Pyruvate May be a Novel Intervention of Diabetes

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Abstract

Recent advances in pyruvate studies indicate that pyruvate may be a novel therapy in care of diabetes and its organ complications. The major action of pyruvate protection against diabetes may be in rejuvenation of glucose oxidation by preserving glycolysis and reactivating pyruvate dehydrogenase activity in the tricarboxylic acid cycle, reversing the Warburg effect in diabetic glucometabolic disorders. Pyruvate preservation of glucose metabolism plus its beneficial effects, such as anti-hypoxia, -oxidative stress, -acidosis, -apoptosis and -advanced glycation end products and stimulation of insulin secretion, may turn diabetic vicious circle virtuous in initiation and development of diabetic process. This review proposed a novel opinion focused on pyruvate superior biomedical and pharmacological properties in diabetes treatment and experimental and clinical evidence of pyruvate intervention in diabetes. The novel pyruvate modified oral rehydration salt (Pyr-ORS), based on WHO-ORS, may be helpful in the prevention and treatment of diabetes in a large population. Further studies and clinical trials are urgently required.

Keywords: Acidosis; Diabetes; Hypoxia; Oral rehydration salt; Pyruvate

Introduction

Pyruvate of sodium salt has been studied, in vitro and in vivo, in animals and humans since as early as the 1930s. In past over half a century it was extensively and intensively investigated in laboratories as well as clinical tests. Numerous findings demonstrate that pyruvate is a unique anion, superior to prevailing anions in current medical fluids: acetate, bicarbonate, chloride, citrate, gluconate, lactate, phosphate and even malate [1]. The paramount biomedical advantages of supraphysiological doses of exogenous pyruvate are potently protective of organ metabolism and function in various pathogenic attacks, including anoxia, hypoxia/ischemia, trauma/burn, infection/sepsis, hypo/hyperglycemia or diabetes and even poisoning. The beneficial biological and pharmacological features underlying the cellular and molecular mechanisms of pyruvate protection from a variety of pathogenic assaults, specifically as to high glucose or diabetes [2,3], are summarized below.

Pyruvate Beneficial Metabolic Attributes in Diabetes

Enhancing anoxia/hypoxia tolerance

By the reductive reaction with Lactate Dehydrogenase (LDH) free of energy, exogenous pyruvate reduction spontaneously coupled with Nicotinamide Adenine Dinucleotide reduced form (NADH) oxidation generates lactate and oxidized form (NAD\(^+\)) on an equal molecular basis in anoxic conditions, consuming hydrogen \((\text{proton, } [\text{H}^+])\) in cytosol. Thus, the LDH reduction is a systemic alkalizing reaction throughout the body; the reaction results in raising the NAD\(^+/\)NADH ratio that is essential for glycolysis at Glyceraldehyde 3-Phosphate Dehydrogenase (G-3PD) and improving glycolytic rate limiting enzymes, like Phosphofructokinase-1 (PFK-1) and Pyruvate Kinase (PK), which are pH-sensitive, contributing to preservation of canonical glycolytic pathways [1,4,5]. Therefore, exogenous pyruvate maintains anaerobic glycolysis and glycolytic-ATP generation that are indispensable for cellular basic activities, such as Na\(^+\)-K\(^-\)-ATPase and islet insulin secretion [6-8]. Further, exogenous pyruvate can reactivates the depressed Pyruvate Dehydrogenase (PDH) activity-induced by various insults, including hypoxia and high glucose or diabetes, via the direct inhibition of promoted PDH Kinase (PDK) activity as a PDH stimulator like Dichloroacetate (DCA) free of oxygen [3,4,9]. Furthermore,
pyruvate also prompts the anaplerotic flux via the Pyruvate Carboxylase (PC) in the Tricarboxylic Acid (TCA) cycle though no direct evidence yet in diabetes [4,10]. As a result, pyruvate additionally as an energy substrate stimulates the TCA cycle in mitochondria, enhancing lactate oxidation and mitochondrial ATP production in hypoxic/ischemic and diabetic conditions. Notably, diabetes may initiate with the PK and PDH inhibition, leading to glucometabolic disorders as the Warburg effect as pseudohypoxia with the NADH/NAD⁺ rise [11,12]. Hypoxia in tissues is also involved in diabetes development. Accordingly, exogenous pyruvate can improve these aberrant metabolic alterations, promoting glucose oxidation and reversing the Warburg effect [3,11,12]. A scheme of the post-pyruvate metabolic profile was illustrated previously [1,3-5].

Correcting severe acidemia

Hypoxic lactic acidosis and diabetic ketoacidosis, which both are fatal complications of critical illnesses with or without diabetes. By the renovation of lactate and ketone oxidation in the TCA cycle with pyruvate stimulated PDH, [H⁺] is consumed in addition to the LDH reduction with [H⁺] consumption. Besides, pyruvate-based gluconeogenesis in cytosol is additionally a process of [H⁺] consumption, thereby preventing [H⁺] accumulation in hypoxia/ischemia [1,4]. Alternatively, the lower pyruvate dissociation constant (pKa) of 2.49 (weaker buffering capacity) quickly facilitates a higher intracellular pH [4]. Therefore, only can pyruvate correct hypoxic lactic acidosis with survival improvement in resuscitation from severe shock, neither lactate, nor citrate, acetate or bicarbonate can do in shocked animals, despite equimolar alkalizers administration [13-15]. It is worthy of note that diabetic patients with ketoacidosis show more lower PDH activity relative to non-ketoacidosis patients [3]. It is potentially perspective that intravenous pyruvate may cure ketoacidosis and lactic acidosis in diabetic patients even without insulin addition in selective clinical conditions [3,4].

Exerting powerful anti-oxidative stress/inflammation/apoptosis

Exogenous pyruvate can directly react with reactive oxygen and nitrogen species (oxidative or nitrosative stress) in a non-enzymatic and stoichiometric manner, producing carbon dioxide or acetate and water: It also indirectly exerts as an anti-oxidation by increasing the redox potentials. In addition, pyruvate is an inhibitor of inflammatory mediators (cytokines, TNF-α and NF-kB) and inflammatory cell (neutrophils) infiltration in tissues [3,16]. Also, pyruvate protects mitochondrial function and endoplasmic reticulum (ER) from stress and apoptosis induced by hypoxia and high glucose [2,9]. Importantly, all these pathogenic factors participate in the initiation and progression of diabetes, specifically Type 2 [3,11].

Stimulating insulin secretion from islets and inhibiting AGEs

Other than previous conception, recent findings are preliminarily considered effective of sodium pyruvate as an insulin-stimulator. Pyruvate metabolism in mitochondria is critically involved in glucose-stimulated insulin secretion (GSIS) and the PC that pyruvate partially depends on enhancement of the anaplerotic flux also plays a pivotal role in insulin secretion from islets [17,18]. Thus, exogenous pyruvate facilitates insulin secretion in islet β-cells even in Type 1 diabetic patients [19,20]. On the other hand, several findings demonstrate that pyruvate attenuates advanced glycation end products (AGEs) generation and tissue deposition, which is one of major pathogenic triggers in organ complications, in hypoxic or diabetic tissues [3,21,22]. Evidently, both unique characteristics of pyruvate are of robust clinical significance in diabetic reversal. All above pathogenic factors and β-cells disorders as well as insulin resistance are intricately interacted as a vicious cycle in initiating and developing diabetes and its organ complications. In contrast, exogenous pyruvate multifactorial protection against the above alterations, specially from the glucometabolic disorders by restoration of PK, PDH and PC activities to sustain the normal glucose oxidation in the TCA cycle and mitochondrial function, reverses the Warburg effect. Therefore, pyruvate as DCA and its new derivatives may be a novel intervention of obesity and diabetes and its organ complications by rejuvenation of glucose oxidation, turning diabetic vicious cycle virtuous, other than the current concept with restriction of carbohydrate intake (weight loss and bariatric surgery) plus GLP-1 (glucagon-like peptide-1) receptor agonists and increase of glucosuria with SGLT-2 (sodium glucose linked transporter-2) inhibitors [3].

Evidence and Possibility of Pyruvate Effects on Diabetes

Many animal experiments and clinical tests have demonstrated that exogenous pyruvate is beneficial in caring clinical diabetes. In 1990s, it was first found that pyruvate prolonged human pancreatic islets viability and protected from diabetic cataract both in, in vitro experiments [23,24]. Subsequent studies not only indicated that pyruvate is an effective therapy in islet transplantation in diabetic rats, but also substantiated that oral pyruvate attenuates diabetic cataract after onset of cataract in, in vivo, investigations [21,25]. These findings were duplicated and further studies displayed that oral pyruvate effectively protected from diabetic retinopathy in rats [26,27]. Although lack of studies on pyruvate effects on diabetic islets in vivo, a recent experiment showed the pyruvate treatment preserved insulin secretion from β-cells and avoided hyperglycemia in a non-diabetic rat model with multiple organ failure syndrome-induced by burn and septic injuries [28]. Newly, a human renal tubular epithelial cell-line (HK-2) was showed as a robust pyruvate protection in high glucose cultures, demonstrating the effectiveness against ER stress and apoptosis induced by high glucose [2]. Notably, as illustrated in diabetic oculopathy, oral pyruvate in drink water also revealed a significant therapeutic effect on diabetic nephropathy accompanied with the fast blood sugar/insulin decrease/increase during an 8-week treatment in db/db mice [3]. It is worthy of noting that albeit just a few of clinical case reports, oral pyruvate with a large dose daily (30-60g/d for 7-10d) efficiently controlled 6 patients with Type 1 diabetes. The clinical signs of hypoglycemia with the decrease in postprandial
blood sugar were observed and 4 of them had to reduce the Total Daily Dose (TDD) of insulin injection due to hypoglycemia [19]. One case with mitochondrial diabetes orally ingested pyruvate (0.5g/kg, thrice daily for 10 months), improved clinical symptoms and reduced insulin TDD from 32 IU/d to 20 IU/d after the treatment for 6 months followed by 22 IU/d 2 months after the termination of therapy [20]. Interestingly, 10 children with citrin-deficiency displayed a significant rise of fasting insulin secretion after oral pyruvate treatment (0.3g/kg/d) for 3-6 months without fasting blood sugar changed [29].

Despite the long history of pyruvate in food supplemental markets for weight loss and in nutrition textbooks for obesity with a question marker, it has been well known recently that oral single pyruvate dosage between 7-25g/d does not enhance blood/plasm pyruvate levels and effects are limited due to malabsorption, but the large dosage shows gastrointestinal irritation in humans [1]. Fortunately, a novel low pyruvate in pyruvate-enriched oral rehydration salt/solution (Pyr-ORS, pyruvate in 3.5g/L with glucose in 13.5-20.0g/L) was innovated in 2012 [30,31], i.e., pyruvate in Pyr-ORS substitutes the equimolar alkalizers: bicarbonate or citrate in WHO-ORS that saves a couple of million lives of young patients suffered from acute diarrhea or cholera worldwide yearly since 1970s [1]. In comparison, Pyr-ORS profoundly prompts intestinal absorption of sodium and water along with pyruvate and protects systemic cardiovascular dynamics, visceral organ and intestinal barrier function with a marked rise of blood pyruvate, resulting in correcting lethal lactic acidosis and prolonging survival in enteral rehydration of shocked animals superior to WHO-ORS, which was developed according to the physiological basis of the Na+-glucose co-transporter in intestinal epithelium in 1950s [1,14,15,30-32]. Newly, findings of Pyr-ORS robust protection against diabetic nephropathy in diabetic db/db mice and acute brain injury after cardiac arrest in rats strongly suggest its potential clinical value in fighting diabetes and aging, like Alzheimer’s disease [3,33,34]. Besides intravenous pyruvate would benefit in critical care diabetic patients with or without lactic acidosis and ketoacidosis, pyruvate may be also advantageous over bicarbonate (at least partial replacement) in hemodialysis solutions and lactate in peritoneal dialysis solutions, specifically in diabetic patients [35,36]. In addition, Pyr-ORS may be useful in geriatric and sport medicine. In these respects, further intensive research is valuable. Its clinical safety and feasibility concerning, in vivo, cytotoxicity and long-term stability in aqueous solutions were recently discussed with a favorable prospect [1,37].

Conclusion

Pyruvate has beneficial effects on clinical diabetes treatment. The key pyruvate action may rejuvenate glucose oxidation in diabetes, making diabetic reversal. Oral Pyr-ORS (the formula may be improved as needed, and/or by adding favorable additives) as a novel approach or a functional drink may be helpful in prevention and treatment of diabetes and its organ complications in a large population. Pyruvate applications would indicate a novel superior medical intervention in clinical settings, specifically in diabetes treatment. Further studies and clinical trials are urgently warranted in diabetes as well as in critical care patients.

Authors Declaration

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Note

The opinions or assertions contained herein are not a reflection of the view of Fresenius Medical Care, Dialysis Centers in Chicago, Illinois.

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