose (7%), sucrose (1%), similar to inverted sugar with only 50% glycemic index of sucrose. It has all the negative attributes of free fructose
Agave syrup	Extract from agave, a medicinal plant, is used as sweetener and fermented to make tequila drink in Mexico. It is as good a calorie source as sucrose but 50% more sweet. It is a mixture of glucose and fructose like most syrups but has a very high fructose (up to 80%). Because of abundance of fructose it shares the concern of health risk of insulin resistance and elevation of triglycerides
Coconut palm sugar	Made from the sap of coconut palm. It is light brown in color, retains other accompanying minor constituents and flavor as unprocessed common sugar, contains upto 80% sucrose and has same food value as sucrose. It has a low glycemic index (35%) because it contains inulin, an indigestible fructose polymer fiber, which slows glucose absorption



Sucralose Aspartame Cyclamate Erythritol Xylitol Stevia

sugars with same calories as sucrose but lower in glycemic index. However, their high fructose content is a matter of concern.

Artificial sweeteners induce glucose intolerance!

The current popular artificial sweeteners are recommended to reduce glucose load in hyperglycemic patients. Primarily, they are several times sweeter than sucrose and therefore, smaller quantities will suffice. Little or no calories are added at that level of intake. Additionally, they have low glycemic index, or metabolically inert or bypass intestines and excreted in urine. These valuable properties indeed justify large scale over-the-counter use of these products. But this proved to be a false sense of safety. It is known for some time that use of artificial sweeteners, such as in 'diet soda', increased risk of type 2 diabetes[41]. Direct experimental work with mice and humans now confirmed this suspected

connection beyond doubt. Chronic consumption of the three commonly used non-caloric artificial sweeteners of saccharin (synthetic benzoamide derivative), sucralose (chlorinated sucrose) or aspartame (dipeptide) developed typical symptoms of glucose intolerance after 11 weeks in experimental mice. Saccharin, the longest in use as sugar substitute, showed the most pronounced effect[42].

This unexpected activity on glucose intolerance of these compounds gets blocked on treatment with Gram-negative-targeting broad-spectrum antibiotics. Dietary components that pass through intestines alter gut microflora which influence host physiological responses. These three tested compounds must have been involved in 'compositional and functional alterations to the intestinal microbiota'. In saccharin-treated mice, altered abundance of *Bacteroides* genus and *Clostridiales* order, along with *Lactobacillus reuteri* was part of the 'dysbiosis'. This effect of increased glucose intolerance by consuming artificial sweeteners was also reproduced in a human study consisting of normal, healthy, non-diabetic adults. Higher fasting blood glucose, glycated hemoglobin (HbA1c% indicative of average glucose concentration over the previous 3 months) and impaired glucose tolerance indicated by enhanced retention of glucose in blood after meal correlated with consumption of artificial sweeteners. Their effect of intolerance to glucose was never thought of and probably was never tested as they were anyway consumed by persons with high blood glucose. It is scary to think that these sweeteners, now found their way in some "sugar-free" foods and drinks, cause glucose intolerance.

Some plant materials in management of blood glucose

Plant extracts showing hypoglycemic effect in animals are legion: *Abroma augusta*[43], *Aegle marmelos* (L.)[9], *Allium sativum* (garlic), *Andrographis panniculata* (Burm. F.)[14], *Annona squamosa* Linn.[7], *Azadirachta indica*[43], *Brassica juncea* L.[8], *B. nigra* (L.) Koch[44], *Bougainvillea spectabilis*, *Cassia auriculata* L.[45], *Centella asiatica* (L.)[46], *Coccinia indica*, *Combretum leprosum*[17], *Costus igneus* Nak.[47], *Cyclea peltata* Lam.[48], *Embelia ribes* Burm[49], *Enicostemma littorale* Blume[50], *Eugenia jambolana*, *Ficus bengalensis*, *Gymnema sylvestre*, *Momordica charantia*[51], *M. cymbalaria* Fenzl[13], *M. foetida*, *Morus indica*. L.[47], *Pterocarpus marsupium Roxes* (Vijayasar), *Salacia oblanga*[52], *Syzygium cumini* Linn.[53], *Terminalia belerica* Roxb.[54] *Trigonella foenum graecum*-fenugreek[55], *Zizyphus zujuba*, etc., and also polyherbal formulations[56-58]. Some of these have been tested in experimental animal models and their effects confirmed. In most cases these preparations showed no toxicity. A few of them are vegetables and spices commonly used in local diets while some are in use in traditional medicine since long. The latter are briefly discussed below with the active principles identified in them.

Galega officinalis (French lilac)

Flowers, leaf, stem, and seeds of this plant are known since middle ages to relieve the symptoms of diabetes. The plant contains a large variety of minor chemical constituents such as triterpenoids, alkaloids, flavonoids, common with many plants. It contains guanidine, a group present in arginine molecule. It is also present in galegine (isopentenyl guanidine), capable of decreasing blood sugar. Galagene is known to enhance glucose uptake and inhibition of acetyl-CoA carboxylase, and thus contribute to weight loss[59]. Both guanidine and galegine are not suitable for human use. But these studies led to discovery of less toxic biguanide derivatives, including metformin, currently the favored drug in use.

Momordica charantia [Bitter gourd, *Karela* (Hindi), *Kakara* (Telugu)]

It is an edible vegetable in common use in food for a long time, without any side-effects. It is also used as antidiabetic in traditional medicine[51,56,57]. The extracts are known to decrease gluconeogenesis, increase glucose uptake and potentiate action of insulin. The fruit contains several bioactive compounds belonging to terpenoid glycosides, charantin and momordicin. It is known to have guanides which might contribute to its antihyperglycemic effect. Researchers have already isolated orally active hypoglycemic compounds from Kakara[60].

Trigonella foenum-graecum (Fenugreek)

The leaves and seeds of this plant are known to have antidiabetic principles in traditional medicine**.** The active ingredients are the alkaloid, trogonelline and the lactone, coumarin from the fiber-rich fraction of fenugreek seeds. The seeds have guanides too. Fenugreek lowers blood sugar without changing insulin levels, thus improves insulin action. It also inhibits intestinal disaccharidases and slows glucose absorption as well as glycation of hemoglobin. These actions could be due to 4-hydroxyisoleucine, an unusual amino acid present in its seeds[10,42,55,61], a possible inhibitor of gluconeogenesis.

Gymnema sylvestre [*Madhunaashini* (Sanskrit), *Gur-mar* (Hindi), *Chakkarakolli* (Malayalam), *Podapatri* (Telugu)]

It is one of the main herbs (leaves and roots) used for treating diabetes. Treatment with extracts from gurmar decreased blood glucose and glycosylated haemoglobin and plasma proteins, and absorption of glucose from the intestine[56,59,62]. Gurmar may also increase the amount of insulin in the body possibly by regenerating pancreatic beta cells. Bioactive constituents are triterpenoid oleanane saponins known as gymnemic acids. The active gymnemic acid has the peculiar property of blocking perception of sweetness of sugar.

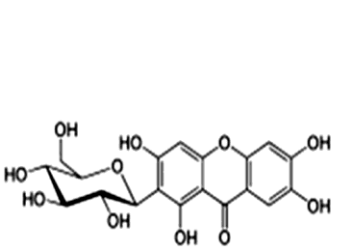
Emblica officinalis, syn: *Phyllanthus emblica* [*Amla* (Hindi)]

The Indian Gooseberry, amla (amlaki) is an edible fruit native to south-east Asia and southern India. A popular item in ayurvedic medicine[57], dried and fresh fruits have many medicinal properties, including decreasing blood glucose[60,63]. Amla, a rich natural source of vitamin C, contains a variety of polyphenols (phenolics and tannins), flavonoids (quercetin, rutin, kaempferol), and alkaloids (phyllantine and phyllantidine).

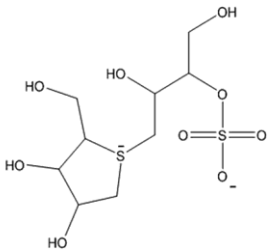
Salacia oblonga [*Saptarangi* (Sanskrit), *Ponkoranti* (Tamil)]

Saptrangi is a perennial woody climbing vine native to India and Sri Lanka. The extract of its roots is used for centuries in traditional Indian ayurvedic medicine for oral treatment of diabetes[52]. *Salacia* species contain a variety of nutraceuticals, anthocyanidins, catechins, phenolic acids, quinones, triterpenoids among others. The major bioactive constituents in *S. oblonga* are a xanthonoid glucoside, mangiferin, and two unique thiosugar sulfonium sulfate compounds, salacinol and kotalanol[64]. Consumption of salcacia extract decreased insulin and glycated hemoglobin (HbA1c) proportionate with decrease in glucose. Other enzyme activities in the tissues including at some post-insulin-receptor sites as indicated by stimulation of glucose uptake are also regulated by salacia extracts.

S. oblonga extract and its bioactive components lower the rate of glucose availability by inhibiting α-glucosidase. The side-effects of salacia extract are mild discomfort of diarrhea (soft feces) and flatulence (rectal gas passages), typical of inhibitor action of α-glucosidases (maltase, sucrase and isomaltase). This inhibitory action is due to salacinol and kotalanol. Mangiferin, the other component also inhibited sorbitol-generating aldose reductase and α-amylase, in addition to α-glucosidase. These



Mangiferin



Salicinol

actions restrain glucose availability from digestion into blood, regardless of insulin status and action. Consequently, postprandial glucose and consequent glycation of proteins decrease. Further, mangiferin in salacia extract also has direct stimulating effect on glucose uptake in muscle cells, indicative of increase in the GLUT transporter in the plasma membrane.

Cinnamomum cassia/Cinnamomum zeylanicum (Cinnamon)

It is obtained from the inner bark of the tree and is used as a spice in both sweet and savoury foods. The flavour and the pungent taste of cinnamon are due to the essential oil containing cinnamaldehyde (about 90%). Other minor chemical components are ethyl cinnamate, eugenol, beta-caryophyllene, linalool and terpenes (pinene, cymene). Cinnamon is a popular product used in the treatment of diabetes (type 2) and insulin resistance and is known to reduce glucose, triglyceride, and total cholesterol in blood.

Vanadium containing edible plants

Notable vanadium containing edible plant materials are the commonly used black pepper, tea leaf and cocoa powder. Generally, flowering plants have high vanadium content (average, 763 µg/kg) distributed in leaves (682 µg/kg), roots (600 µg /kg), flowers (352 µg/kg) and fruits (112 µg/kg). Wild thyme (*Thymus pulegioides*), a favorite American culinary item, accumulates vanadium from 263 µg/kg to whopping 76300 µg/kg depending on the location. Other vanadium-rich species are *Geum urbanum* (225-18500 µg /kg), *Urtica dioica* (133-14500 µg /kg), *Hypericum perforatum* (92-2060 µg /kg) and *Valeriana officinalis* (72-1846 µg /kg)[65]. Locally called *Mushk-e-Bala*, *V. officinalis* is considered to be an important medicinal herb in Kashmir valley[66].

The extractives of these plants will become acceptable therapeutics, if toxicity of their natural concentrates of vanadium is within limits. An example is provided by the fermented product of a mushroom (*Coprinus comatus*) enriched with vanadium showed antidiabetic related activities in animal models: blood glucose and HbA1c decreased,

insulin secretion and glycogen synthesis increased, gluconeogenesis decreased, glucose tolerance improved as co-effect of the ferment and vanadium therein. These are short-term experiments showing effectiveness of the ferment, with unstated expectation that the edible nature of the mushroom makes it safe from vanadium toxicity[67].

Apart from the plants and plant parts, Zinc ash (*Jasada bhasma*) is also used in ayurvedic medicine for treating diabetes and also it has been scientifically validated[68].

Renewed interest in finding alternatives for insulin in natural products or other chemicals is now resurgent. Even the limited cases of herbals listed here have diverse bioactive components and act at different targets in manifesting the primary observation of decreasing blood glucose. They have a variety of active components, guanidine derivatives, terpenoid glycosides and saponins, alkaloids, polyphenols, xanthonoid glycosides, sulfonium compounds and others. They show one or more of the following actions: lowering blood glucose and HbA1c, increasing glucose uptake from blood, stimulating post-insulin-receptor sites, potentiating insulin action, regenerating pancreatic cells, blocking gluco-neogenesis in liver, and inhibiting glucosidases in intestines. The overall decrease in blood glucose is likely to be a combined effort of many effectors present in herbals and many targets in tissues. All these either slow down flux of free glucose into blood or hasten its removal into tissues, the two significant parts that determine blood glucose levels. In addition to herbal sources, some mushrooms described above enriched with vanadium are likely to be beneficial.

General observations

During the last 6 decades, a shift occurred to diets high in sugar, carbohydrates and saturated fat. The accompanying dependence on processed and stored food items unwittingly depleted of some yet-unknown essential nutrients. According to the recommendation of World Health Organization intake of sugar should be kept below 10% of total energy which works out to less than 50 g per day. A diet high in sugar and fat is shown to induce glucose intolerance, reduced insulin sensitivity as well as insulin resistance[15]. High sugar intake, among others, is contributing to the current, worldwide diabetes epidemic. The number of worldwide diabetics in 2015, 90% of type 2, is estimated at 415 million (about 8.8% of the total population) and galloping to reach 642 million by 2040[69]. Top 3 countries are China (109.6), India (69.2) and USA (29.3 million). Globally, more than half a million children are known to suffer from type 1 diabetes. Curiously, more than 20% of the population is diabetic in some small island countries in Pacific and Micronesia region. The highest figures are for Tokelau (29.7%) and Maritius (24.3%)[69]. It is a coincidence that they depend on import of processed foods.

Glucose intolerance and insulin resistance are parts of the same overall phenomenon — inability for blood glucose to quickly transfer to storage forms. Insulin is believed to act through activation of its receptor. Post-insulin-receptor intracellular cascades have more than one activation mechanism that apparently cross-talk, such as phos-dephos and redox (eg. activation of MAP kinase). These seem to have evolved as built-in safety yet offer no security. All proposals of control of blood sugar, and its failure, are centered on insulin. That hyperglycemia can occur by other means is now becoming clear.

Issues of glycogen synthesis and storage have not received sufficient attention. Inborn errors with defective genes related glycogen synthesis are known to show hyperglycemia. For example, carriers of mutant gene of glycogen synthase in muscle show impaired glycogen synthesis but normal glucose tolerance[70]. But hyperglycemia precipitated at later age as in diabetes points to losing the existing capacity for controlled synthesis and storage of glycogen in normal individuals. Content and synthesis of glycogen in muscle[71] and liver[72] were indeed decreased in type 2 diabetes by about half. Insulin is known to stimulate muscle glycogen synthesis by increasing activity of glycogen synthase[73]. This is accomplished in two ways, first by activating protein phosphatase1 and second by inactivating glycogen synthase kinase, thus increasing the active dephosphorylated form. The corollary of keeping the glycogen synthase in inactive phosphorylated form could mean loss of glycogenosis and consequent hyperglycemia.

Some approaches to further research

Focus for controlling hyperglycemia had been on agents that increase available insulin (eg. sulfonylureas), increase sensitivity to insulin and decrease insulin resistance in target tissues (eg. thiazolidines), decrease output of glucose from

liver (eg. biguanides) and decrease rate of generation and absorption of glucose in the intestines unconnected with insulin (eg. α-glycosidase inhibitors).

The area of failure to synthesize and store glycogen is glaringly ignored. Glycogen synthase is the critical step. Two proteins are essential for this enzyme to be effective in glucose polymerization. Glycogenin, to which the first few glucose units are added, acts as a primer for the action of glycogen synthase[74]. Activation of glycogen-bound glycogen synthase depends on its binding to glycogen-targeting regulatory subunit 3A of protein phosphatase1 (PPP1R3A). Some clinical examples with glycogen deficiency were traced to mutant variants of PPP1R3A[75] Exercise is commended for control of blood glucose[76]. The rapid use of glycogen associated as granules with fibres of muscle in action might stimulate its replacement. Children unable to synthesize glycogen in muscle were intolerant to exercise[77]. Targeted inhibition or decrease of these proteins can also suppress glycogen synthesis leading to accumulation of glucose.

Insulin resistance is always associated with non-response of the insulin receptor to activate the intracellular cascade. It is understood as desensitization of the receptor which can be either poor insulin binding or its autophosphorylation response. Is glycation of the receptor protein itself a possible cause? The newly discovered dihydroxybenzoquinone derivative acts as insulin mimic at the receptor level, presumably as an oxidant in parallel with the insulin-disulfide. It will be a welcome addition if it can functionalize desensitized receptor.

A significant action of insulin is to inhibit gluconeogensis in the liver. The critical step is phosphoenolpyruvate carboxylase that reverses glycolytic steps for synthesis of glucose, responding to signal of low blood glucose. It is of interest to know how insulin inhibits the activity. Would it increase some endogenous effector to inhibit the activity of this enzyme?

The issue of hyperglycemia that develops later in the life-time needs to be addressed from the perspective of chemical and physical environmental stress. An awesome variety of factors sustain increased blood sugar such as food enriched by sugar, particularly fructose, or chemical sweeteners used in place of sugar that disturb intestinal microflora, or unsuspecting exposure to steroids taken either as pain-saving drugs or inadvertent entry of chemicals in the food chain what with the trendy food processing, defective genes, trauma, surgery and others. Deranged glycemic control, it is surmised, may be due to yet-unknown endogenous effector molecules that appear due to metabolic disturbance. It is worth exploring if they directly act on some critical steps by modulating enzyme activities and gene expressions.

Acknowledgement

We acknowledge the contributions of large number of workers and their innumerable publications on the biochemical basis of hyperglycemia. We gave only a few references on observations that are not so well known, on novel findings not in the main stream and on some unbelievable or unnoticed discoveries waiting for recognition in this general perspective article. The task of finding failures in the path from glucose to glycogen store is still daunting. This article is dedicated to (late) Prof. PS Murthy (deceased, March 28, 2015), a friend for over six decades to one of us (TR), who motivated preparation of the review on vanadium connection with diabetes (ref 26). TR thanks Indian National Science Academy, New Delhi, for support under Hon. Scientist programme.

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