Potential clinical applications of alpha-ketoglutaric acid in diseases (Review)

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Abstract. As an intermediate of the tricarboxylic acid cycle, also known as 2-oxoglutarate, α-ketoglutaric acid (AKG) plays an important role in maintaining physiological functions and cell metabolism. AKG is involved in both energy metabolism, and carbon and nitrogen metabolism; thus, exhibiting a variety of functions. Moreover, AKG plays an important role in various systems of the body. Results of previous research indicated that AKG may act as a regulator in the progression of a variety of diseases; thus, it exhibits potential as a novel drug for the clinical treatment of age-related diseases. The present review aimed to summarize the latest research progress and potential clinical applications of AKG and provided novel directions and scope for future research.

Contents

1. Introduction

α-Ketoglutaric acid (AKG) is involved in the metabolism of carbohydrates, fatty acids and proteins via numerous mechanisms (1). As an important intermediate product in the tricarboxylic acid (TCA) cycle, AKG is involved in both the source and pathway of carbon in the body. Through the action of transaminase and the combined deamination, AKG is converted into glutamic acid (2). In the presence of ammonia, L-glutamate dehydrogenase also reverses the production of glutamate from AKG to form other non-essential amino acids in the body. Ammonia is produced in the amino acid catabolism process, and toxic ammonia is eliminated via the urea cycle (3). AKG also plays a key role in the urea cycle, and is metabolized in a similar manner as it is during the purine nucleotide cycle (4). During this cycle, AKG acts as an intermediate and participates in the development, maturity and aging of the body. This cycle demonstrates both the nutritional and physiological functions of AKG, and provides a theoretical basis for the role of AKG in clinical practice (5).

A previous study has demonstrated that AKG may act as a dietary supplement, together with arginine and other amino acids, to help athletes recover in a timely manner (6). In the cardiovascular system, AKG may prevent or even reverse the aging of animals with arteriosclerosis (7). During exercise, AKG acts as a synthetic metabolic signal and promotes protein synthesis, which in turn contributes to skeletal muscle development and increases collagen metabolism, thus affecting bone structure through the interaction between glutamate and glutamate receptors (8-10). In the digestive system, AKG, as a glutamate family metabolite, participates in the TCA cycle to provide energy for intestinal epithelial cells, helps to maintain intestinal mucosal integrity, promotes intestinal structural development and improves the intestinal absorption of nutrients (11). Recent studies have suggested that AKG may play a key role in promoting healthy aging (12,13). Following the increase of aging populations worldwide, further investigations are required to focus on improving the quality of life as the rates of life expectancy increase. Therefore, current research has focused on the potential role of AKG in age-related diseases, such as cancer, obesity and diabetes. In recent years, increasing attention has been paid to the metabolic and regulatory effects of AKG, but few reviews have been carried out on the clinical application of AKG. Combining these advances with the role of AKG in clinical practice may provide a novel theoretical basis for the use of AKG in improving long-term human health (Fig. 1).

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2. Synthetic paths and methods

AKG is an intermediate metabolite of the TCA cycle. It is involved in the synthesis and energy metabolism of amino acids, vitamins and organic acids. It has a wide range of application prospects and exhibits key applications in the field of medicine, food, animal husbandry and agriculture (14-16). The method of synthesis mainly involves the biosynthetic pathway and fermentation.

AKG is an intermediate product of the microbial TCA cycle, and three important metabolic nodes are selected in the biosynthetic pathway, namely, the phosphoenolpyruvate-pyruvate-oxaloacetate node, the citric acid node and the AKG node. Oxaloacetate is an important precursor for the synthesis of AKG. In addition to originating from the TCA cycle, it can also be obtained through the replenishment pathway, which is catalyzed by pyruvate carboxylase and phosphoenolpyruvate carboxylase. The former uses biotin as a coenzyme, and the latter is usually feedback-inhibited by aspartate and AKG. Different microorganisms contain either one or two of the aforementioned carboxylases. For example, *Escherichia coli (E. coli)* only contains phosphoenolpyruvate carboxylase, *Bacillus subtilis* and *Yarrowia lipolytica* only contain pyruvate carboxylase, and *Corynebacterium glutamicum* only contains pyruvate carboxylase. The citrate node is an important metabolic node controlling the metabolic flux of the TCA cycle, and citrate synthase is the key enzyme of this node. Notably, its activity is often feedback-inhibited by citric acid, adenosine triphosphate (ATP) and NADP (17,18). The AKG node determines its metabolic destination, and AKG synthesizes succinyl-CoA and glutamate under the catalysis of α-ketoglutarate dehydrogenase and glutamate dehydrogenase, respectively. Moreover, α-ketoglutarate dehydrogenase uses thiamine as a coenzyme. Therefore, when thiamine is insufficient in the medium, AKG will flow to glutamate due to the weakened metabolic flux of the TCA cycle (18).

The production of AKG using fermentation was initiated by Lockwood and Stodola (19) using *Pseudomonas fluorescens*. Subsequently, various microorganisms were found to be able to synthesize AKG in excess (20). *Corynebacterium glutamicum*, *Yarrowia lipolytica* (21), *Saccharomyces glabrata* and other yeasts are considered ideal for the production of AKG using fermentation, due to their notable physiological and genetic characteristics, and their rapid growth (22). Therefore, current research focusing on breeding AKG-producing strains mainly uses the three aforementioned microorganisms, and the main strategies include enhancing the supply of AKG precursors and weakening the competitive metabolic branch (Fig. 2).

AKG, ketoglutaric acid, industrial synthesis method, circulatory system, locomotion system, endocrine system, digestive system and productive system were searched as keywords. Four major electronic databases (PubMed, Springer, Wiley, and ScienceDirect) were used to retrieve relevant literature in the past three decades. After reading the articles, articles with relatively complete experimental verification of the role of AKG in the body were selected to be included in the references. The systemic association between AKG and the development of diseases in the body was summarized, and potential clinical application of AKG was determined.

3. AKG in the circulatory system

At present, there is an increasing number of aging populations in society, and cardiovascular disease attracts high levels of attention as it is age-related (23). AKG exists as an important keto acid in the blood. In previous clinical trials, blood samples of participants were collected in test tubes containing ethylenediaminetetraacetate. Following centrifugation, the plasma samples were frozen at -80˚C, until the sample was thawed and centrifuged at 10,000 Hz for 10 min at 4˚C. A total of 300 μl of each sample was transferred to a 5-mm NMR tube, 200 μl of 0.2 mol/l phosphate buffer and 50 μl D_2O were added, and the levels of AKG were determined using liquid chromatography-mass spectrometry/mass spectrometry.

The content of AKG in the blood indicates the conditions of vital organs and other systems. When hepatic encephalopathy occurs, changes occur in both the mental state and the blood components of the individual, and AKG levels in the blood will rise. The concentration of AKG in the blood of patients with diabetes significantly decreased ($r=0.367$; $P<0.05$) (24). AKG can be used as an antioxidant in a multi-component solution to aid oxidative stress, and may be used for the suppression of Kupffer cell activation during liver transplantation and attenuates hepatic ischemia-reperfusion injury (25). Results of a previous study have demonstrated that AKG protects ischemic organs by inhibiting dioxygenase Egln1, which may provide a novel method for solving ischemic preconditioning in organ transplantation (26). The decrease of blood vessel elasticity directly affects the function of the circulatory system (27). Previous cellular experiments have demonstrated that AKG can increase the activity of glutathione peroxidase, while inhibiting the activity of superoxidase, protecting the body from a stable redox state, and avoiding free radical damage (28). The serum levels of AKG can reflect the clinical severity of chronic Heart Failure(CHF) in non-diabetic patients, but not in those with type 2 diabetes mellitus, and it may also be used as a potential indicator of systolic dysfunction of the left ventricle. These data are in accordance with observations that support the role of certain metabolites in CHF severity (29). In addition, AKG improves myocardial hypertrophic remodeling and fibrosis in stress-overloaded hearts, by promoting mitophagy to clear damaged mitochondria and reduce reactive oxygen species production (30).

Results of a previous study demonstrated that a combined solution containing AKG and 5-hydroxymethylfurfural may exhibit antitumor potential due to its antioxidant activity. These substances exhibited both caspase-3 and apoptosis-activating effects on cell proliferation in Jurkat and HF-SAR cells, highlighting them as anti-leukemia cell/antitumor combinations (31). Levels of AKG in the blood indicate the state of various organs in the circulatory system. Therefore, the AKG content of the circulatory system is mainly used as a pathological detection index for various cardiovascular diseases. Moreover, novel treatment options for ischemic preconditioning and cardiovascular protection may be developed due to the antioxidant properties of AKG.

4. AKG in the locomotion system

Previous research demonstrated that in humans and primates, the cortical motor system includes a collection of brain regions

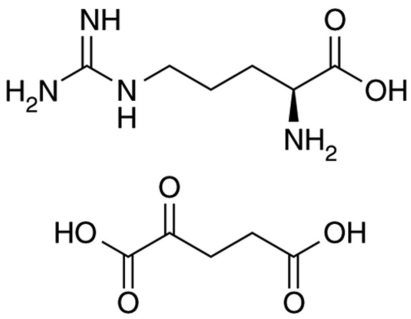

Figure 1. Chemical structure of α-ketoglutaric acid.

mainly associated with motor control (32). AKG also plays an important role in the anabolism of skeletal muscle (33).

Using animal models, results of a previous study demonstrated that adding AKG to a low-protein diet significantly increased amino acid synthesis and improved protein metabolism in skeletal muscle by activating the mammalian target of the rapamycin (mTOR) pathway (34). AKG activates mTOR complex 1 and promotes the expression of collagen (35). Additionally, AKG notably inhibits the degradation of collagen in fibroblasts, which is associated with the mechanism mediated by AKG through PHD3/ADRB2. These findings provided a molecular basis for the potential use of AKG produced by exercise in the treatment of muscle wasting, and identified PHD3 as a potential target for the development of muscle-wasting therapy (33).

During bone formation, AKG activates the JNK and mTOR/S6K1/S6 signaling pathways independently of GPR99 activation, thereby promoting osteoblast differentiation (36). In addition, AKG increases serum proline levels, and AKG-Ca causes beneficial changes in serum C-terminal cross-linking telopeptide of type I collagen in women with postmenopausal osteopenia, which is consistent with the retention of lumbar bone mass (37). AKG can also be supplemented in the postpartum diet for newborns and exhibits the potential to improve/maintain the bone structure of animals treated with the maximum therapeutic dose of dexamethasone (Dex). When a group of children were exposed to synthetic glucocorticoid (GC), adverse effects, such as GC-induced osteoporosis and growth retardation were apparent (38). Using AKG as a supplement may act as a novel treatment method for children receiving GC therapy. AKG can also be used as an important supplement following surgical trauma. It prevents the reduction of free glutamine that is often produced following surgery (39). AKG can also maintain the amino acid concentration and protein synthesis in muscles, and reduce the adverse effects caused by surgery (40). As a synthetic precursor of important amino acids such as glutamate, AKG also has the physiological function of activating pathway targets (41). Therefore, the main clinical application of AKG will focus on promoting protein synthesis to improve muscle function and bone cell differentiation.

5. AKG in the endocrine system

In the present review, two common metabolic endocrine diseases associated with AKG are explored, namely, diabetes and obesity. Diabetes is a complex disease that is not yet fully understood. It often manifests as hyperglycemia and exhibits complications of abnormal metabolic conditions associated with systemic damage to the vascular bed (42). Accumulating evidence has demonstrated that the endocrine system of patients with diabetes is not functioning properly, and the metabolic mechanisms require further investigation. Most patients at risk of developing type 2 diabetes suffer from hyperinsulinemia, which may be a response to insulin resistance (43).

AKG also causes insulin secretion in B6 and BTBR pancreatic islets. Therefore, the formation of AKG is a necessary step for the response of mouse pancreatic islets to ketoisocaproate. Existing evidence demonstrated that AKG directly stimulated insulin secretion (44). According to the analysis of mitochondrial mechanisms, AKG may be converted into AKG intermediates, such as citric acid or glutamic acid, for mitochondrial synthesis. Moreover, the mitochondrial 2-oxoglutarate carrier is part of the metabolic pathway that mediates insulin secretion stimulated by glucose and glutamine (45,46). In addition, AKG regulates the formation of insulin by inhibiting glutamate dehydrogenase (47). These results demonstrated that the causes of abnormal insulin secretion are complex; however, these findings suggested that AKG affects hyperinsulinemia. During the development of complications associated with diabetes, AKG also plays a role in determining prognosis. It is associated with delayed diabetic wound healing (48), and high levels of matrix metalloproteinase-9 (MMP-9) can predict poor healing of diabetic foot ulcers. Results of a previous study demonstrated that compared with non-diabetic wounds, the levels of AKG, TET2 and MMP-9 in diabetic wounds were significantly increased ($P=0.01$). This increase in AKG was associated with a local hypoxic-ischemic state and poor systemic blood sugar control (48).

Obesity is a nutritional disorder caused by a long-term imbalance between energy intake and consumption (49). It may lead to premature death, preventable disease and disability (50). Obesity affects a variety of endocrine systems. It also affects the changes in sex steroids and thyroid hormones, in addition to the dynamic balance of the hypothalamic-pituitary axis and vitamin D. AKG also plays an important regulatory role in the metabolism of obesity (51).

Results of previous study have demonstrated that AKG regulates the differentiation and function of brown fat by regulating histone methylation through IDH1. Ectopic expression of IDH1 inhibits the formation of brown fat, while suppression of IDH1 levels promotes the differentiation of brown adipocytes. Moreover, overexpression of IDH1 leads to increased levels of intracellular AKG and inhibits the expression of genes involved in brown fat formation. The IDH1-AKG axis plays an important role in regulating the differentiation of brown adipocytes, and may therefore represent a target for the treatment of metabolic diseases. Results of previous studies have also demonstrated that in the early brown fat formation process, the cellular level of AKG, a key metabolite required for TET-mediated DNA demethylation, is greatly increased, and it is the PRDM16 promoter required for active DNA demethylation (52,53). AMPKα1 excision reduces isocitrate dehydrogenase 2 activity and cellular AKG levels. Notably, the activation of AMPK with AICAR or metformin after delivery reverses inhibition of brown fat formation and thermogenesis caused by obesity. In

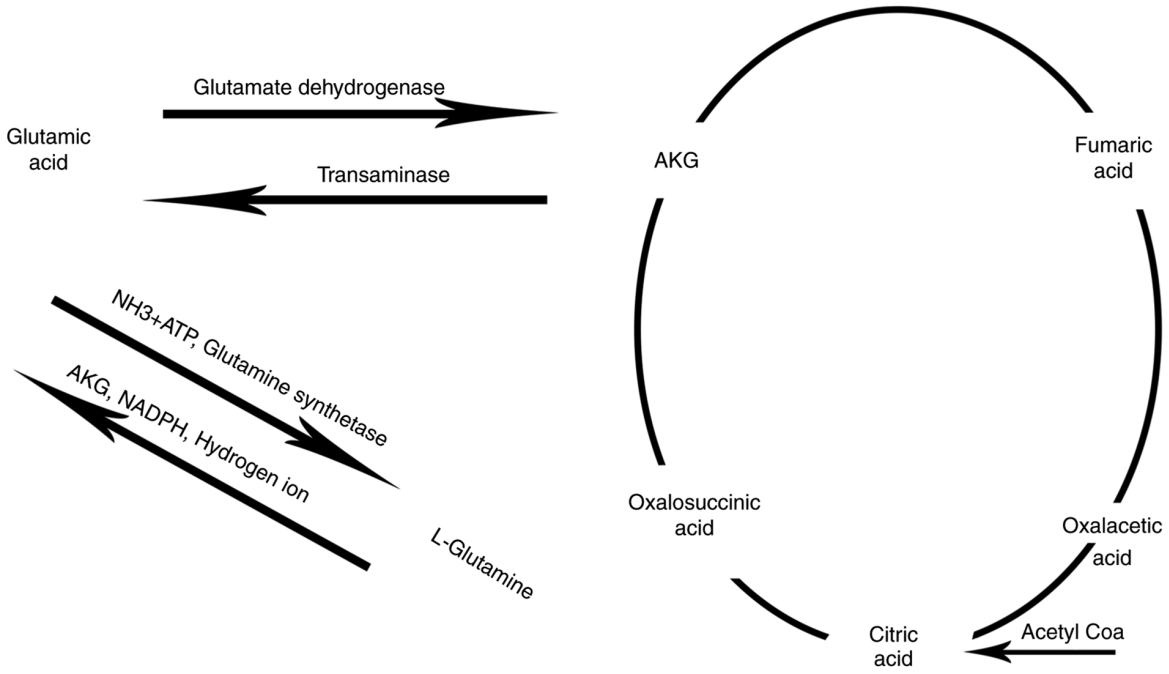

Figure 2. Cell cycle process of α-ketoglutaric acid.

summary, AMPK is essential for the epigenetic control of BAT development through AKG. Obesity is also associated with macrophage infiltration and metabolic inflammation (54), both of which promote the progression of metabolic diseases.

As a metabolic intermediate product of the TCA cycle, AKG participates in regulation. Existing study have confirmed that melatonin reduces fat inflammation by increasing AKG and transferring fat-derived exosomes to mouse macrophages. Melatonin reduces fat inflammation by increasing exosomal AKG. It is transported to macrophages and promotes TET-mediated DNA demethylation, reduces inflammation of fat cells, and increases the ratio of M2 to M1 macrophages. In addition, exosomal AKG attenuates signal transducers and activators of transduction-3 (STAT3)/NF-κB signaling in adipocytes through its receptor oxoglutamate receptor 1. AKG can be used to determine the presence of non-alcoholic fatty liver in morbidly obese patients, but it is not an effective biomarker of steatohepatitis (55). Further research is required to examine whether AKG can be used as an effective biomarker for other obesity-related endocrine system diseases. In the endocrine system, AKG mainly participates in the circulation and exerts a role through its keto acid properties. Previous study have demonstrated that AKG affects the production of insulin and the development of hyperglycemia, but further experimental evidence is required for the development of clinical treatment options for diabetes. AKG can affect the differentiation of brown fat by regulating the methylation of histones, and can also affect the inflammation of adipose tissues, which may further guide clinical studies on AKG intervention in obesity.

6. AKG in the digestive system

Certain functions of the digestive system deteriorate as the body ages (55). The blood supply of the digestive system is rich with both internal and external components. Intramural blood vessels have plexiforms in different layers of the intestinal wall, and function at the junction of the liver, small intestine and gastro-esophagus to adapt to the functions of these organs (56).

As an important intermediate product of the TCA cycle, AKG in the blood is used as a biological indicator of the health of the digestive system. Existing evidence has suggested that compared with those in normal tissues, the levels of Krebs cycle components, such as AKG, succinic acid, fumaric acid, malic acid and oxaloacetic acid in gastric cancer tissues are significantly increased (57). In addition, compared with those in normal tissues, the levels of glycolysis products, including pyruvate and lactic acid, and the level of ketone bodies, such as 3-hydroxybutyrate in cancer tissues are also significantly increased. The levels of ketone bodies in cancer tissues with different histological characteristics are notably increased. Similarly, trimethylamine oxide, hippurate, 3-indolyl sulfate, 2-oxoglutarate and citrate can be used as useful urine biomarkers for gastric tumorigenesis in a mouse model (58).

On one hand, this suggests the complexity of cancer metabolism in the digestive system, and on the other hand, it provides novel theories for the early diagnosis of digestive system cancer. Cachexia occurs after tumors have formed in the digestive system and is characterized by extreme weight loss, anemia, weakness and inability of patients to take care of themselves. Increased AKG and decreased glucose are observed in cachexia gastrocnemius. *In vitro* experiments demonstrated that AKG promotes the proliferation of myoblasts and reduces myotube atrophy caused by glucose deficiency, providing a novel theoretical basis for the development of novel treatment options for cachexia (59).

The functioning of the digestive system is closely associated with the growth and development of newborns. As a prenatal preventive drug, AKG can also be used to treat the side effects of Dex (60). Results of further animal experiments have demonstrated that 2-oxoglutaric acid increased cell proliferation in the duodenum and jejunum, as well as

Table I. Clinical application of α-ketoglutaric acid in disease.

Application of AKG	Test subject	Dose	Supplementary method	Author, year	(Refs.)
Continuous infusion of AKG protects ischemic organs	Lewis male rat	10 mg/kg/min	Perfusion	Olenchock *et al*, 2016	(26)
As an indicator of the severity of CHF in diabetic patients	Clinical patient serum	Measure content		Chen *et al*, 2018	(29)
As an indicator of left ventricular systolic dysfunction	Clinical patient serum	Measure content		An *et al*, 2021 Greilberger *et al*, 2021	(30) (31)
AKG supplementation reduces protein degradation caused by corticosterone	C57BL/6J male mice	2% Drinking water	Drinking water	Ge *et al*, 2018 Xiong *et al*, 2018 Zurek *et al*, 2019	(34) (35) (36)
AKG supplementation to reduce bone loss after menopause	Clinical patient	6 g AKG and 1.68 g Ca daily	Oral	Sliwa *et al*, 2006	(38)
AKG supplementation reduces osteoporosis and growth retardation caused by dexamethasone	Large polish white breed sows	0.4 g/kg/day	Oral	Hammarqvist *et al*, 1991	(39)
AKG supplementation causes increased insulin secretion	B6 and BTBR mouse cells	15 mM		Macdonald, 2003	(45)
Increasing AKG affects slow healing of diabetic wounds	Clinical patient serum, urine, wound fluid	Measure content		Ren *et al*, 2019	(49)
AKG supplementation is beneficial to early brown fat recruitment and activation	C57BL/6J male mouse/C3H 10T1R cells	1 mM		Yang *et al*, 2016	(53)
AKG supplementation helps reduce fat inflammation	C57BL/6J male mice	2 g/kg/day	Oral	Liu *et al*, 2016	(54)
As an indicator of non-alcoholic fatty liver in morbidly obese women	Clinical patient serum	Measure content		Shamburek and Farrar, 1990	(55)
As a biomarker for gastric cancer	Clinical patient gastric cancer tissue/mouse	Organic acid mass spectroscopy/ NMR spectroscopy		Hur *et al*, 2014 Kim *et al*, 2010	(57) (58)
Supplementation of AKG reduces intestinal injury induced by dexamethasone	Piglet	0.4 g/kg/day	Oral	He *et al*, 2017	(61)
AKG supplementation helps regulate intestinal water and ion homeostasis	Piglet	1% diet	Diet	Junghans *et al*, 2006	(62)
AKG supplementation is beneficial to reverse the intestinal damage caused by lipopolysaccharide	Piglet	1% diet	Diet	He *et al*, 2018	(64)
AKG supplementation is beneficial to slow down the decline of mammalian fertility	Clinical patient/pig/ mouse/cell etc.			Tanaka *et al*, 2021	(67)
AKG supplementation is beneficial to *in vitro* maturation of porcine oocytes	Pig oocyte	5-20 mM		Plaitakis *et al*, 2017	(69)
A potential life-extending compound formulation	A group of 42 self-reported healthy individuals (14 females and 28 males) who had submitted saliva samples	Each dose contained 1 g of calcium α-ketoglutarate	Oral	Demidenko *et al*, 2021	(72)

the number and maturity of peripheral blood lymphocytes. It supports the integrity of the epithelium and adapts the shape of the nerve plexus. Administration of 2-oxoglutarate to piglets during lactation completely eliminated intestinal damage caused by Dex. Moreover, AKG reduced the incidence of diarrhea and reversed the concentration of these serum parameters, as AKG upregulates the expression of intestinal epithelial Water and ion absorption via sensitive aquaporins and reduces the expression of ion transporters (61). Lipopolysaccharide reduces both gene and protein expression of components in the AMPK pathway, including AMPKα1, AMPKα2, SIRT1, PGC-1α, ACC and TORC2, in the jejunum and ileum. Notably, supplementing with AKG enhanced the abundance of these proteins in piglets treated with lipopolysaccharide. In addition, AKG plays an important role in maintaining the homeostasis of water and ions by regulating the AMPK pathway. Duodenal injection of AKG also reduced the growth energy consumption of piglets (62). Furthermore, 1% AKG combined with 0.5% allicin in the diet improved the microbial composition and diversity of the cecum, which may further promote the volatile fatty acid metabolism of growing pigs.

AKG also altered the expression and energy status of AMPK in the intestinal mucosa of piglets affected by *E. coli* lipopolysaccharide (63). AKG reversed the adverse effects of lipopolysaccharide and plays a key role in the prevention and treatment of neonatal intestinal dysfunction. AKG also prevented oxidative stress by activating constitutive-androstane-receptor signals and regulating the expression of key antioxidant-related targets, both *in vivo* and *in vitro*, by improving cell respiration and antioxidant capacity (64). The *in vivo* and *in vitro* effects of AKG indicated that it may be used to reduce oxidative stress and subsequently prevent gastrointestinal diseases in both animals and humans. As an intermediate product of glucose and lipid metabolism, AKG is present in the gastrointestinal system, functioning as an indicator of gastrointestinal diseases. Moreover, the nutritional function of AKG may also reduce cachexia, thus improving intestinal development of newborns, and preventing the occurrence of gastrointestinal diseases. These factors demonstrate a novel direction for the future clinical application of AKG.

7. AKG in the reproductive system

As the human body ages, the function of the reproductive system gradually declines. Previous research demonstrated that AKG is closely associated with the reproductive aging of mammals, such as mice, pigs and humans (65).

In the female reproductive system, a potential association was notable between the level of AKG in human follicular fluid and the age of patients (66). In addition, AKG promotes porcine oocyte maturation *in vitro* through an increase in the excretion rate of polar bodies, and an increase in the rate of parthenogenetic blastocysts and total cell number (67). Results of a previous study have demonstrated that reducing the uptake of pyruvic acid into the mitochondria in fetal mouse ovarian tissue culture resulted in the inhibition of early follicular formation, a negative effect that can be partially reversed by AKG (68). This highlighted the importance of this metabolite.

In the male reproductive system, the lactate hydrogenase isoenzyme LDHC in the testis converts pyruvate into lactic acid, and AKG into S-2HG, thereby altering histones or DNA methylation, and controlling epigenetics (69). hGDH2 (rather than hGDH1) is densely expressed in Sertoli cells, which are known to provide sperm with lactic acid and other nutrients. AKG, as a product of glutamate dehydrogenase, catalyzes the reversible deamination of L-glutamate (70). In addition, results of previous study have demonstrated that the addition of AKG when culturing sperm *in vitro* significantly enhances the levels of tyrosine phosphorylation protein and provides sufficient ATP for sperm movement. Moreover, AKG can be used as an effective antioxidant to protect rat sperm from hydrogen peroxide attack, which may improve the antioxidant capacity of Biggers, Whitten and Whittingham medium (71).

Results of a previous study also demonstrated that an AKG-based formula received by 42 individuals reduced biological aging by an average of eight years ($P=6.538x10^{-12}$). Thus, such interventions may demonstrate potential in slowing the process of biological aging (72).

8. Conclusion

AKG is an essential metabolite of almost every organism and plays an important role in numerous biological systems (73). Not only is it a central metabolite, but also an important ketoacid. It exerts numerous functions, including energy metabolism, antioxidant defense, signal transduction and genetic regulation (64,74,75).

Further investigations into AKG are required. For example, systematic clinical data demonstrating its presence in healthy human serum is lacking, which highlights that the role of AKG in different disease states must be further elucidated. In addition, the numerous therapeutic and preventive effects of AKG supplementation on the body are almost all based on the results of animal experiments. A lack of clinical experimental data indicates that AKG cannot yet be directly used as a dietary supplement. Thus, further animal experiments are required and additional clinical sample data must be obtained.

Results of the present study demonstrated the role of AKG in aging, and further highlighted AKG as one of the most effective solutions for age-related diseases, such as diabetes, hyperlipidemia and cancer. AKG may be involved in aging-related chronic diseases through the regulation of oxidative stress and other pathways, and therefore exhibits potential as an adjuvant therapy drug (Table I) (76).

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Availability of data and materials

Not applicable.

Authors' contributions

SL and WH designed the outline for this review. XM, HL and LP wrote the manuscript The final version of the manuscript has been read and approved by all authors. Data authentication is not applicable.

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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