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Journal of Nutrition and Diabetes Research

Review Article | Volume: 1.1 | Open Access

The Biochemistry of Serum Sugars

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Abstract

The biochemical reactions, the compounds formed and the biochemical control mechanisms involving serum sugars are described. It is demonstrated that serum sugar control involves both the insulin-glucagon system and the conversion of glucose to mannose and fructose by the Bruyn-Ekenstein sugar transformation.The formation of malic acid from glucose is shown to initiate and terminate production of insulin and glucagon. The origin of obesity associated with both types of diabetes is demonstrated. Biochemical reactions leading to the formation of advanced glycation end products associated with Type 1 diabetes and ageing effects are defined.

Keywords: Mono phosphoric acid; Poly phosphoric acid; Hydrogen peroxide; Hydroxylamine

Introduction

Nearly one hundred years have passed since the demonstration that insulin protein is involved in the control of serum glucose by conversion of glucose to glycogen and the conversion of glycogen to glucose involving glucagon protein. The biochemical conditions and reactions which initiate and terminate the formation of insulin and glucagon by the cell of the pancreas are not known. In the metabolism insulin can be formed at the required rate, at a higher rate than required, at a lower rate than required or produced at the correct rate and not used effectively. The latter two conditions result in hype Glycaemia which is the origin of various forms of diabetes. Hyperglycemia can lead to more serious medical conditions. Type 1 diabetes has been proposed as an auto immune condition [1]. Several metabolic compounds are proposed as the antigens involved, including insulin. The origin of Type 2 diabetes is not yet defined.It is also proposed that sugars are circulated in metabolic fluids and pass through cell membranes in combination with specific proteins under the mechanism developed from the chemiosmotic membrane theory. These proteins are designated glucose transporter isoforms. The combinations are used in studies aimed at glucose control in Type 2 diabetes, for example gliflozin a sodium salt transporter. It is presumed that the equivalent proteins are available for mannose and fructose. Hexoses with or without attachments can also enter cells by the colloidal fluid mixing mechanism membrane mechanism [2]. In addition to insulin numerous compounds have been developed and tested for control of variations in the concentration of glucose in serum.None of these is as effective as insulin. Glucose, mannose and fructose hexosesaccharides enter the metabolism through dietary intake. These sugars are all equally available from this origin. The dietary concentrations are not in accord with the measured concentrations in serum indicating either preferred use of one over the others or the presence of a mechanism for conversion of the sugars one to the other. Metabolic control of the three serum sugars involves one or more of the basic cell reactions namely hydration, dehydration, oxidation, reduction, decarboxylation and deamination. One or more of these reactions are involved in the insulin-glucagon control of serum glucose and other dietary sugars in the serum. The types of diabetes have been linked experimentally to the phosphate chemical group (PO_4^{3-}) for a considerable period [3]. A high dose insulin infusion induces a rapid and a significant fall in mean plasma phosphate concentration [4]. Control of the concentration of therapeutic insulin leads to a reduction in the metabolic loss of phosphorus through phosphate excretion. Sensitivity to insulin is associated with serum phosphate levels in non-diabetic individuals. Serum alkaline phosphates is also increased in instances of Type 1 diabetes [5,6]. Phosphate ion is the dominant anion in metabolic cells and can exist in metabolic cells as mono phosphoric or poly phosphoric acids. The sodium and potassium salts of these acids are present in intracellular fluids [7]. The acids are reversibly changed from one to the other by the addition or loss of water and are identified as cellular hydration and dehydration reagents. The formation of insulin is also experimentally linked to calcium, magnesium and potassium ions and serum hypo magnesia is linked to both Type 1 and Type 2 diabetes [8,9]. Sodium, chloride and potassium ions are excreted in Type 1 diabetes and insulin affects renal handling of sodium, potassium, calcium and phosphate [10,11]. Type 1diabetes is linked with a deficiency of metabolic iron and Type 2 diabetes is linked with an excess of metabolic iron. Type 1diabetes is also associated with the formation of a group of metabolic compounds known as advanced glycation end products which are proposed as being formed by serum glucose reacting with proteins, lipids and nucleic acids. These compounds are considered to cause ageing through disturbance of the chemical and physical properties of metabolic components such as tissue. This proposal is supported by reduced lifespan displayed by individuals with Type 1 diabetes [12].

Physical and Chemical Conditions Involved in Serum Saccharide Control

Compound formation in metabolic cells requires the persistent presence of primary compounds which initiate and continue the formation of cell compounds at ambient conditions (Normal Temperature and Pressure, NTP). Mono phosphoric and poly phosphoric acids are identified as the two of these primary compounds which are interchangeable by addition and removal of water. This hydrating-dehydrating action is involved in protein and other similar reactions the former acid is released from dietary phosphates by biochemical reactions involving hydrochloric acid of the digestive system and hydrolyses dietary proteins producing amino acids and poly phosphoric acid. The latter enters cells principally as soluble potassium polyphosphate which is derived from di potassium

Received date: 18 Jul 2017; **Accepted date:** 02 Oct 2017; **Published date:** 16 Oct 2017

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Citation: Robertson DS (2017) The Biochemistry of Serum Sugars. J Nutr Diabetes Res. 1(1):

hydrogen phosphate (K_2HPO_4). This compound has a strong tendency to form poly-forms as evidenced by being difficult to crystallise. These conditions account for the dominance of potassium and phosphate ions in intracellular fluid. The presence of polyphosphoric acid in cells is maintained by water leaving the cells under osmotic transfer, electro-osmotic transfer, and exit of hydrated amino acids or transported by the hydration shell of proteins. Mono phosphoric acid exists in a single molecular stereo chemical form and poly phosphoric acid exists in linear, rectangular, and hexagonal molecular stereo chemical forms. The latter act as molecular templates influencing the molecular form of biochemical's produced by polyphosphate reactions. The stability of poly phosphoric acid depends on the pH value, temperature and the ion type and concentration in the fluid involved. The pH of the intracellular fluid changes as mono phosphoric acid is changed to poly phosphoric acid and the reverse [13]. Potassium and magnesium ions enhance the hydrolysis of polyphosphoric acid increasing the rate of biochemical dehydration reactions [13].

The compounds of calcium, magnesium and iron are generally insoluble in the aqueous component of the hydrophilic colloidal fluids which comprise biological fluids. The ions of these elements are rendered soluble by the formation of soluble complex ions (sequestration) with poly phosphoric acid or soluble polyphosphates [14,15]. Sequestration of calcium ion is supported by the observation that serum calcium is divided approximately equally into two types, designated ionized and non-ionized. The first of the types is identified as the concentration of calcium mono phosphate (also known as calcium orthophosphate) and the second type as sequestered calcium polyphosphate (also known as calcium pyrophosphate). Hydroxylamine and hydrogen peroxide are identified as the oxidation and reduction biochemicals and are known to be present in cells and metabolic fluids. The Raschig reaction is the only known reaction which can produce these compounds at the normal temperature and pressure conditions of the intracellular fluid [16]. The oxidizing/reducing properties of these compounds are related to the pH value of the metabolic fluid involved [17,18]. The intracellular pH alters as mono phosphoric acid is changed to poly phosphoric acid due to differences in ionising properties [16]. All four reagents operate by association or enclosure in various different protein structures either alone or as complexes (peroxyacids H_3PO_5, $H_4P_2O_8$, hydroxylamine perphosphates which comprise enzymes [19]. The spatial structural characteristics of the proteins involved allow selective enclosure and controlled access to these reagents. The number of molecules of the above reagents associated with a given weight of a specific protein is limited by structure considerations. A hydrating enzyme encloses mono phosphoric acid and cellular hydration reactions convert this acid to poly phosphoric acid. This combination is structurally unstable and disintegrates. Under conditions where the enclosed mono phosphoric acid remains unreacted the enzyme is decomposed by internal hydration. An enzyme enclosing poly phosphoric acid is a dehydrating enzyme and gives rise to mono phosphoric acid which decomposes the enzyme. Enzymes therefore have a fixed lifetime and are normally continuously formed and reformed. Biochemical reactions precede until a specific concentration of a reaction product or products is present in the reaction zone. The reaction rate slows and can stop at this point and can proceed in reverse until a reaction product or products leave the reaction zone. The figure 1 shows the formation of insulin and glucago are through dehydration of amino acids by linear poly phosphoric acid. The formed insulin encloses lengths of poly phosphoric acid and the dehydrating action of this acid links glucose molecules producing glycogen. The condition of inactive insulin is the result of deficiency of poly phosphoric acid. Glucagon encloses mono phosphoric acid as a result of structural differences from insulin protein. The associated mono phosphoric acid hydrolyses the glycogen releasing glucose. A given weight of insulin and glucagon each contain a specific weight of poly phosphoric acid and mono phosphoric acid respectively when the entire polyphosphoric acid associated with insulin has been converted to monophosphoric acid by the formation of glycogen the protein is hydrated liberating the amino acids. This complies with the observed metabolic degradation of insulin and the measured half-life of insulin at five minutes. Glucagon has a specific lifetime in the metabolism when not involved in the liberation of glucose from glycogen as a result of being self-degraded by any unused mono phosphoric acid. This is supported by the glucagon half-life of two minutes. At present the majority of insulin is considered to be degraded in the intracellular fluid or by processes in cell membranes [20,21].

Control Mechanisms and Chemical Reactions of Serum Saccharides

The insulin-glucagon serum saccharide control system requires a means of initiating and ceasing the production of one or other of these compounds according to the metabolic conditions involved. On entry into serum from the digestive source glucose and mannose are converted to methanol (formaldehyde) and fructose is converted to glycoaldehye through oxidation by hyroxylamine and/or hydrogen peroxide supported by the dehydrating action of polyphosphoric acid (Figure 2). Cell hydroxylamine and/or hydrogen peroxide are produced by the Raschig reaction [22]. Formaldehyde is converted to malic acid by the same reagents.Increasing concentration of glucose results in increased serum malic acid which reduces the pH value (moreacid) ofthe intracellular fluids of cells which the acid enters, such as alpha and beta the cells of the pancreas. The formation of different proteins has been shown to be dependent the intracellular pH value [16]. The reduction of the pH value

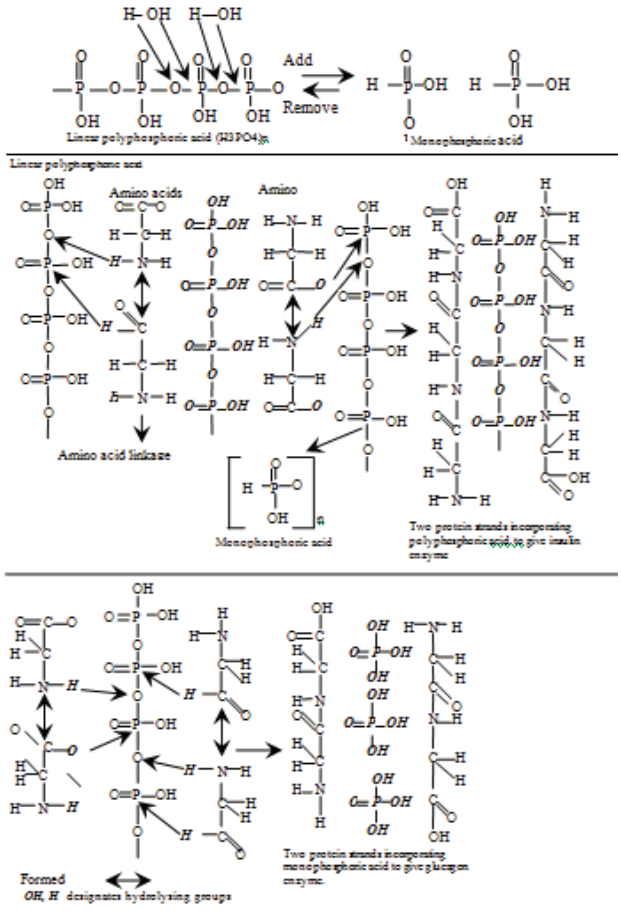

Figure 1: The formation of insulin and glucagon

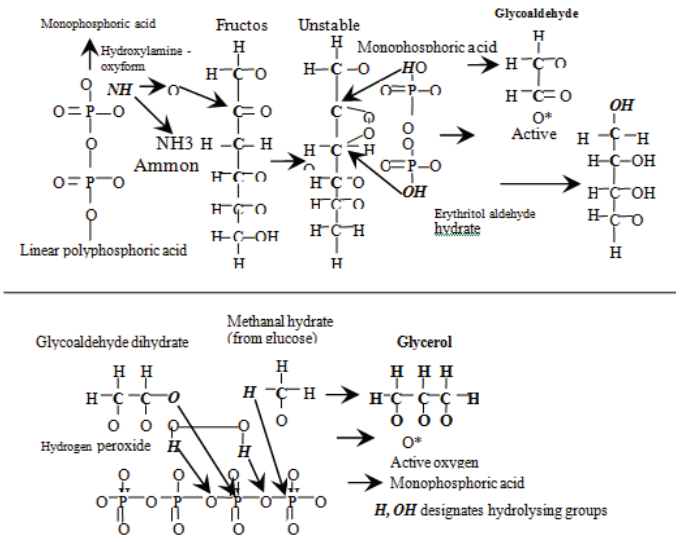

Figure 2: The Lobry de Bruyn–van Ekenstein transformation

of the beta cells favors the formation of insulin protein which converts the increasing glucose to glycogen. As the metabolic use of glucose decreases by lowered metabolic activity and digestive supplyof malic acid decreases and the pH value ofintracellular fluids increases (more alkaline). The change favors the formation of glucagon protein which releases glucose from glycogen. This control mechanism is supported by the observation thatcombination of malic acid and insulin has been shown to be more effective in reducing diabetic ketosis than the same amount of insulin alone [22,23,24]. Compounds involved in ketosis are derived from malic produced by a metabolic excess of hydroxylamine/hydrogen peroxide [25]. The addition of malic acid to the metabolism under these circumstances encourages insulin formation producing the effect observed. In addition plasma glucagon concentrations are elevated in cases of diabetes where insulin production is suppressed. This indicates that the metabolism contains a lowered content of malic acid [26].

An additional control mechanism for serum sugars is the Lobry de Bruyn–van Ekenstein transformation which results in the establishment of a reversible equilibrium between glucose, mannose and fructose [27]. This transformation has been neglected as a serum sugar control mechanism even though it has been shown to occur with phospho-saccharides under the influence of muscle enzyme thus supporting the existence of the transformation in the human metabolism [28]. The process takes place in warm alkaline or acid solutions of saccharides. The conditions in metabolic fluids are compatible with the conditions of the transformation, that is, a pH value in the range 7.35 to 7.45 and a temperature of 37.0° Celsius. Several mechanisms have been proposed as being involved in the transformation and a mechanism is shown in figure 3 involving monophosphoric and polyphosphoric acid. Under this transformation any change in the concentration of serum glucose will result in a corresponding change in mannose and fructose and the reverse.

Metabolic Reactions of Serum Sugars

Serum sugars undergo a series of biochemical reactions producing chemical energy which appears as heat and/or other compounds involved in metabolic functions. Glucose and fructose are decomposed in the same manner by the oxyform of hydroxylamine (NH_3-O) or hydrogen peroxide (H_2O_2) as shown in figure 3. The reaction is supported by the hydrating action of linear polyphosphoric acid and the cell hyroxylamine is formed by the Raschig reaction [22]. It is observed experimentally that metabolic hydroxylamine is linked with insulin [29]. The products are methanal, penitol aldehyde hydrate and active oxygen. The latter reacts with water producing hydrogen peroxide. The product is glycoaldehyde which reacts with methanal forming glycerol and lipids [22]. (Figure 4) shows the formation lactic acid, alloxan and urea from fructose. Alloxan has been identified in serum of insulin dependent individuals [30]. A high fructose intake enhances the production of glycoaldehyde producing an excess of lactic acid, urea, alloxan and lipids. A high glucose intake is partly converted to fructose by the Bruyn–Ekenstein transformation producing the same result. In some mammals injected alloxan induces Type 1 diabetes which occurs through a reduction in the formation of alloxan from fructose. The consequent increase in fructose is converted to sucrose by the Bruyn–Ekenstein transformation. Under these conditions malic acid production has not occurred to induce increased insulin formation. As a result of the available insulin is inadequate to deal with increased sucrose and Type 1 diabetes occurs. Serum succinic acid is produced in the metabolism by reduction of malic acid demonstrating the existence of an effective metabolic reducing agent. This is identified as hydroxylamine with hydrogen peroxide as an auxiliary reagent.

Advanced glycation products include hydroimidazolone, N-carboxymethyl-lysine, pentosidine, glucosepane. Biochemical groups involved in the production of these compounds include imidazole which is formed by reaction ofmethanal (formaldehyde), glyoxal, andammonia. The first two of these compounds are formed from glucose and fructose as shown and ammonia is formed as the result of the operation of the mechanism controlling metabolic hydroxylamine. Imidazole is also formed from glycine, hydroxylamine and methanal [31]. The figure 5 shows the formation of N-carboxymethyl-lysine by the linking of two

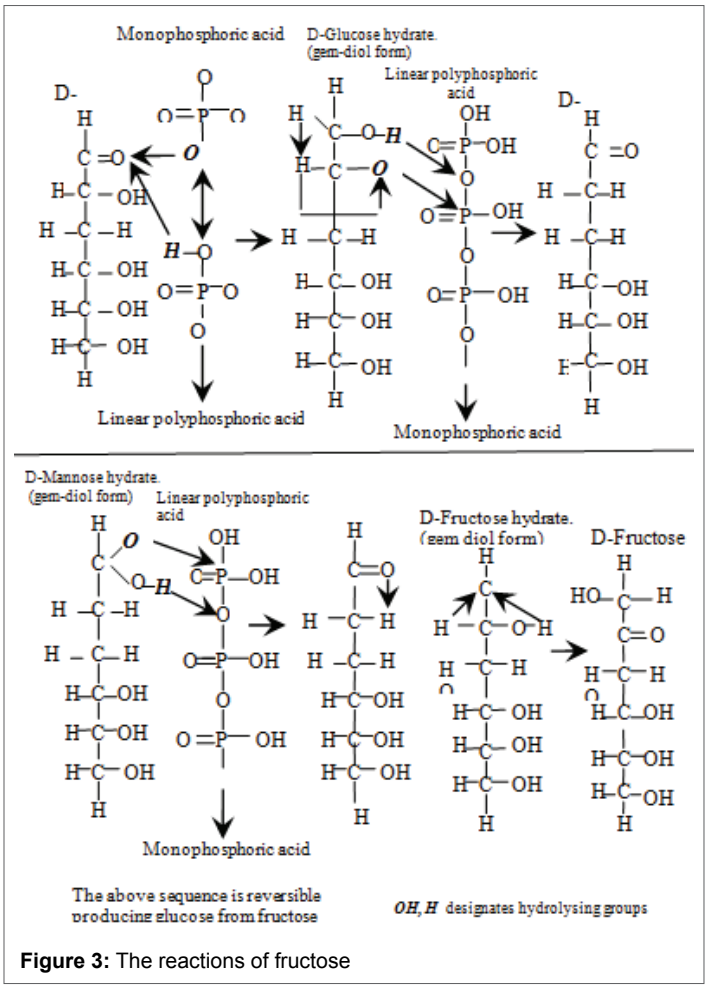

Figure 3: The reactions of fructose

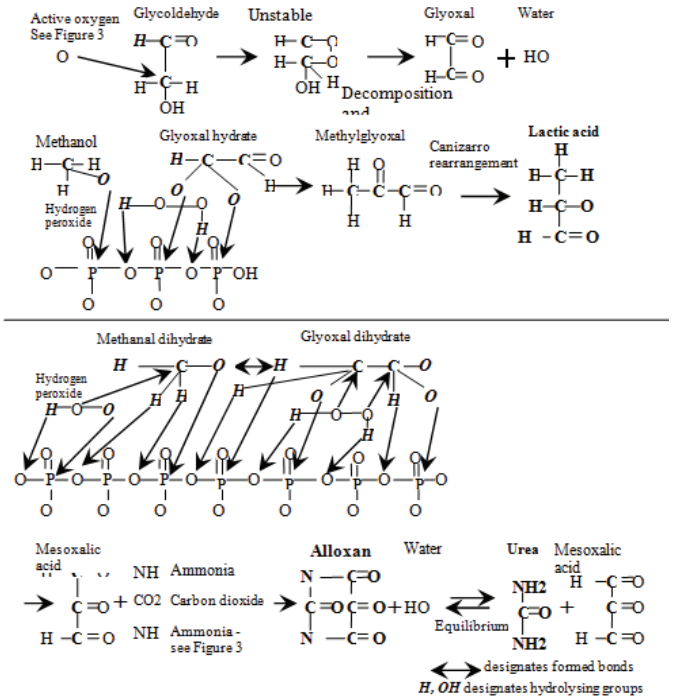

Figure 4: The formation of lactic acid, alloxan and urea

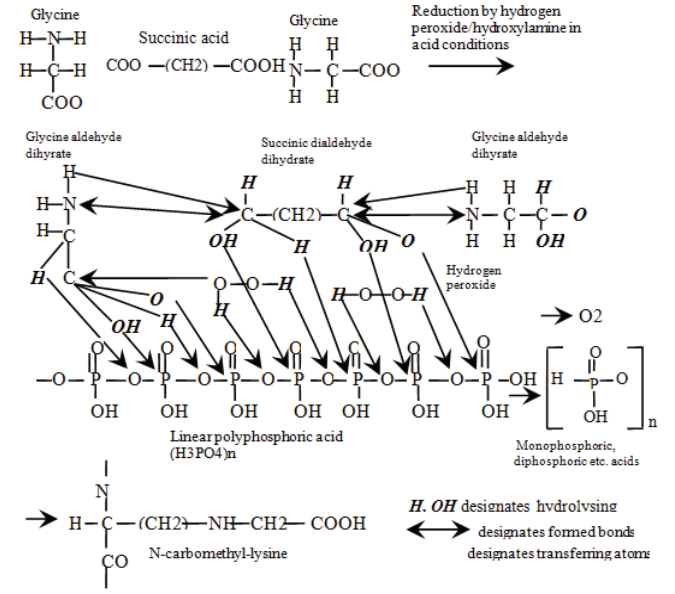

Figure 5: The formation of N-carboxymethyl-lysine

glycine molecules with one molecule of succinic acid. Succinic acid is formed by reduction of either malic or tartaric acid both of which are linked to serum sugars. Tartaric acid is involved in the six sided ring of glucosepane which is formed in the same manner as N-carboxymethyl-lysine. All the advanced glycation products are formed similarly. The involvement of hydroxylamine and hydrogen peroxide in the above reaction necessitates a metabolic control mechanism for these compounds to prevent overproduction. This is provided by the ions of iron. When the intracellular fluid is acidic the Fe^{3+} state of iron is reduced to the Fe^{2+} state by hydroxylamine producing nitrous oxide. Under alkaline conditions hyroxylamine and oxidises Fe^{2+} to Fe^{3+} producing ammonia. Hydrogen peroxide can act similarly producing water in each case. The change of intracellular and intercellular pH when monophosphoric acid is converted to polyphosphoric acid and the reverse by the reactions described establishes is the origin of the pH change involved.

Discussion

A series of observations support the reactions presented. The generation of methanol from glucose is supported by the observation that ingested methanol produces symptoms common to Type 1 diabetes, namely the development of hyperglycaemia and coma [32]. Formic acid is produced in the brain by oxidation of the ingested methanol and results in tissue inflammation causing diabetic coma. Simultaneously ingested methanol reduces the production of methanal from glucose giving rise to hyperglycaemia. Glucose is present in the cerebrospinal fluid and will undergo the same reactions. In cases of Type 1 diabetes the serum concentration of fructose increasesin sympathy with the increased glucose. This indicates that part of the glucose increase is converted to fructose by the Bruyn–Ekenstein transformation. The result is an increase in the production of lipids from glycerol contributing to the development of obesity associated with both types of diabetes. Hypophosphatemia linked to Type 1 diabetes is the result of the use of polyphosphoric acid to form ketone bodies deriving insulin of this component [22]. Type 1 diabetes is linked to decrease in the concentration of metabolic nitrates which reduces the formation of the oxidation/reduction reagents by the Raschig reaction affecting all the reactions described [33]. Potassium ion supports the hydration of polyphosphoric acid and hypokalemia has been linked to the initiation of Type 1 diabetes [34]. Deficiency of this ion reduces the hydration rate of polyphosphoric acid enclosed in insulin and consequently the reduces the rate of conversion of glucose to glycogen. Serum hypomagnesia associated with diabetic conditions and has the same effect. Intravenous iron is observed to cause pancreas cell degradation plus failure of insulin production and induction of Type 1 diabetes [35]. The intravenous iron forms soluble polyphosphate diverting polyphosphoric acid from the formation of insulin.

Treatment of Type 2 diabetes with biguanidine (metformin) gives rise to a reduction in serum glucose concentration. This compound is a water soluble strong base (biguanidine p^{K1} =11.52, p^{K2} = 2.93 cf. ammonia p^{K1} = 9.61). Biguanidine is not degraded in the metabolism. The effect of the compound is to increase the pH (increased alkalinity) of metabolic fluids.An excess use of biguanidine leads to lactic acidosis as a result of transformation of glucose to fructose by the Bruyn–Ekenstein transformation. The increase in serum urea and lactic acid associated with Type 2 diabetes are produced from increased metabolic fructose formed by the same transformation from increased glucose. Sulphur and nitrogen containing compounds which reduce serum glucose concentration (thiazolinine dione, sulphonyl urea, miliglinide) are a source of sulphite and nitrite for the Raschig reaction increasing the formation of hydroxylamine/hydrogen peroxide. The overall effect is increased conversion of glucose to methanal thereby lowering serum glucose. Both types of diabetes are associated with thirst, an increase in arginine vasopressin antidiuretic plus urine with reduced metabolic products and increased loss of water from the metabolism [36]. These results indicate an increase in protein/enzyme formation resulting in transfer of water from the cells by protein halo. The enzyme involved is serum alkaline phosphatase which is observed to increase in both types of diabetes [37]. Advanced glycation product compounds are the result of formation of unusual links between amino acids and dicarboxylic acids.The presence of amino adipic acid in serum has been advanced as predicting the development of diabetes [38]. This is possible based on the formation of dicarboxylic acids from from serum sugars [22]. Advanced glycation product compounds are considered to interrupt the production tissue by the formation of abnormal links between amino acids such as glycine

which is involved in the formation of collagen.The link to diabetes occurs by diversion of amino acids such as glycine from use in the formation of insulin. Advanced glycation product compound formation indicates an excess of hydroxylamine or ammonia in the cells involved. This is the result of over production due to reduced metabolic iron. Healthy adults manifest a low-grade diet-dependent metabolic acidosis, the severity of which increases with age. This condition interferes with the first stage of the iron ion control of hydroxylamine and/or hydrogen peroxide leading to an increase in these compounds [39].

Conclusions

Production of insulin and glucagon are initiated by alteration of the pH of the intracellular fluid of the alpha and beta cells of the pancreas by change in the concentration of serum malic acid formed from glucose. Under normal conditions these pH changes from the start/stop mechanism for insulin/glucagon release. The reduced serum iron observed in case of for Type 1 diabetes results in an excess cell production of hydroxylamine and/or hydrogen peroxide which converts malic acid to ketone bodies bodies and stops insulin production [22]. The reduction in malic acidfavors the formation of glucagon which is known to increase in the case of Type 1 diabetes [26] the result is an increase inglucose from glycogen. When combined with the dietary intake of glucose causes the hyperglycaemia associated with Type 1 diabetes. The operation of the Bruyn–Ekenstein sugar transformation under these conditions converts part of the glucose increase to fructose leading to lipid formation through glycerol as described. In the case of Type 1 diabetes the low metabolic iron concentration is linked to reduced metabolic polyphosphate which sequesters iron which could be improved by the ingestion of iron sequestered in potassium polyphosphate. Type 2diabetes is linked with an excess of metabolic iron which gives rise to areduction of metabolic hydroxylamine and /or hydrogen peroxide. The consequent reduction in the formation of malic acid and the increase in alkalinity (increased pH value) of the intracellular fluid of the alpha cells of the pancreas favours the formation of glucagon. This leads to increased conversion of glycogen to glucose producing an increase in serum glucose. The increase in serum alkalinity also favours the operation of Bruyn–Ekenstein sugar transformation. Although the latter r converts glucose to fructose controlling the onset of hyperglycaemia tis change also leads to lipid production as observed. A supportive treatment for Type 2 diabetes is the controlled ingestion of hydroxylamine phosphate ($(NH_3OH)_3PO_4$) or hydroxylamine dissolved in dipotassium hydrogen phosphate solution. Hyroxylamine has a measured LD50 toxicity rating of 0.4 to 1.0 gm per kilogram of body weight [40]. The formation of advanced glycation end products originates with a progressive increase in the metabolic concentration or the accumulation of hydrogen peroxide/hydroxylamine with age. This change occurs though progressive development of anaemia with age or from any other origin which reduces the iron ion control of these cell oxidation/reduction compounds.

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