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Review

Alpha-Ketoglutarate dietary supplementation to improve health in humans

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Alpha-ketoglutarate (AKG) is an intermediate in the Krebs cycle involved in various metabolic and cellular pathways. As an antioxidant, AKG interferes in nitrogen and ammonia balance, and affects epigenetic and immune regulation. These pleiotropic functions of AKG suggest it may also extend human healthspan. Recent studies in worms and mice support this concept. A few studies published in the 1980s and 1990s in humans suggested the potential benefits of AKG in muscle growth, wound healing, and in promoting faster recovery after surgery. So far there are no recently published studies demonstrating the role of AKG in treating aging and age-related diseases; hence, further clinical studies are required to better understand the role of AKG in humans. This review will discuss the regulatory role of AKG in aging, as well as its potential therapeutic use in humans to treat age-related diseases.

Highlights

Alpha-ketoglutarate (AKG) is a key molecule for cellular energy and protein synthesis.

AKG functions as an antioxidant, in nitrogen and ammonia balance, as well as in epigenetic and immune regulation.

These functions of AKG have a beneficial effect on the treatment of diseases such as in the heart, brain, liver, and skeletal muscle.

AKG could modulate aging in humans thus, AKG could potentially extend healthspan and promote healthy longevity.

Introduction

Extensive research in the biology of aging has to a large extent galvanized thinking of aging mechanisms around several pillars or hallmarks [1,2]. Among these are oxidative stress, macromolecular damage, epigenetic changes, abnormal metabolism, impaired proteostasis, the decline in adult stem cell function, and chronic inflammation [1]. These overlapping processes undergo functional decline over the life course; influencing aging and enabling the onset of age-related diseases. However, they can be modified by lifestyle and pharmacologic interventions, at least in animals, with human data beginning to emerge. Several compounds such as metformin, resveratrol, rapamycin, and AKG are reported to slow the process of aging [3]. AKG is regarded as a safe supplement with the potential to extend healthspan and even compress morbidity [4,5].

AKG is a crucial intermediate of the Krebs cycle and plays an important role in multiple metabolic processes. It is involved in the oxidation of fatty acids, amino acids, and glucose, and is involved in cellular energy and metabolism [6]. AKG is also a significant source of **adenosine triphosphate (ATP)** for cells, specifically in the gastrointestinal tract [7], as well as a precursor for amino acid biosynthesis in the liver, skeletal muscle, heart, brain, and adipose tissue [7]. The use of AKG in animal models has been widely studied and several beneficial effects of AKG have been established [8–13]. There are few studies probing potential beneficial effects of AKG supplementation in humans [14–18]. These studies were conducted in the 1980s and 1990s, with limited recent follow-up. One recent study in 42 healthy individuals, showed that AKG (Rejuvant® for 7-months) reduced biological age by 8 years as measured by the TruAge DNA Methylation test [19]. In this review, we will focus on the use of AKG in humans. First, we will discuss the biochemical properties and pharmacokinetics of AKG. Second, we will focus on the role of AKG in aging and age-related diseases, such as in the brain, kidney, heart, liver, bone, and skeletal muscle. Finally, we will discuss clinical perspectives on AKG.

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Biochemical properties

In mammalian cells, AKG is generated and decomposed by a variety of metabolic pathways: (i) decarboxylation to succinyl CoA by AKG dehydrogenase; (ii) oxidative decarboxylation of isocitrate by isocitrate dehydrogenase; and (iii) oxidative deamination of glutamate by glutamate dehydrogenase [5]. AKG has several functions; first, AKG mediates the formation of amino acids, such as glutamine, proline, arginine, and lysine [20]. Second, AKG also regulates cellular carbon and nitrogen utilization, preventing nitrogen and carbon overload in the body [20,21]. Third, AKG as an antioxidative agent plays an important function in the wide range of oxidation reactions [21,22]. Fourth, AKG regulates hypoxia-inducible factor (HIF)-1 activity and inhibits tumor growth by inducing hypoxia [23–26]. Finally, AKG is a regulator of gene expression and cell signaling pathways related to growth and aging, including the **mechanistic target of rapamycin (mTOR)** and **AMP-activated protein kinase (AMPK)** [7] (Figure 1).

Pharmacokinetics

At the cellular level, AKG participates in many biochemical processes, including substrate and redox metabolism, amino acid synthesis, nitrogen transport, and innate immune regulation. However, it may not be possible to use AKG directly from the Krebs cycle for the synthesis of amino acids because of its short half-life (less than 5 minutes) [4,27,28]. Furthermore, AKG is a weak acid, which limits its permeability through the cell membrane [29]. In animal studies, it has been shown that compared to other parts of the gastrointestinal tract, AKG was better absorbed in the upper small intestine [27]. Low pH, Fe^{2+} and/or SO_2^{-4} ions in the upper small intestine might enhance this absorption [27]; however, this has not been confirmed in human studies. Upon oral administration, around 80% of dietary AKG is rapidly removed from the bloodstream [30]. The remaining AKG is passed to the liver and kidney via the sodium–potassium pump, which follows the common metabolic pathway and is converted into proline, leucine, and other amino acids [31,32]. There was a very small increase in plasma AKG, 1 hour after oral loading of 3.6 g of AKG. Plasma glutamate concentration peaked at 60 minutes (68% increase compared to basal concentrations) [28]. Moreover, the serum concentration of AKG is lower with advanced age, [33,34] due to the decline in metabolic influx into cells, [33] and reduced absorption in the small intestine [35]; hence, AKG may need to be provided in some other form as a regular dietary supplement in older adults.

In the following section, we will describe advances in AKG research as a dietary supplement in aging and age-related diseases in humans.

Aging

Abnormalities in protein metabolism have been attributed to aging [36]. AKG impacts protein metabolism, synthesis, and absorption from the alimentary canal [27,36]. Dietary AKG may improve protein metabolism and synthesis in older adults [13,36]. A recent study showed that 2% calcium-AKG (Ca-AKG) extends lifespan and healthspan in both male and female C57BL/6 mice by 9.6–12.8% and 16.6–19.7% respectively [13]. Dietary supplementation of AKG in those mice also showed a decrease in systemic inflammatory cytokines, suggesting AKG suppresses chronic inflammation with improvements in several health outcomes such as reduced frailty, reduced hair loss, maintenance of body weight, and enhanced longevity [13]. In a recent human study, AKG reduced biological age by 8 years as measured by DNA methylation [19]. Thus, AKG has pleiotropic functions, which has implications for its use as a longevity enhancing mimetic.

The first indication that AKG supplementation leads to enhanced lifespan was reported by Chin *et al.* [34], where *Caenorhabditis elegans* fed the metabolite had increased lifespan in a dose-

Glossary

Adenosine triphosphate (ATP): an energy carrying molecule in all living organisms. When a cell requires energy, ATP is broken down via chemical process to release energy, which is used by the cell for various cellular process.

Mechanistic target of rapamycin (mTOR): mTOR is a kinase (enzyme that facilitate the phosphorylation process to produce high energy molecules) which in human is encoded my *MTOR* gene. It is major regulator of growth in humans.

AMP-activated protein kinase (AMPK): a protein complex involved in maintaining cellular energy homeostasis, by activating glucose and fatty acid oxidation and uptake, at a state of low cellular energy. It is expressed in several human tissues such as liver, brain, and skeletal muscle, where there is great demand of cellular energy.

Autophagy: a prominent cytoprotective mechanism in response to resistance and external stress. It is naturally conserved fundamental cellular process to eliminate unnecessary dysfunctional cellular components such as proteins, lipids, and amino acids, to maintain cellular homeostasis, development, differentiation, and survival.

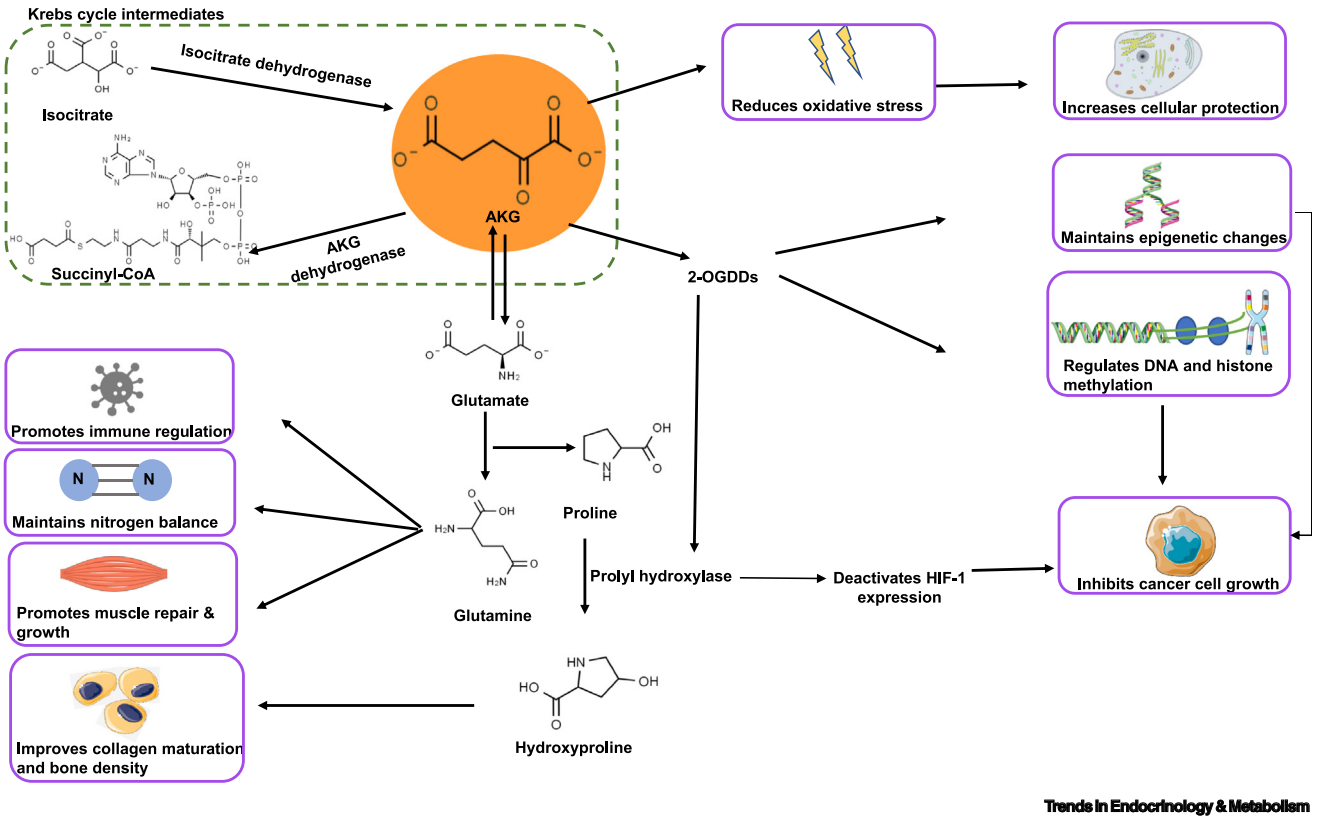

Figure 1. Schematic representation of the activity of AKG. Abbreviations: AKG, alpha-ketoglutarate; 2-OGDDs, 2-oxoglutarate dependent dioxygenase; HIF, hypoxia-inducible factors; DNA, deoxyribonucleic acid; succinyl CoA, succinyl coenzyme A.

dependent manner, with maximum effects of almost 50%. The mechanism for lifespan extension was linked to the downregulation of mTOR kinase activity [34]. A recent study has also documented the antiaging effects of AKG in *Drosophila*, that also mediates its effects via mTOR inhibition [37]. However, AKG may activate mTOR signaling pathway [38,39]. In intestinal porcine epithelial cells, AKG activated mTOR to stimulate protein synthesis [40]. In mammary epithelial cells, AKG was found to enhance milk protein production by activating mTOR signaling pathway [41]. Like AKG, caloric restriction, a widely acknowledged longevity-promoting regimen [42], also enhances longevity, at least in part by downregulation of mTOR activity [43]. Calorie restriction increased levels of AKG in yeast and *C. elegans* [34,45]. Similarly, antiaging mechanisms of calorie restriction and inhibition of mTOR rely on **autophagy** [45]. One study on human osteosarcoma cells showed that AKG inhibits autophagy [45]. While such findings demonstrate that AKG may be a key evolutionarily conserved mediator of aging, the molecular links and targets of AKG that may relate to longevity remain to be elaborated.

Loss of muscle mass

AKG increased muscle strength and endurance, in part by preventing muscle protein breakdown through a mechanism involving prolyl hydroxylase-3 and the β2 adrenergic receptor [8]. In addition, AKG downregulated the expression of proline hydroxylase-3 and blocked muscle protein degradation [8]. Likewise, AKG also inhibited the interaction between β2 adrenergic receptor and prolyl hydroxylase-3, leading to increased receptor protein levels and reduced muscle atrophy [8]. Similar results were also found in patients who underwent gallbladder resection, although

a different mechanism was proposed. The addition of AKG in their postoperative parenteral nutrition promoted muscle protein synthesis and prevented muscle protein breakdown by reducing free glutamine concentration, leading to faster recovery [46]. In patients with major abdominal operation, combined intravenous administration of AKG with total parenteral nutrition significantly increased nitrogen balance, compared with controls (prescribed with only amino acid) [47]. AKG might have prevented post-operative muscle protein breakdown in those patients by controlling residual glutamine breakdown [46–48]. Some degree of muscle atrophy is inevitable after surgery or trauma due to increased efflux of glutamine from the muscle to the intestine as a fuel source, leading to a decrease in muscle protein synthesis and eventually muscle loss [46,49]. Sarcopenia, low muscle mass, strength, and function is highly prevalent in older adults [50] and associated with negative outcomes such as falls, fractures [51], and mortality [52]. Hence, AKG should be tested in older adults with sarcopenia and younger individuals to preserve muscle mass and strength.

Osteoporosis

AKG has been shown to have a protective effect against osteoporosis [31]. One study in post-menopausal women with osteopenia showed that a daily dose of oral Ca-AKG (6 g AKG for 6 months) increased bone mass density by 1.6% from baseline [31]. There was a significant decrease in the C-terminal crosslinking telopeptide of type-I collagen (a biomarker of bone reabsorption) in patients receiving Ca-AKG supplement compared to those only receiving calcium [31]. The mechanism may be related to the effect of AKG on epigenetic regulation [39,53]. AKG increased bone mass, attenuated age-related mass bone loss, and stimulated osteogenic differentiation in 18-month-old mice via regulating histone methylation [53]. In those mice, AKG decreased the level of H3K9me3 and H3K27me3 and upregulated bone morphogenetic protein signaling and *Nanog* expression [53]. In human osteoblast cell lines, AKG upregulated the expression of transcription factors such as Runt-related transcription factor-2 and Osterix, as well as increased levels of alkaline phosphate, type-I collagen, osteopontin, and osteocalcin [39]. AKG promoted the differentiation of osteoblast via activation of c-Jun N-terminal kinases and mTOR signaling [39]. Therefore, it is important to understand the primary mechanism of action and potential therapeutic role of AKG in preventing osteoporosis.

Neurodegenerative disease

AKG is deaminated to form the excitatory neurotransmitter; glutamate. Glutamate in the presence of vitamin B6 can then be decarboxylated into the inhibitory neurotransmitter gamma-aminobutyric acid. Therefore, AKG may be essential in long-term potentiation, memory, and neurotransmission [54,55]. High concentrations of ammonia and nitrogen in the brain lead to several neurological symptoms, such as impaired memory, poor attention, seizures, and coma [56]. AKG plays important role in the detoxification of ammonia in the brain by reducing the levels of lactate dehydrogenase, malondialdehyde, and reducing oxidative stress [7,21].

Oxidative stress leads to neurotoxicity [57]. Several neurological diseases, such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis, have been associated with increased oxidative stress [57,58]. AKG can prevent the brain from oxidative damage by increasing neuronal concentrations of antioxidative enzymes [59,60] and quenching reactive oxygen species [61]. This raises the question, whether AKG supplementation in older adults may reduce the risk of cognitive impairment, dementia, and other neurological disorders.

The use of ornithine AKG (O-AKG) (1 g/kg infused intravenously) in mongrel dogs increased brain oxygen utilization and glucose utilization while reducing metabolic disturbances caused by hypoxia [62]. Similar results were obtained in patients with stroke. On administration of 25 g/day

intravenous infusion of O-AKG within 96 hours of stroke, patients showed greater improvement in consciousness and neurological impairment scores compared to placebo [63]. The mechanism how AKG improves brain oxygenation is linked to the post-cerebral ischemic decrease in glutamate concentration, protein degradation, and change in amino acid transporters [62,64], which affects functional activity in the brain [64]. The fact that AKG replenishes protein synthesis and maintains glutamate concentration, and increases oxygen utilization in the brain would support this hypothesis [40,62,63]. Similarly, AKG also improves blood vessel elasticity by reducing free radical related changes [12] and increasing nitric oxide production, which leads to coronary and peripheral vasodilation [65,66]. Such vasodilation would increase brain oxygenation and nutrient delivery, and removal of waste products.

Cardiovascular disease

Intravenous AKG has been used to reduce vascular insufficiency during cardiovascular surgery. Several studies have shown the cardioprotective effects of AKG [36,67–69]. During heart surgery, myocardial AKG concentration is critically low, hence cardiac cells are in a low energy state [70], leading to myocardial ischemic injury [69]. One clinical trial showed that the addition of 28 g of AKG to cardioplegic blood reduces the appearance of ischemic biomarkers, such as creatine kinase and troponin, compared to controls [69]. Another study in male patients undergoing heart operations showed that the addition of 28 g of AKG in blood cardioplegia during cardiac surgery showed increased myocardial oxygen extraction and reduced myocardial lactate production in blood cardioplegia [70]. This may be explained by the fact that AKG enhanced myocardial oxidative capacity, increased energy production, and attenuated ischemic injury [69,70]. Moreover, it has been shown that the use of AKG after cardiac surgery improves renal perfusion and function, reducing the risk of postoperative acute renal failure [68]. The use of AKG has been shown to reduce plasma low-density lipoprotein and cholesterol concentration in humans [36,67], implicating the metabolite in the downregulation of hyperlipidemia by inducing the production of nitric oxide [71].

Liver disease

So far there are a few studies that investigate the role of AKG in the treatment of liver disease in humans. However, results from these studies and those in animals indicate that AKG may be useful in treating non-alcoholic fatty liver disease and reducing brain ammonia and glutamate level in patients with hepatic encephalopathy [72,73]. In mice, AKG (1% AKG in drinking water) inhibited liver disease progression by increasing lipid metabolism, while reducing steatosis and cholesterol levels [74].

Hepatic encephalopathy is seen in several liver diseases; impaired detoxification by the liver can lead to the accumulation of various deleterious substances, most commonly ammonia [75]. AKG may reduce levels of ammonia in patients with liver disease [76]. Mechanistically, oxidation of AKG by enterocytes may suppress glutamine degradation and thereby reduce ammonia production by intestinal epithelial cells [40]. Similarly, another study in comatose patients due to liver disease showed that O-AKG could decrease levels of ammonia, but without any improvement of consciousness [77]. However, there are no other human studies evaluating the role of AKG in liver disease, despite several human studies suggesting that AKG can maintain nitrogen and protein balance [47,48].

Renal disease

Ca-AKG has been shown to improve kidney function and nutrition in patients with chronic renal failure [78]. In those patients, daily use of Ca-AKG showed a higher level of plasma arginine compared to healthy controls over 1 year follow-up [78]. Those patients also showed a decrease in the

plasma concentration of urea even after 6 months of administration of AKG [78]. AKG also regulates acid–base balance in renal tubules and increases renal function [79]. Under normal conditions, AKG is actively absorbed by the proximal tubule and loop of Henle [79]. In an acidic environment, absorption of AKG increases resulting in low urinary AKG, whereas under the basic condition, absorption of AKG decreases while maintaining normal urinary pH [79,80]. It has been speculated that luminal AKG concentration is influenced by the AKG receptor: 2-oxoglutarate receptor 1, expressed on the connecting tubule and the cortical collecting duct [79]. These functions of AKG may help in maintaining normal kidney function, faster recovery, and good clinical outcomes in patients with chronic kidney disease.

Cancer

AKG regulates signaling pathways linked to oncogenesis, making it one of the potential anticancer agents [32,81]. The anticancer effect of AKG has been attributed to its ability to reverse the metabolic response to hypoxia and restore oxidative phosphorylation in cancer cells [26,32,82–84]. When a tumor grows, it creates a hypoxic environment in the nearby blood vessels and tissues, activating HIF-1 and promoting secretion of several angiogenic factors such as vascular endothelial growth factor, epidermal growth factor, placental growth factor, and also leading to increased glycogen synthesis and increased glycolysis [25]. It has been proposed that AKG regulates HIF-1 activity and inhibits the carcinogenic effects of hypoxia [23–26,83].

Moreover, mutation of mitochondrial genes encoding Krebs cycle enzymes, such as succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase (IDH), occur in carcinogenesis [85–87]. Mutation in genes encoding SDH and FH leads to the accumulation of succinate, fumarate, and other oncometabolites, which promote cancer cell proliferation by inducing pseudohypoxia [87]. Mutation in IDH genes reduces AKG and promotes cancer cell growth by upregulating HIF-1 activity [87,88]. It has been hypothesized that exogenous AKG may inhibit tumor growth, in part by reducing levels of HIF-1, suppressing the secretion of angiogenic factors, and regulating epigenetic processes [25,26,83].

Epigenetic modifications are important in regulating DNA repair, replication, and damage, [32] which may affect the expression of genes that activate tumor growth and maintenance. *In vitro* and *in vivo* studies have shown that AKG affects DNA methylation status and thereby reduces tumor growth [32,89]. AKG also affects tumor growth through p53 mediated tumor suppression [90]. p53 is known to modulate cellular and metabolic pathways in cancer cells, and it accumulates in response to cellular stress and regulates gene expression to prevent tumor development [90]. On the contrary, in human glioblastoma cells, AKG activated nuclear factor kappa B signaling, promoted glucose uptake by tumor cells, and increased their survival [91]. However, these results were drawn from *in vivo*, *in vitro*, and animal model studies; the mechanism, mode of action, and effectiveness of AKG may be different depending on the cancer type. Until human studies and clinical trials are conducted, it is still not conclusive whether AKG can be effective as an anticancer agent.

Other clinical applications

Topical application of AKG can diminish skin wrinkle formation by increasing collagen production through a pathway that involves prolidase activation [92]. In human dermal fibroblasts, AKG stimulated procollagen production and increased the activity of prolidase [92]. AKG may be used for cosmetic purposes and the treatment of scars.

There are a few studies showing the effect of AKG on burn patients [14,93–95]. The use of 20 g/day O-AKG for 21-days in severe burn patients showed positive nitrogen balance and lower body weight

loss compared to a placebo [14]. Similarly, another study on severely burned patients enterally receiving 10 g O-AKG twice/day for 28 days showed lowered protein catabolism compared to controls [93]. It has been hypothesized that AKG mediates the secretion of insulin and human growth hormone, which promotes wound healing [93]. One clinical trial analyzing the effectiveness of AKG on wound healing time in severe burn patients showed that O-AKG (2 × 10 g/day) significantly shortened wound healing time (70 versus 90 days) [95].

Gastrointestinal disorders such as Crohn's disease, ulcerative colitis, and gastric ulcer are associated with intestinal epithelial damage, dysbiosis, and impaired immune response [96,97]. Proper nutrition supplementation and lifestyle modifications can help in epithelial restitution and protection against stress-induced epithelial damage [98]. Emerging evidence has shown that AKG supplementation might affect intestinal innate immunity through influencing intestinal microbiota [99] and inhibiting intestinal villi apoptosis, hence maintaining gut integrity [97]. In early-weaning piglets (6.20 ± 0.11 kg, 28 days old) showed that 1% AKG supplementation (three times/day for 30 days) improved growth performance and intestinal morphology compared to a basal diet [97]. An AKG supplemented diet in those piglets also alleviated the intestinal inflammatory response by decreasing the concentration of inflammatory cytokines and improving epithelial restitution and nutrient-sensing ability under stress injury [97]. Another study in lipopolysaccharide-challenged piglets (23-day-old) has shown that 1% AKG alleviates mucosal damage and intestinal absorption via mTOR activation [38].

AKG supplementation influences the levels of circulating hormones, such as growth hormone, insulin, and insulin-like growth factor-1 [5], and also promotes the synthesis of metabolites such as glutamine, polyamines, arginine, and ketoacids [15]. These hormones and metabolites are essential for maintaining our body's normal nutritional status. Malnutrition is common older adults [100], which has significant consequences on muscle mass loss, impaired digestion, morbidity, and mortality [100]. Malnutrition in older adults may be attributed to age, reduced food intake, stress, and chronic diseases [100]. Hospitalized older adults with chronic diseases receiving O-AKG (5–20 g/day) showed a significant increase in appetite and body weight compared to those without the metabolite [17,100]. Similar results were also found in older adult patients with acute illness who received 10 g/day AKG [18]. Over a 4-month follow-up, those patients receiving AKG required fewer doctor visits, nursing care, prescription, and decrease in medical costs [18].

Perspectives

AKG is an important metabolic intermediate that acts as a cofactor for several epigenetic regulatory enzymes that are involved in DNA demethylation, transcriptional, and epigenetic changes [53,89]. Even though AKG is not absorbed by cells (with exceptions of enterocytes of the gastrointestinal tract and renal cells) [84], dietary AKG (1% AKG) was shown to increase DNA demethylation in *Prdm16* gene in adipose tissue of 10-month-old mice [33]. An *in vitro* study showed that cell-permeable AKG directly supports embryonic stem cell self-renewal, and contributes to the maintenance of cellular identity, thus maintaining pluripotency [89,101]. AKG levels are expected to modulate these demethylase activities as well as transcriptional and epigenetic changes in embryonic stem cells, macrophage activation, and aging [102], however the role of AKG in cellular metabolism in regulating cell differentiation and proliferation needs to be studied in detail.

AKG can be administered in pure form or in combination with calcium, arginine, ornithine, or sodium. A large number of clinical and preclinical studies were performed on O-AKG compared to sodium-AKG (Na-AKG) and Ca-AKG. So far, there is no clear study demonstrating the pharmacokinetic effect of AKG when administered in different forms: pure and in combination with other compounds. One study demonstrated that O-AKG (3.6 g of AKG and 6.4 g of

ornithine) increased levels of amino acids and insulinemia and glucagonemia, whereas AKG and ornithine did not show such effect when administered separately [28]. Another study in the rat trauma model showed higher plasma and muscle amino acid concentration when fed O-AKG compared to AKG only [103]. Administration of AKG together with ornithine salt has a synergistic effect, which in turn, increases the synthesis of glutamine and other amino acids [16].

The optimal daily dose of AKG also varied among studies, ranging from 3.6–6 g [28,31], whereas in burn patient, three different doses of O-AKG; 10, 20, and 30 g was used, with 30 g showing maximum benefit on wound healing and recovery [14,93,104]. Another study conducted in hospitalized patients receiving either 0 versus 5, 10, 20 g/day of O-AKG, showed an increase in albumin and transferrin concentration, with maximum effect observed in those receiving 10 g of O-AKG [17]. A study in pigs showed that not all AKG is oxidized into glutamate and glutamine irrespective of the route of administration; intravenous, intragastric, or intraduodenal [105]. Likewise, when AKG was given as a bolus there was a significant improvement in burn wound healing compared to continuous infusion; however, the response was dose-specific [104].

AKG as a weak acid cannot freely pass through the cell membrane [29]. The ability of AKG to penetrate the cell can be increased by the use of its esters [84]. Furthermore, with the short half-life of

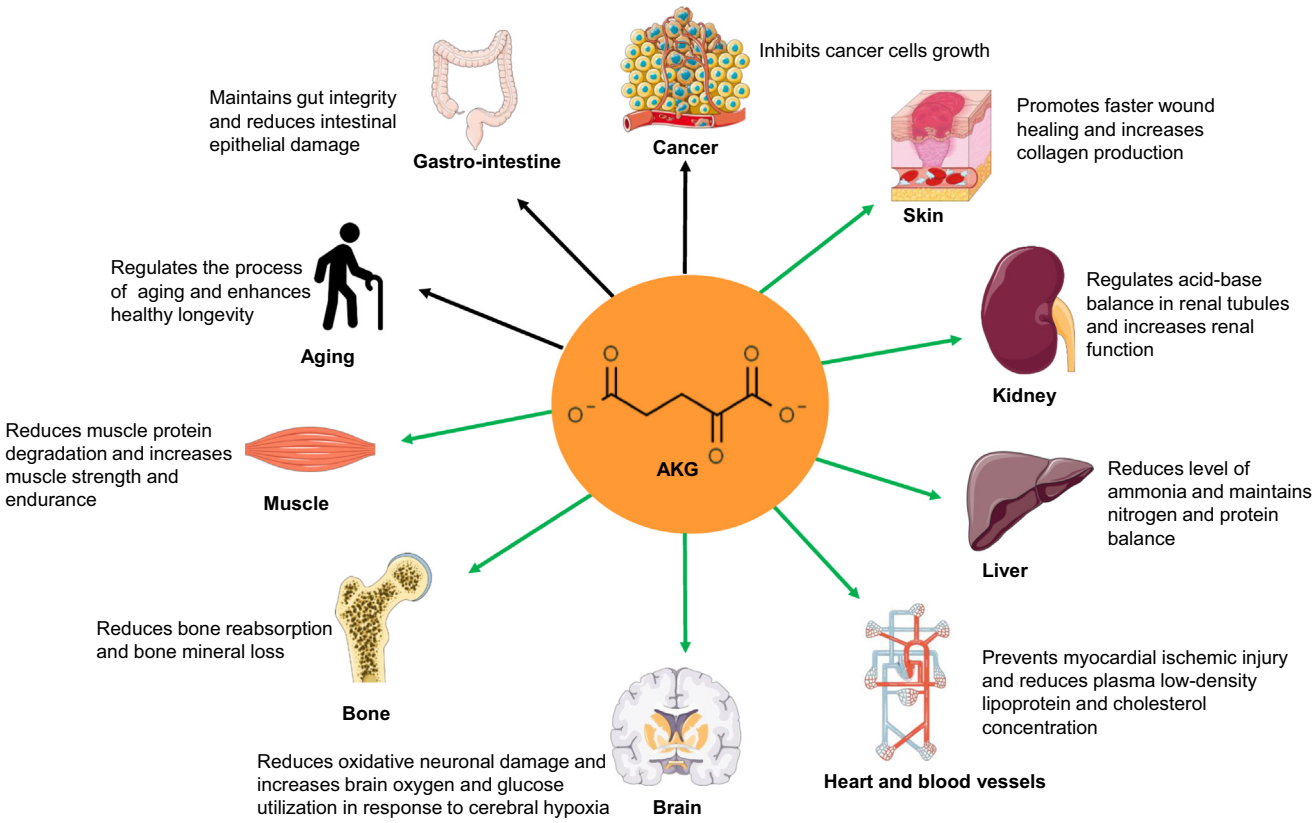

Figure 2. Summary of effects of AKG on aging and age-related diseases in human. AKG is involved in redox metabolism, amino acid synthesis, nitrogen transport, innate immune and epigenetic regulation, and reduction in chronic inflammation and oxidative stress. There is evidence that these functions of AKG helps in the maintenance of liver and kidney function, prevention of myocardial and cerebral injury, and reduction of muscle protein degradation and bone mineral loss. It is hypothesized that AKG may affect cancer cell growth, reduce intestinal epithelial damage, and also delay the process of aging and enhance healthy longevity.

AKG, it cannot be retained in the body for a longer duration [29], which may be prolonged by the use of sustained-release technology such as the wet granulation technique [106]. AKG is safe when taken up to 6 g/d for 6 months [31]. A few gastrointestinal side effects of AKG have been reported [107,108]. In HIV-positive patients taking 10 g/d of O-AKG reported nausea, bloating, vomiting, and diarrhea [107]. Patients undergoing abdominal surgery reported nausea and vomiting after administration of AKG enriched enteral nutritional solution [108]. While no major adverse effects of AKG supplementation have been reported, at higher dose there may be a possibility of non-compliance. It is important to study the most effective route of administration in humans (oral versus intravenous or bolus versus continuous, or in the form of nano-molecules), and mode of release (sustained versus extended versus rapid) as well as the long-term safety and efficacy of AKG in humans.

Concluding remarks

AKG has a very important role in cellular energy, metabolism, antioxidative stress, immune response, and epigenetic regulation. Yet, many actions and mechanisms of AKG are not fully understood. AKG has been used in the treatment of several diseases in model organisms, as well as in humans (Figure 2). Today, AKG can be synthesized exogenously and produced in several forms. Exogenous AKG has been used in wound healing, treatment of kidney dysfunction, gastrointestinal disease, and cancer. Many studies have indicated that AKG can prevent muscle breakdown and improve bone mineral density. Dietary supplementation of AKG has a positive effect on reducing chronic inflammation. Recently, it has been hypothesized that AKG can regulate the aging process and have an effect on prolonging healthspan. Exciting results from preclinical studies indicate that mTOR is involved in human chronic diseases, where modulation of mTOR activity by AKG may play important role in aging. However, the therapeutic effects of AKG are still unclear; hence, to better understand the mechanism of AKG, we recommend more research focusing on the potential use of AKG as an antiaging supplement to increase healthspan in humans (see Outstanding questions).

Outstanding questions

What is the optimal daily dose of AKG that could be prescribed in humans to maintain healthy longevity?

Which form of AKG has the maximum effects on enhancing longevity: in pure form or in combination with other compounds such as sodium, calcium, ornithine?

What are the other undelaying mechanisms that AKG enhances longevity?

How does AKG affect gut integrity and gut microbiome and what are the implications?

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Author contributions

B.G., J.G., and B.K.K. conceptualized the idea. B.K.K. and A.B.M. supervised the manuscript. B.G drafted the manuscript. Z.X.L, J.S, C.L, and S.P.G. revised the manuscript and provided intellectual comments.

Declaration of interests

B.K.K. is a board member and equity holder at Ponce de Leon Health, a company aimed at developing nutritional supplements for aging, which manufactures several products related to AKG. All authors declare no competing interest regarding this manuscript.

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