D-ribose: Potential clinical applications in congestive heart failure and diabetes, and its complications (Review)

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Abstract. The quality of life of patients with certain diseases may be improved through the development of technologies and advancements in pharmacology, with the aim of prolonging their life. However, congestive heart failure (CHF), as well their complications, continue to be the leading cause of disease-associated death. The mechanisms underlying the development and progression of diabetes and CHF have been uncovered in a stepwise manner and the understanding of these mechanisms has improved the management of these diseases, resulting in reduced mortality and morbidity rates; however, CHF remains the leading cause of death worldwide, particularly in developed countries. In the past decades, research has indicated that several supplements and naturally occurring compounds may be used to treat muscle weakness, for cardiac failure management, rehabilitation following myocardial ischemia-reperfusion and various complications of diabetes. D-ribose is an essential component of the respiratory, skeletal and nervous systems and is a popular compound, as its supplementation may have beneficial effects. In the present review, the physiological roles, toxic reactions and the potential use of D-ribose in the management of clinical diseases are summarized.

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Abbreviations: ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; IMP, inosine monophosphate; PRPP, phosphoribosyl pyrophosphate; CHF, congestive heart failure; GSP, glycated serum protein; RAGE, receptors for advanced glycation end products; PARP-1, poly (ADP-ribose) polymerase-1; SGLT-2, sodium-glucose transporter-2; EV, extracellular vesicle

Key words: D-ribose, physiological function, congestive heart failure, toxic reactions, diabetes, potential clinical application

Contents

1. Introduction

The biochemical agent ribose is present as L and D enantiomers (1). The L-ribose enantiomer is unstable and thus, D-ribose is the primary functional isoform of ribose (2). D-ribose is a highly water-soluble 5-carbon sugar, also known as D-furanose, which is present in different types of RNA molecule, including mRNA, transfer RNA and ribosomal RNA (3,4).

D-ribose was first identified as a physiologically important molecule in humans in 1958; however, its physiological and pathological roles in humans, and in particular in diseases, are still being studied (5). Until 1970, D-ribose had only been known to serve as a means of increasing blood sugar levels in states of low energy (6). D-ribose was subsequently indicated to be clinically beneficial for treating certain diseases, such as congestive heart failure (CHF) (7-10). Although D-ribose is not stored in cells, it is essential in cell resynthesizing (7,11,12), remedial synthesis and ischemia and hypoxia (13-15). D-ribose may also be supplemented intravenously, via oral therapy or via other exogenous means, and is utilized in several

scenarios, including the clinic (9,16), in athletes (17,18) and in healthcare (19), and energy is rapidly recharged via the synthesis of adenosine triphosphate (ATP).

In the present review, the potential physiological functions of D-ribose, its toxic effects, clinical value and its utility for the treatment of several diseases are discussed.

2. Physiological roles of D-ribose

Conversion of D-ribose to ATP. ATP, an adenine nucleotide, is the primary molecule that is utilized as a means of readily available energy and is an essential molecule for life. The principal nucleotide that generates ribose is D-ribose, such that ribose-5-phosphate joins the pentose phosphate pathway to produce ribokinesis ATP (Fig. 1). In addition, ribose 5-phosphate may be used in various forms for glycolysis and pyrimidine and/or purine nucleotide synthesis. D-ribose may serve as the substrate for the formation of phosphoribosyl pyrophosphate (PRPP), the precursor for *de novo* ATP synthesis; therefore, D-ribose may be used to produce ATP in order to meet the demands of the body under certain circumstances (13).

Effects of D-ribose on the heart. CHF is a severe clinical syndrome of the heart, which may be the result of various heart diseases developing to a severe stage. Due to the reduced function of ventricular pumping or filling, the cardiac output cannot meet the metabolic needs; thus, blood perfusion of tissues and organs is insufficient and pulmonary circulation or systemic circulation congestion develop as a result. CHF is the end-stage event of heart disease progression and one of the primary causes of death in patients with various cardiac diseases (20). Shecterle *et al* (21) reported that lower concentrations of ATP in cardiac myocytes induced ventricular diastolic dysfunction. In order to maintain adequate ATP supplies in the human heart, the adenosine diphosphate (ADP)/ATP ratio must be kept as low as possible. If the absolute concentration of ADP or Pi increases, or the relative ratio of ADP/ATP increases, cardiac dysfunction may occur. This abnormal energy state is caused by a limited ability to convert ADP to ATP in the circulation. Therefore, a sufficiently high energy supply of phosphate is essential to maintain cell integrity and function. Indeed, the relatively slow synthesis of adenine nucleotides underlies a decrease in ATP concentration in myocardial cells following myocardial ischemia and the impact of ATP deficiency is long-term (22). Thus, it has been proposed that supplementing ischemic myocardium with D-ribose may accelerate PRPP synthesis directly to increase ATP levels in myocardial cells and thus to reduce diastolic ventricular dysfunction. A time-dependent association between ATP levels and diastolic function following myocardial ischemic injury has been reported (23). Supplementation with D-ribose during and after ischemia may quickly restore the levels of ATP and improve the phenomenon of diastolic dysfunction caused by ischemia, such as systemic hypertension and angina pectoris. The possible mechanisms by which D-ribose improves function and limits damage may be due to its ability to bypass the rate-limiting step in the pentose phosphate pathway, resulting in an increase in the content of PRPP nucleophosphate. PRPP is indispensable in the *ab initio* and remedial pathway of ATP synthesis. Therefore, D-ribose may improve the recovery of myocardial ATP content following ischemia by increasing the *de novo* synthesis rate of adenine nucleotides. In addition, following myocardial ischemia, D-ribose improves distal myocardial function. Furthermore, D-ribose supplementation may also efficiently target 'hibernating' myocardium and reduce cardiomyocyte loss of ATP attributed to ischemia in patients with coronary artery disease, as well as enhance early diastolic filling and the respiratory performance of patients with CHF. However, the effects of D-ribose as a myocardial protective agent prior to ischemia have remained to be assessed, to the best of our knowledge.

Use of D-ribose to counter fatigue. The human body requires a large amount of energy to perform its activities. Ribose is an excellent source that may be converted to ATP and therefore alleviate excessive fatigue. The fatigue that is being referred to in the present review is caused by exercise. Yuan *et al* (24) used mouse models to assess the effects of D-ribose and other anti-fatigue products, such as ginseng and maca extract, on physical fatigue caused by exercise. They determined that D-ribose was only effective against short-term fatigue in mice compared with ginseng and maca. This may be due to the fact that D-ribose increases aerobic respiration by increasing the concentration of ATP in cardiomyocytes, thus reducing lactic acid produced by glycolysis during anaerobic respiration. When the human body cannot produce sufficient energy via glucose metabolism and lipid metabolism, protein degradation occurs to provide additional energy and the increase in ammonia entering the ornithine cycle leads to an increase in plasma urea nitrogen levels. D-ribose may also reduce the plasma urea nitrogen content and the decomposition rate of proteins by increasing liver glycogen reserves. However, the detailed mechanisms have remained to be fully determined and require to be further explored. D-ribose cannot be used to counter liver glycogen shortages, whereas ginseng and maca class compounds may be capable of this.

Just as combination therapy may be used to treat cancer (25), it has been indicated that D-ribose may also be used in combination with other drugs to counter physical fatigue. D-ribose combined with ginseng extract and morphine produced better results compared with either product alone (26,27) and exerted long-term anti-fatigue effects (28). Likewise, studies have indicated that D-ribose serves an important role in both patients with fatigue caused by CHF (9) and mental fatigue (29) by regulating the metabolism of high-energy phosphate. It was also determined that the swimming time of mice treated with D-ribose alone was significantly longer than of those treated with a combination of caffeine and D-ribose (30). According to the measurement of different substances in the gastrocnemius of fatigued mice immediately after swimming, the combined action of D-ribose and caffeine significantly increased the concentration of ATP, ADP and AMP in the gastrocnemius of mice in comparison with those in the D-ribose alone group. The concentration of inosine monophosphate (IMP) decreased in the former and increased in the latter. The concentration of AMP in the caffeine alone group increased, but there was no significant difference in IMP. After three days of recovery,

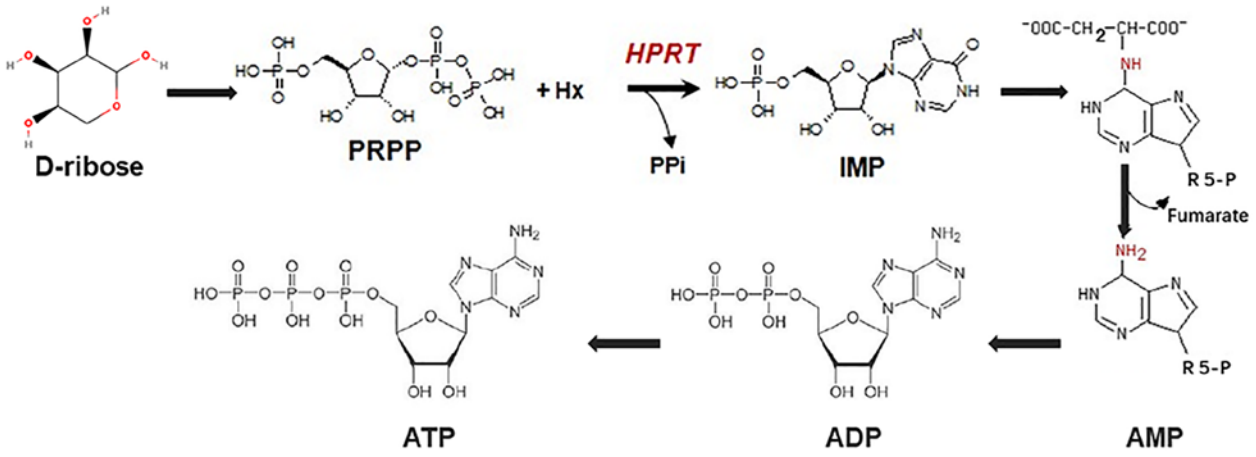

Figure 1. Overview of the biochemical processes to synthesize ATP from D-ribose. The generation of ATP from D-ribose involves PRPP, IMP, AMP and ADP. ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; IMP, inosine monophosphate; PRPP, phosphoribosyl pyrophosphate; HPRT, hypoxanthine phosphoribosyl transferase; PPi, pyrophosphoric acid; R5-P, ribulose 5-phosphate.

the ADP concentration of the D-ribose alone group decreased and the IMP concentration increased significantly, and the ADP concentration in the combined caffeine and D-ribose group decreased significantly. The IMP concentration was not significant compared with the same group before the 3 days recovery. These results support the view that D-ribose is essential for fatigue relief.

D-ribose-mediated regulation of blood sugar levels. Insulin is intricately involved in the regulation of blood sugar levels and exogenous insulin is irreplaceable for diabetics (31,32). Insulin resistance (a lack of response to insulin) is the major barrier in the treatment of patients with diabetes (33-35). Increasing the response of cells to insulin is the goal of the majority of studies on diabetes. Hong *et al* (36) indicated that D-ribose reduced fasting blood glucose levels considerably after 10 and 20 days of intraperitoneal injection, suggesting that D-ribose was able to control blood sugar levels by modulating the sensitivity to insulin in mice. Therefore, on the one hand, D-ribose increased the sensitivity of cells to insulin, but on the other hand, D-ribose is a monosaccharide. After ingestion, it causes an increase in insulin secretion, resulting in an increase in oxidative decomposition of sugars and a decrease in blood glucose levels. In addition, using an oral glucose tolerance test, the above study also determined that D-ribose rapidly improved glucose tolerance. By measuring serum insulin levels, it was indicated that the serum insulin concentration was significantly increased after 10 or 20 days of treatment with D-ribose and then returned to normal levels. Although these results indicate that D-ribose may, in part, increase insulin and glucose tolerance, this method may not be applicable to humans due to physiological differences between mice and humans.

3. Clinical applications of D-ribose

Amelioration of CHF using D-ribose. Both in developed and developing countries, CHF remains a serious health problem and is the leading cause of death worldwide, particularly amongst elderly populations of developed countries (37). A large amount of work has been performed to understand the pathogenesis of CHF and to improve targeted therapeutic medicines (38,39). Pauly and Pepine (8,12) indicated that D-ribose supplementation is associated with rapid ATP production in cardiac cells under ischemic and hypoxic conditions, and that it may preserve cardiovascular energy levels. Exposure to transient ischemia-reperfusion in isolated rat hearts suggested that the recovery rate of ATP levels doubled following D-ribose treatment; the ATP levels in the isolated perfused rat heart with simulation of ischemia for 15 min and reflux for 10-15 min was only 66-69% of the baseline of the control heart, whereas in the D-ribose-treated hearts, it was 89-96% of the baseline levels. This suggests that D-ribose may effectively increase ATP synthesis and thus its levels, reducing the damage caused by cardiac ischemia and tissue hypoxia. However, D-ribose is not the preferred substrate for cardiac energy production and cannot provide comparable oxidative energy compared with glucose or pyruvate. D-ribose serves a role in providing PRPP and adenine nucleotide in models of reversible myocardial injury and related hypertrophy and regional infarction (12). The beneficial effects of D-ribose are attributed to ATP supplementation by increasing the availability of PRPP and increasing *ab initio* ATP synthesis. As other pathways, such as ion homeostasis, substrate utilization, proteolytic protein degradation, oxidative stress and mitochondrial function are all affected by transient ischemic injury, metabolic supplementation of D-ribose is most favorable when PRPP is the primary limiting factor.

Likewise, Ma *et al* (40) reported that D-ribose increased ATP concentrations during myocardial ischemia-reperfusion injury in myocardial cells. Of note, inflammation of myocardial cells caused by free radicals and enzymes without oxygen also significantly increased following D-ribose therapy. The mechanism underlying this is that D-ribose, via increasing the recovery of myocardial energy, reduced the activation of NF-κB by oxygen free radicals, such as hydrogen peroxide, thereby decreasing the expression of chemokines in activated neutrophils and significantly attenuating the activation, infiltration and degranulation of neutrophils, as well as reducing the release of myeloperoxidase in myocardial tissues. The

activity of other myocardial enzymes is significantly reduced, thus significantly reducing the inflammatory response. In addition, D-ribose supplementation may also reduce dobutamine-induced left ventricular ischemic dysfunction, providing a more predictive assessment of function after surgical revascularization.

Association between D-ribose and chronic diabetic complications. The prevalence and incidence of diabetes is increasing and has become a major public health concern worldwide (41). However, it is not the disease itself that eventually leads to a decrease in the quality of life, physical impairments or even death of patients with diabetes, but several chronic complications (41). Several clinically used methods may exacerbate the complications of chronic diabetes. Increased screening of patients is thus required to manage the conditions and a telemedicine project has been suggested to reduce the impairments caused by chronic complications of patients with diabetes and to improve their quality of life (42). However, studies such as that by Salci *et al* (43) tested preventative measures (For example, blood pressure control, psychosocial concerns and detection and treatment of chronic complications) for chronic diabetes mellitus complications and the results indicated that they were not sufficiently useful. This indicates there are various deviations in implementing certain precautionary steps and also demonstrates the nature and difficulty of controlling and treating patients with diabetes (44).

There is a requirement for improved methods to diagnose chronic complications in patients with diabetes early and more effectively. Certain clinicians use glycosylated hemoglobin as a biomarker (45,46). A study reported that patients with diabetes had anti-D-autoantibodies against riboglycosylated hemoglobin, which may be used as a marker for early diabetes detection, and inhibition of its output may be used to minimize diabetes progression and the incidence and development of subsequent complications (47). Furthermore, Chen *et al* (23) also studied the physiological functions of D-ribose in the pathogenesis of type 2 diabetes, suggesting that D-ribose may react with hemoglobin to generate glycosylated hemoglobin. Of note, the glycated serum protein (GSP) caused by D-ribose is more effective than other sugars, such as D-glucose. In addition, Chen *et al* (48) reported that D-ribose may also enhance serum protein glycosylation to produce GSP, leading to a series of complications of chronic diabetes. The authors also indicated that serum protein glycosylation caused tissue damage in the previous 1-3 weeks, whereas hemoglobin glycosylation caused tissue damage in the previous 8-12 weeks. These two types of non-enzymatic glycosylation related tissue damage are the leading causes of the complications of chronic diabetes. D-ribose may lead to the formation of advanced glycation end products (AGE) and complications of chronic diabetes, such as diabetic nephropathy (36).

Regarding the possible mechanism, as compared with glucose, D-ribose is able to rapidly interact with the amino residues of non-enzymatic protein to form early glycosylation products (for instance, reversible Schiff base) in patients with diabetes; these early glycosylation products may be further rearranged, dehydrated and condensed to form AGE, which bind to receptors for AGE (RAGE), which results in increased expression of vascular endothelial growth factor and vascular cell adhesion factor to enhance vascular permeability, angiogenesis and local inflammation. Furthermore, the activation of the AGE-RAGE pathway in monocytes may also increase the secretion of various cytokines and cause a series of oxidative stress reactions, so as to serve a role in the chronic complications of diabetes (49).

Although D-ribose may lower blood sugar levels over a short period of time, it may also trigger complications of chronic diabetes following long-term accumulation. The mechanism by which D-ribose is implicated in complications of chronic diabetes is via a D-ribose-induced increase in glycosylated hemoglobin, further resulting in the generation of AGEs. Therefore, high D-ribose concentrations are associated with chronic diabetic complications. These results indicate that D-ribose is a double-edged sword in the management of diabetes. It may be possible to measure the content of glycosylated proteins or D-ribose in patients with diabetes to predict potential clinical complications and thus introduce effective preventative steps; however, further studies are required to confirm this hypothesis.

Drug therapy. As indicated above, the potential importance of D-ribose in two world-leading diseases, CHF and diabetes, is well established. The efficacy of D-ribose in other diseases has also been assessed. The term restless leg syndrome was coined in 1672 and was previously known as Willis Ekbom disease since 1944 (50,51). Restless leg syndrome is characterized by uncomfortable feelings and discomfort, frequently when resting in the lower limbs, followed by an uncontrollable movement for relief. It is a movement-dominated sensory nerve condition which can cause sleep disorders. This disease severely affects the quality of life of patients and has thus attracted significant attention. It has been indicated that intake of D-ribose does not completely eradicate the symptoms of the disease (52); however, it may improve a patient's quality of life, reduce the severity of the effects and prevent disease progression. The effect of D-ribose, which may rapidly replace ATP in muscle cells, has also been used for the treatment of fibromyalgia and chronic syndrome. Teitelbaum *et al* (53) and another study (15) reported that D-ribose may significantly alleviate fibromyalgia and chronic symptoms and improve quality of life. Likewise, Gebhart and Jorgenson (54) indicated that if traditional therapy fails in patients with muscle fiber pain, D-ribose may be considered, which has certain beneficial effects on the disease. Furthermore, according to one study, D-ribose may have cosmetic properties (55). Indeed, D-ribose enhances the metabolism of skin cells and regulates ATP production. The results were also confirmed by Shecterle and St Cyr (56).

D-ribose has numerous applications; however, there are side-effects to its use. Several studies have indicated that administration of certain concentrations of D-ribose in various animal models is healthy and does not cause any adverse effects regarding behavior, hematology, biochemistry, histology or general pathology (57-59). Thus, it may be hypothesized that D-ribose has beneficial effects on the function of local muscle cells or tissue cells, is able to relieve symptoms and has no apparent toxicity in any area and is thus appropriate for widespread use.

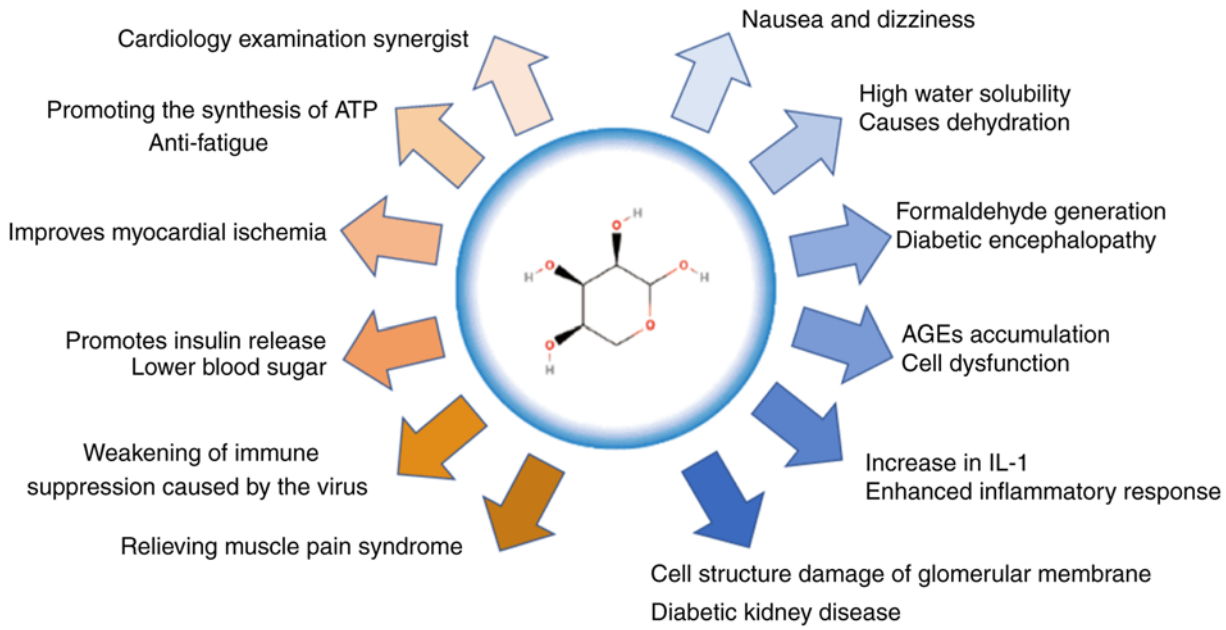

Figure 2. Dual roles of D-ribose: Therapeutic implications and side effects. AGEs, advanced glycation end products.

4. Potential hazards of high concentrations of D-ribose

The correlation between high concentration of D-ribose and various system diseases. The uses of D-ribose for treating or detecting certain diseases described in detail above have several advantages; however, if the concentration of D-ribose in the body is too high, adverse effects may occur. The potential implications of high concentrations of D-ribose are discussed in detail below.

AGEs may exhibit notable cytotoxic effects, a major cause of chronic diabetes complications (Fig. 2) (60). Several studies have also suggested that the clinical complications of type 2 diabetes are related to the accumulation of AGEs and the inflammatory response mediated by RAGE (49,61). However, high D-ribose levels are associated with AGE accumulation. By assessing the impact of D-ribose on human nonenzymatic glycosylation of myoglobin, Yamamoto and Yamamoto (49) determined that D-ribose may accelerate glycosylation of myoglobin and other proteins more efficiently than D-glucose. Yu *et al* (62) also suggested that the urine concentration of D-ribose in patients with type 2 diabetes was substantially higher than that of normal individuals, which also indicated high levels of D-ribose in the body of patients with diabetes. In addition, high D-ribose concentrations may also cause chronic diabetes complications by other means. D-ribose may glycosylate insulin to form ribosyl insulin, activate Caspase-9 and -3/-7, trigger transcription factor NF-κB and produce intracellular reactive oxygen species (ROS) that may cause cytotoxic damage to the surrounding tissues and cells, eventually leading to the manifestation of chronic complications (63). Thus, high concentrations of D-ribose may be a cause of the complications of chronic diabetes (Fig. 3). D-ribose may cause a variety of chronic complications, such as nervous system-related diseases and diabetic nephropathy. How D-ribose causes these chronic complications is discussed further below.

Nervous system-related diseases. Alzheimer's disease is a disorder of the central nervous system characterized by progressive cognitive dysfunction and behavioral impairment. It is a common disease amongst the elderly, results in severe memory losses and renders an individual unable to socially function properly. It has become a significant issue impacting global public health systems and sustainable social growth. In the course of researching the pathogenesis and treatment of Alzheimer's disease, several scientists have identified a certain association between D-ribose and Alzheimer's disease. Javed *et al* (64) studied the pathogenesis of Alzheimer's disease caused by D-ribose and indicated that detecting D-ribose concentrations in the plasma may help doctors to better characterize the disorder. Han *et al* (65) inferred that excessive D-ribose concentrations increased the levels of glycosylated proteins and accumulation of AGEs in mice, resulting in corresponding cytotoxicity. Wei *et al* (66) reported that D-ribose induced protein misfolding and aggregation faster than other monosaccharides and induced apoptosis in SHSY5Y neural cells. The results indicated that D-ribose may affect certain age-associated diseases. Studies have also suggested that uncontrolled diabetes may increase the risk of Alzheimer's disease and vascular dementia (67). In addition, D-ribose serves an important role in type 2 diabetic encephalopathy. D-ribose has been demonstrated to cause the rapid saccharification of α-synuclein to form a molten spherical polymer, leading to oxidative stress and high cytotoxicity (68). It was hypothesized that diabetic encephalopathy is linked to D-ribose-induced Tau protein glycosylation (69). To test this hypothesis, Wu *et al* (70) examined age-related cognitive decline and diabetic encephalopathy using intragastric long-term D-ribose administration in mice to induce type 2 diabetic encephalopathy. The results indicated that D-ribose glycosylation was enhanced. In addition, it has been shown in a previous study that AGEs were able to inhibit brain-derived neurotrophic factor expression and tropomyosin-associated

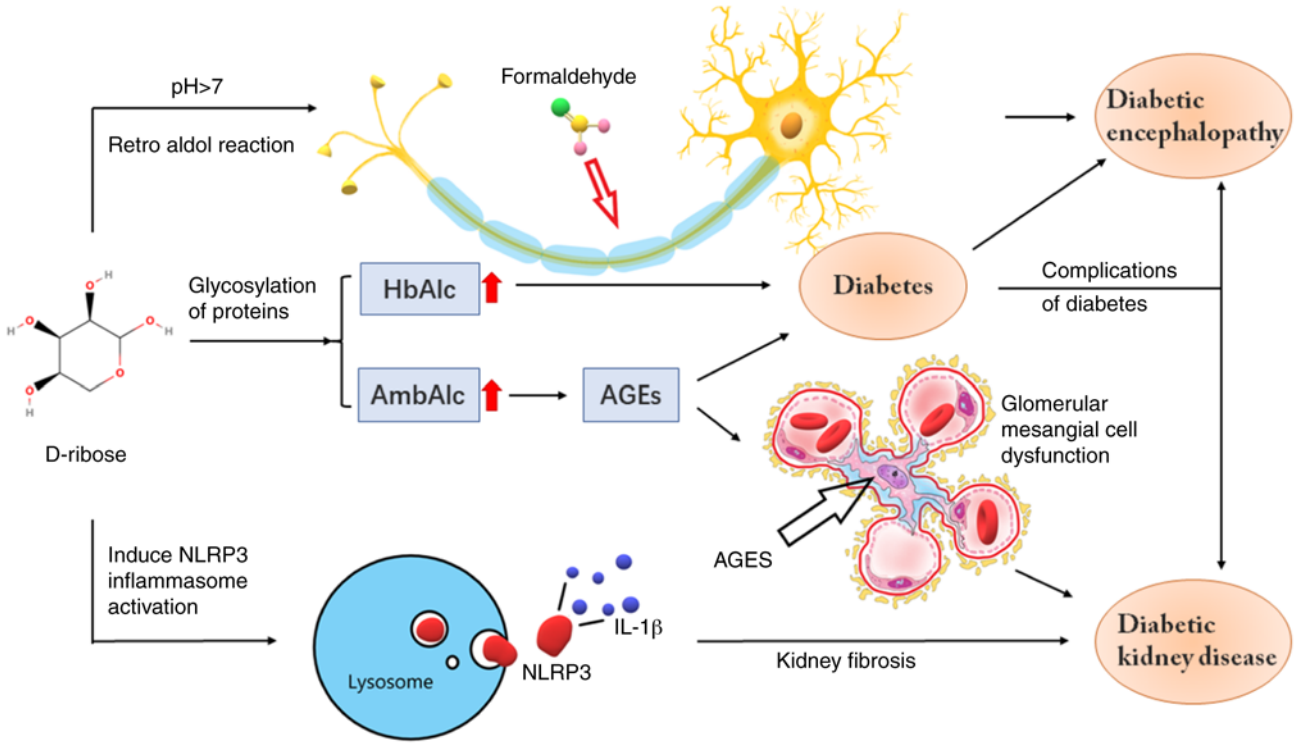

Figure 3. Schematic of the pathological processes of D-ribose-induced diabetes. The production of formaldehyde is triggered by the high concentration of D-ribose and a condition of pH>7 via the retro aldol reaction in nerves cell, which is one of the mechanisms leading to diabetic encephalopathy. On the other hand, the presence of a high concentration of D-ribose, which can act as an activation signal, leads to the release of NLRP3 inflammatory bodies from lysosomes following the activation of NLRP3 inflammatory bodies, thereby promoting the occurrence of diabetic kidney disease. This is caused by the gradual renal fibrosis which is induced by the release of the pro-inflammatory cytokine IL-1β. Additionally, D-ribose can also lead to the glycosylation of HbAlc and AGEs, that both contribute to the development of diabetic associated complications. AGEs, advanced glycation end products; NLRP3, nucleotide-binding oligomerization domain-like receptor family protein 3.

kinase B, resulting in hyperphosphorylation of the Tau protein. It is therefore proposed that selective inhibition of ribose glycosylation may be used as a therapeutic strategy for the prevention of Alzheimer's disease and type 2 diabetic encephalopathy (71). Wang *et al* (72) also indicated that in alkaline environments, D-ribose may decompose to formaldehyde by the reverse aldol reaction, and that by determining the content of formaldehyde in various parts of mice, it was suggested that formaldehyde produced by D-ribose accumulates in the brain of the mice and that the accumulation of endogenous formaldehyde to pathological concentrations may lead to disturbance of consciousness and cognition. However, it was also hypothesized that accumulation of D-ribose-induced AGEs is an important means underlying the occurrence and development of diabetic encephalopathy (62). Han *et al* (65) reported that D-ribose glycosylation led to the accumulation of AGEs in the nervous system, leading to spatial cognitive impairment and astrocyte-mediated RAGE-dependent inflammation. This indicates that D-ribose-induces cognitive dysfunction linked to type 2 diabetic encephalopathy (73). The study by Gheith *et al* (74) agreed with this hypothesis and proved that the accumulation of AGEs may lead to neuronal dysfunction and death. According to a recent study, high levels of D-ribose in type 1 diabetes may suggest that D-ribose is involved in complications associated with type 1 diabetes, including encephalopathy (62). Several of the above studies have indicated possible damage to the nervous system caused by high concentrations of D-ribose in the body and provided an alternate means of understanding the potential pathogenesis of Alzheimer's disease and diabetic encephalopathy. Whether Alzheimer's disease and diabetic encephalopathy may be prevented or delayed by reducing the concentration of D-ribose or by cutting off the D-ribose pathway involving glycosylation of related proteins and generation of AGEs remains to be determined. To assess this, additional in-depth studies, novel treatment agents and clinical trials are required.

Role of a high concentration of D-ribose in the pathogenesis of diabetic nephropathy. Diabetic nephropathy is one of the most severe diabetic complications and a leading cause of end-stage renal disease worldwide. Within 20-25 years of diabetes onset, 20-40% of patients with diabetes develop diabetic nephropathy (74). Therefore, research on the pathogenesis and care for diabetic nephropathy has gained increasing attention from numerous academics, including analysis of poly (ADP-ribose) polymerase-1 (PARP-1). Various experiments have suggested that inhibiting PARP-1 is able to prevent or alleviate diabetic nephropathy (75,76). Furthermore, it has been indicated that inhibiting aldose reductase activity was also able to minimize nitrosation stress and PARP activation of glomerular mesangial cells in a high-glucose environment (77). Studies on sodium-glucose transporter-2 (SGLT-2) and its involvement in renal tubules have also been performed. It has been indicated that SGLT-2 inhibition combined with renin-angiotensin system therapy inhibition was able to better protect the long-term health of the kidney and help delay

the development of renal diseases in patients with type 2 diabetes (78,79).

Furthermore, an increasing number of studies are assessing the pathways that underlie AGE-mediated diabetic nephropathy (80,81) and the AGE-RAGE-oxidative stress system theory (82). Several studies have indicated increased expression of RAGE in advanced chronic kidney disease, which indirectly demonstrates the close relationship between AGEs and diabetes (83). The increase in AGE-modified plasma proteins is associated with the production of ROS caused by RAGE, the activation of transcription factor NF-κB and the pathological changes in gene expression levels in several cell types (84). It is well established that D-ribose influences the incidence and development of diabetic nephropathy via AGE accumulation. To confirm this point, Zhang *et al* (85) used murine mesangial cells as an experimental model. They indicated that D-ribose induced nonenzymatic glycosylation of related proteins and led to the accumulation of AGE-induced glomerular cell dysfunction. At the same time, it was also determined that D-ribose upregulated Bax protein expression, downregulated Bcl-2 protein expression and disrupted the Caspase-9/-3 pathway to facilitate glomerular mesangial cell apoptosis. Increasing D-ribose concentrations may also lead to increased ROS and cytokine levels, leading to podocyte inflammation and renal fibrosis. In addition, Hong *et al* (36) formulated the AGE-RAGE-oxidative stress system theory and other mechanisms by which D-ribose causes diabetic nephropathy. One approach was the induction of both exogenous and endogenous D-ribose to form and distinguish NOD-, LRR- and pyrin domain-containing protein 3 inflammatory bodies in podocytes and to secrete podocytes via extracellular vesicles (EVs). Therefore, releasing cytokine IL-1β may trigger glomerular injury, and D-ribose may also reduce interactions between lysosomes and multivesicular bodies (MVBs), increase the fusion of MVBs and plasma membrane and increase cytokine IL-1β release via EV secretion. Another potential mechanism is the increase of the D-ribose content of ceramide in the lysosome to control the lysosome-ceramide sphingolipid mechanism of interaction with MVBs, enhancing the ability of podocytes to release EVs and increasing the release of IL-1β to enhance the inflammatory response (86). Together, in addition to daily blood sugar regulation, patients with diabetes should consider monitoring the concentration of D-ribose daily to avoid diabetic nephropathy. This may improve the quality of life of patients with diabetes.

5. Conclusions and future perspectives

Currently, research on the clinical use D-ribose is still in the relatively early stages and a considerable amount of further investigation is required. However, based on the body of literature available, it is well established that D-ribose has several and broad prospects in various areas, including medicine and healthcare, as well as sports and athletics. For instance, in emergencies, such as during myocardial ischemia-reperfusion injury caused by cardiac operations or cardiac arrest, D-ribose may directly accelerate PRPP synthesis, thereby rapidly increasing the ATP concentration and other mechanisms in myocardial cells by injecting a certain amount of D-ribose to reduce the occurrence of myocardial ischemic injury. At the same time, further research and confirmation of the appropriate concentration ranges of D-ribose to use during these procedures and whether it may be used in conjunction with other first-aid rescue medications, such as those for cardiac arrest, is required.

Furthermore, a series of existing studies on the relationship between D-ribose and diabetes indicated that the concentration of D-ribose in patients with diabetes is proportional to the incidence and severity of diabetic complications. For the majority of people with diabetes, the primary factors impacting the quality of life or reducing their lifespan is not diabetes itself, but the resulting complications. Whether D-ribose may be used as a medication to treat diabetic complications and the effects of the D-ribose concentration on the body should be further studied. Simultaneously, improving D-ribose concentration determination technologies is particularly important. Thus, assessing D-ribose concentrations in patients with early diabetes may be used to predict the probability and extent of diabetic complications. In addition, reducing D-ribose intake in everyday life in patients with diabetes may be of direct significance. Perhaps, D-ribose analogues or drugs that target D-ribose may be used in advance to minimize patient harm from diabetic complications and reduce the occurrence of diabetic complications. Ultimately, D-ribose may be used to improve the quality of life of patients with diabetes and extend their lifespan.

Finally, D-ribose is also used as an anti-fatigue medication to enhance muscle exercise intensity in athletes and is commonly used as a food additive in food and health products. However, there is still no definitive conclusion on its safe range. In addition, whether excessive use of D-ribose poses other potential health hazards, as well as whether D-ribose is suitable for everyone requires further study.

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Availability of data and materials

Not applicable.

Authors' contributions

SL, JW, YX and LZ contributed to the conception of the study and wrote the manuscript. HQ and MN contributed towards the conception of the study and revised it critically for important intellectual content. JF, NY and ZZ contributed to the preparation of the manuscript and illustration of the figures. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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