Progress in modeling avian hyperuricemia and gout (Review)

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Abstract. Human organ tissue is vulnerable to hyperuricemia (HUA), which negatively impacts quality of life, particularly when it progresses to gout. Chicken uric acid formation and metabolism are similar to human uric acid metabolism; therefore, theoretically, the genesis and progression of human HUA and gout may be similar to those of poultry models. The present review explored HUA and gout and the progress of poultry-induced HUA and gout models. The present study reviewed procedures of modelling chicken gout and HUA and the detection indices and current concerns regarding these models. Notably, In the production of poultry hyperuricemia model, the combined method of water and food induction has a higher success rate and stability. Compared with mice induced HUA and gout models, poultry induced HUA and gout models had less kidney damage, and the models were stable and long-lasting.

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1. Introduction

Hyperuricemia (HUA) is a metabolic disease characterized by abnormalities in purine metabolism and elevated blood uric acid levels, which is often caused by excessive levels or abnormal secretion of uric acid. Persistent high blood uric acid levels accelerate deposition of urate crystals in joints, leading to gout (1). HUA is a metabolic disorder caused by abnormal purine metabolism. The diagnostic criteria involve obtaining fasting blood samples on separate days under usual dietary conditions, and determining blood uric acid levels using the uricase method. Levels >420 µmol/l for males or >360 µmol/l for females are considered diagnostic (2). Typical symptoms include inflammation, oxidative stress and dysbacteriosis. As the economic status and living standards of individuals have improved, diets high in protein, purine, fat and sugar are more common. Previous studies have revealed that HUA is associated with development of chronic renal disease, diabetes mellitus, hypertension, cardiovascular events and other disease (3-6). The incidence of HUA increases annually and it is now recognized as a metabolic disease. Prevalence of Hua in China has increased from 11.1% in 2009 to 18.7% in 2019. The prevalence of Hua in young men (31.9%) in 2019 was almost three times that of the same age group (10.0%) in 2009, and young men were the group with the fastest-growing prevalence of Hua in the last decade (7). In addition, hyperuricemia is also becoming more common in young people (8). Formulating an appropriate animal model is key for further research on HUA.

The final result of the avian purine metabolic pathway is identical to human uric acid, which may provide an appropriate animal model for simulating human HUA. To present review summarizes the literature regarding the establishment of avian HUA and gout models and model induction methods and detection indices.

2. Gout in poultry

Avian gout causes. Avian gout is caused by either overproduction or impaired excretion of avian uric acid in the bloodstream. Uric acid deposits as urates in the joint capsule, articular cartilage and periarticular, thoracic and abdominal cavities, as well as on the surfaces of other mesenchymal tissue and various organs (9). There are numerous factors associated with avian gout, such as high protein content in feed, excessive salt, dietary calcium, phosphorus imbalance, insufficient vitamin A uptake and lack of drinking water. In addition, genetic and disease factors, viral infection and improper use of drugs and feeding can lead to avian gout (10). In nature, spontaneous gout cases have been described in quails, pigeons, chickens, ducks, geese, peafowls and turkeys (11-17).

Birds and mammals have notable differences in ammonia excretion; ammonia is toxic to organisms and is produced

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in the deamination of protein metabolites and amino acids. Ammonia is converted into urea via the urea cycle in the liver in most mammals, or it is excreted by the kidneys via glutamate transport (18). Certain mammals produce uricase, which metabolizes uric acid to allantoin; therefore, serum uric acid levels are not high under normal circumstances (19). However, during evolution, humans and poultry lost the genes for the uric acid enzyme that promotes kidney excretion, thus ammonia cannot be transformed into allantoin. Uric acid is generated by synthesis and decomposition of purine nucleotides and it reaches the kidney through the blood circulation. Following glomerular filtering, uric acid reaches the renal tube. Combined with uric acid, the sodium ions secreted from the proximal convoluted tubule epithelial cells transform into urates that are excreted from the kidney, which results in humans and poultry having higher levels of uric acid than other species. In addition, lack of urea synthesis arginine in the liver of poultry means that they cannot remove ammonia via the urea cycle and as poultry kidneys lack glutamine synthase, they cannot excrete ammonia through glutamine (20). Therefore, synthesis and decomposition pathway of purine nucleotides converts ammonia into uric acid, which is the primary method of ammonia metabolism in poultry. The decomposition and metabolism of poultry purine is as shown in Fig. 1. Under the action of nucleotidase, purine nucleotides are dephosphorylated to produce the purine adenosine; adenine produces hypoxanthine under the action of adenosine deaminase and is then oxidized into xanthine, which is catalyzed by xanthine oxidase. Guanosine is directly hydrolyzed and generates guanine and then generates xanthine through deamination. Ultimately, xanthine produces uric acid catalyzed by xanthine Oxidase (XOD) (21). Because of the lack of uricase in humans, uric acid is the final product of purine nucleotide metabolism in the body, so we think that the metabolism of uric acid in birds is similar to that in humans, poultry can be used as a suitable animal model for human uric acid metabolism (22).

Types of avian gout. The two types of gout in birds are visceral gout and articular gout. Visceral gout, also called 'avian urolithiasis', is characterized by deposition of urate in the thoracic and abdominal cavity and on the surface of the viscera such as the kidney, heart, liver, mesentery and peritoneum, often accompanied by renal failure, similar to human uremia. Articular gout is characterized by urate deposition in the joint capsule, articular cartilage and surrounding tissue (23). Genetic factors are linked to spontaneous articular gout; notably, gout develops in New Hampshire chickens as a result of genetic selection anomalies in the transport of uric acid in renal tubules (24).

Birds with articular gout have a prolonged duration of disease without internal organ damage. In most cases, clinical symptoms appear around the joints. In the early stage, the swelling is soft and painful with no obvious boundaries; the mid-swollen parts gradually become hard, forming pea- or broad bean-sized nodules that are either slightly mobile or immobile (19). When swollen joints are cut open, white, milky urate flows from the joint cavity.

Visceral gout is a common clinical disease in poultry. Typical clinical symptoms include anorexia, depression, strong desire to drink, diarrhea and staining of the feathers around the cloaca with white feces. The disease is often caused by serious failure of multiple organs, such as the kidney, which can result in death (20). White urate crystal deposits, which are detected via microscopic inspection of needle-like crystals, can be found in the pericardium, liver, kidneys, intestine, air sacs and the plasma membrane surface of the ureter (25). The kidney swells and becomes pale in color. Urate obstruction causes the ureters to thicken and harden, leading to larger and hardened kidneys that are pale and have a snowflake pattern on their surface and parenchyma (26).

3. Techniques for creating gout models and avian HUA

Increasing synthesis of uric acid

Purine-rich diet. Changes in food, including the addition of uric acid precursors or supplements, can elevate blood uric acid levels in chickens. Increased consumption of adenine-rich meals can facilitate synthesis of uric acid. Purine- and protein-rich yeast can hydrolyze *in vivo* to form purine and pyrimidine bases, which interfere with purine metabolism, increase XOD activity and thus increase uric acid production. Lin *et al* (27) induced a quail model of HUA via a high-purine diet ordinary feed mixed with yeast dried powder (15 g/kg/d). On days 14 and 21, levels of serum uric acid in the model significantly increased and the oxidation levels also increased. This strategy was also employed by Wang *et al* (28) to generate a quail HUA model. After 14 days, serum uric acid levels in the model group were substantially greater than that in the normal group. Wu *et al* (29) created a gout model in quail via high-purine diet. By day 30, the quail exhibited gout symptoms: XOD activity and uric acid levels were elevated, oxidative stress balance was disrupted, NLRP3 inflammatory vesicles were activated and an inflammatory response was produced. Li *et al* (30) created a mixed diet using yeast powder to formulate a quail model of HUA. From day 4, blood uric acid levels gradually increased in the quail; the levels peaked on days 7 or 10 and stayed high for the next 28 days. Kuang *et al* (31) fed chickens high-purine diet (formulated through a ratio of 90% basal feed, 10% yeast leachate supplemented with 0.4% adenine) with a daily water limit of 50 ml/chicken for 3 weeks, resulting in high uric acid levels (617.54±16.36 μmol/l).

Protein-rich diet. High-protein feed materials mainly include animal offal, meat and bone meal, fish meal, etc. After the body decomposition can produce a large number of purine nucleotides and converted into excess uric acid (32). Li *et al* (33) discovered that feeding chicks 24% crude protein content could cause gout symptoms. Furthermore, by feeding 1-day-old geese high-protein diet (23% crude protein content), Wang *et al* (34) established a HUA model that resulted in elevated blood protein content and uric acid production. Hong *et al* (35) raised 24-week-old male Henleigh chickens on a high-protein diet (34.88% crude protein content) and observed ankle joints were curved and deformed. The synovial fluid, tissue fluid and liver produced sodium urate crystals and their kidneys displayed different degrees of damage. In addition, serum uric acid levels increased within 2 weeks and remained high throughout. Liu (36) fed 50-day-old male Roman chickens high-protein diet (50% soybean meal and 50% basal diet) and limited water to 100 cc/chicken/day. On day 28, blood uric acid increased (>417 μmol/l), HUA model

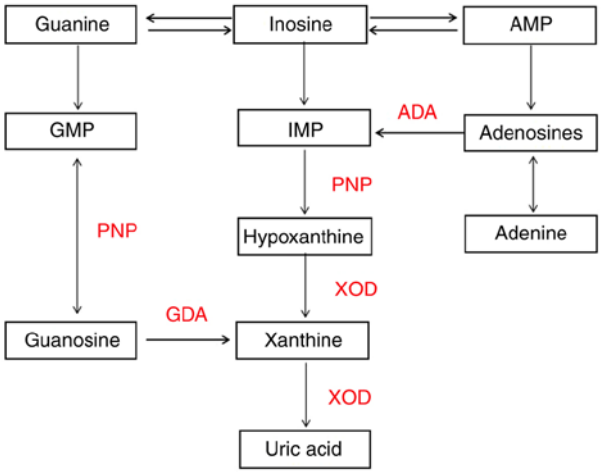

Figure 1. Poultry purine metabolism pathway. Under the action of nucleotidase, purine nucleotides are dephosphorylated to produce the purine adenosine; adenine produces hypoxanthine under the action of adenosine deaminase and is then oxidized into xanthine, which is catalyzed by xanthine oxidase. Guanosine is directly hydrolyzed and generates guanine and then generates xanthine through deamination. Ultimately, xanthine produces uric acid catalyzed by XOxidase. ADA, Adenosine Deaminase; IMP, 5'-inosinate disodium; PNP, Purine Nucleoside Phosphorylase; GDA, Recombinant Guanine Deaminase; XOD, Xanthine Oxidase.

was established successfully. Wang *et al* (37) fed male Huainan sparrow chickens high-protein diet (50% soybean meal and 50% basal diet) and limited water to 100 ml. High levels of uric acid (>476.57 μmol/l) were observed. In addition, it has been reported that the average abundance of enterococci and anaplastic bacilli is positively correlated with serum uric acid concentration and that there is a dose-dependent association between the incidence of gout in goslings and levels of dietary protein, as determined by assessing degree of damage to the kidney and cecum microbiota (38).

As discovered by Lumeij *et al* (39) that eating meat can increase the levels of uric acid in the blood of birds, spontaneous HUA emerges in birds of prey after a meal. In another study, after feeding quail meat to peregrine falcons, plasma uric acid concentrations peaked at 1,881 μmol/l after 3-8 h and plasma uric acid and urea concentrations were considerably increased up to 15 h (40). As reported by Bollman and Schlotthauer (41) turkeys fed diets supplemented with horse meat also exhibit elevated blood uric acid levels, indicating that blood uric acid levels are influenced by the protein or urea of the diet.

Induction by uric acid and sodium urate administration. Since avian species lack uricase, high uric acid levels can be induced by directly administering uric acid monomers *in vivo*. According to Li *et al* (42), broilers were gavaged with saline or ethambutol hydrochloride (200 mg/kg) and adenine (AD, 250 mg/kg), or yeast powder (YEP, 10 g/kg) and AD (100 mg/kg) to map a stable model of broiler HUA. The model exhibited a rise in blood uric acid levels in 49 days. HUA model animals did not lose weight or suffer renal impairment, making them safer and more appropriate for short-term HUA observation. Gout was caused by a buildup of urate in the joints, which resulted in inflammation and impaired joint function. A model of gout was created by injecting sodium urate (0.2 ml; 40 mg/ml) into the left ankle joint of chickens; hens in this model had edematous and stiff ankle joints; pain, indicated by crouching, standing on one foot and lameness, appeared 1-3 h after injection and disappeared after 4 h (43). Uric acid-induced models of HUA and gout in poultry are summarized in Table I.

Uric acid excretion disorder

Calcium-rich diet. The primary byproduct of avian protein metabolism is uric acid, which increases serum levels when uric acid excretion is inhibited. High-calcium diets have also been proven to impair renal function. Increased calcium intake is linked to renal impairment and development of gout among birds (44). According to previous studies, high-protein diets develop the model fastest, the replication model of high calcium and high protein diet had the highest success rate (36,45). Guo *et al* (46) fed chickens meals with up to 3.78% calcium, which caused kidney damage and markedly increased serum uric acid levels on day 17 of the trial. In addition, a high-protein diet (consisting of 36.59% crude protein) increased the serum uric acid level of 1-day-old male Sanhua geese, according to Song *et al* (47). The level of serum uric acid in all groups was higher than that in healthy individuals at 15 days of age, according to Xi *et al* (48); in chicks fed high-protein (22% protein and 1% calcium) and -calcium diets (16% protein and 3% calcium), kidney injury caused by a high-calcium diet was more serious than that caused by a high-protein diet. Zheng *et al* (49) fed 40-day-old quails with yeast (15 g/kg), and the levels of UA, XOD, CR and BUN increased on the 14th day; quails in the HUA model group exhibited reduced activity, dull coat color, reduced appetite, and depression.

Induction via adenine. Adenine administration can disrupt regular purine metabolism, leading to increased uric acid production. It also changes adenine to dihydroxyadenine in the body by the action of xanthine oxidase, deposition of which in the renal tubules causes kidney damage and decreases uric acid excretion (50). By injecting adenine into basic feed, Li *et al* (51) produced a model of HUA in quail. In a study by Ding *et al* (52), intraperitoneal UA injection was used to increase the level of SUA. In this study, the diet of chickens was supplemented with fishmeal to increase the dietary protein level, but it did not increase the the level of SUA in chickens. HUA and gout models induced by inhibition of uric acid secretion are summarized in Table II.

Multi-pathway induction

Protein- and calcium-rich diet. Composite induction instead of single modeling techniques results in faster development of HUA and rapid increase in blood uric acid levels (50). By incorporating yeast and fish meal into regular diets, Zhao *et al* (53) created a model of chicken HUA; high-protein (30.0% protein and 1.0% calcium) and high-protein and -calcium (30 protein and 3% calcium) groups displayed anorexia, weight loss, water-like feces and standing instability and autopsy revealed urate deposition on the surface of heart, liver, spleen and mesentery organ surfaces, thickening of the ureter, enlargement of the kidney and hallmark piebald nephropathy. It was confirmed that a diet high in protein and calcium results in an increase in blood uric acid levels. Huanga (54) discovered that diets high in calcium and protein cause typical visceral gout in chickens; diets high in calcium

Table I. Summary of uric acid-induced poultry hyperuricemia and gout models.

Model animal	Modeling method	Time of peak uric acid levels, days	Experiment duration, days	Performance	(Refs.)
Korea Coturnix-2 male quail	High-purine feed (15 g/kg per quail per day)	14	21	Increased serum UA levels at 14 and 21 days; increased XOD, ADA, G6PD, G6P and NADPH content; decreased SOD activity, increased activity of GSH-PX, GSH-GR, and content of MDA, GSH	(27)
4-week-old male quail	High-purine diet (yeast and bone extraction powder and 10% fruit sugar; drinking water 15 ml per chicken	30	40	Increased XOD and UA; disrupted oxidation stimulus; NLRP3 inflammation activation; inflammatory response	(29)
Yellow feather female quail	Yeast powder hybrid feed (yeast powder: feed, 1:4)	7	28	Increased UA levels	(30)
1-day-old geese	High-protein die (protein mass, 24%)	14	14	UA increased; liver and kidney damage; urate deposition	(33)
1-day-old geese	High-protein diet (protein mass, 23%)	7	14	Increased levels of AlT, AST transport, LDH, TP, UA and GLB	(34)
24-week-old male white Henglai chicken	High-protein feed (34.88% crude protein content)	14	73	Bent and deformed foot join; synovial fluid, joint tissue fluid and liver produce sodium uric acid crystals; kidney damage	(35)
50-day-old male Roman egg chicken	High-protein feed (50% basic diet, 50% soybean meal), 100 ml water/chicken	28	42	Increased blood UA levels (>417 μmol/l) and XOD, ADA and GD activity	(36)
50-day-old male Huainan hemp chicken	High-protein diet (50% basic diet, 50% soybean meal), 100 ml water	28	42	High UA levels (>476.57 μmol/l); increased calcium content in serum	(37)
Male and female 20-week-old Silky chicken	Injection of sodium uric acid (0.2 ml, 40 mg/ml) in the ankle joint	-	7	Pain 1-3 h post-injection, indicated by sitting and lying, standing on one foot, and recovery after 4 h; ankle edema and rigidity	(43)

XOD, xanthine Oxidase; ADA, Adenosine Deaminase; G6PD, Glucose-6-Phosphate DehydrogenaseG6P, Glucose-6-phosphate; SOD, Superoxide Dismutase; GSH-PX, Glutathione Peroxidase; GSH-GR, Glutathione-glutathione Reductase; MDA, Malondialdehyde; GSH, Glutathione reduced; UA, Uric acid; AlT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, lactatedehydrogenase; TP, Total Protein; GLB, globularproteins; GD, Guanosine deaminase.

and high/normal in protein cause severe renal damage and diets high in protein and normal for calcium do not raise plasma uric acid and inorganic phosphorus concentrations but cause renal damage. After feeding 1-day-old Yangzhou white geese (male/female ratio, 1:1) high-protein and -calcium food (22% protein and 3% calcium), Xi *et al* (48) observed that, in 15-day-old goslings, serum uric acid, creatinine, urea nitrogen content, XOD activity and *Enterococcus* spp. abundance were increased, renal damage appeared and bacterial species were malformed, such as *Enterococcus* spp. and *Bacillus*. In addition, other dangerous bacterial flora disrupt the micro-ecological equilibrium and harm the kidneys. Fu *et al* (55) demonstrated that a high-calcium and -protein diet (24.03% protein and 3.04% calcium) interferes with chick intestinal flora via the intestine/liver/kidney axis, inducing HUA. The high-calcium and -protein diet decreased the relative abundance of *Lachnospiraceae, Butyricicoccus pullicaecorum, Ruminococcus torques, Ruminococcus gnavus,* and Dorea and increased the relative abundance of *Collinsella* and *Desulfovibrionales*.

Protein- and calcium-rich diet and water restriction. Severe dehydration or inadequate water intake is a key cause of visceral urate deposition in poultry (56). The solubility of urate increases with the amount of water taken. Water is key

Table II. Summary of poultry hyperuricemia and gout models induced by inhibiting uric acid excretion.

Model animal	Modeling method	Time to peak uric acid, days	Experiment duration, days	Performance	(Refs.)
35-day-old Isa egg hens	High calcium diet (calcium content, 3.78%)	17	17	Weight loss, water-like feces, dehydration and death. Decreased serum inorganic phosphorus levels; increased serum calcium, UA, creatinine and urea nitrogen, levels; visible kidney damage	(46)
1-day-old Yangzhou goose goslings (male:female, 1:1)	High-protein diet (22% protein, 1% calcium), high-calciumdiet (16% protein, 3% calcium)	15	21	Kidney damage; increased serum UA and levels of harmful flora such as *Enterococcus* and Proteus	(48)
4-week-old French male quails	4 g/kg/day adenine in basic feed	28	28	Increased UA kidney damage	(51)

XOD, Xanthine Oxidase.

for physiological and biochemical processes in the animal body. Notably, the body temperature of poultry is 2-3 higher than that of human. Urate is soluble in poultry and can be excreted easily (31).

Chu *et al* (57) revealed that a diet high in purines and calcium (basal feed:yeast extract powder:cow bone meal, 5:2:3) integrated with a 150 ml/day water restriction increases blood uric acid levels and causes urate deposition in the kidney, which results in notable pathological alterations. The etiology and pathology of this model resemble those of gout. Kuang *et al* (31) discovered that a chicken model of HUA could be established through high-calcium and protein diet with water restriction; after 3 weeks of persistent HUA, the circumference of the ankle and tarsus increased significantly; additionally, persistent HUA caused gout, although this was not consistently associated with uric acid levels. Wang *et al* (37) used high-protein and -calcium diet integrated with water restriction to replicate HUA in chickens; high-protein diet increased uric acid production and could also cause renal damage, accelerating the buildup of uric acid and resulting in the typical characteristics of gout. Yan *et al* (58) reported gout symptoms in experimental chickens on day 14. Notably, elevated blood uric acid levels, loss of vitality, feather shedding, a preference for lying down, loss of appetite, kidney damage occurred in response to high-protein and -calcium diets. Wu *et al* (59) discovered that in the HUA group, in which quail were fed with a commercial formulation with added 20% yeast extract powder (high-purine diet), UA was increased and the quails exhibited kidney damage. Qi *et al* (60) developed a model of gout in chickens by mimicking the progress of HUA in humans; high-protein diet and controlling the intake of 100ml water per day, the excretion of uric acid was reduced while the intake of exogenous purine was increased, resulting in an increase in serum uric acid level, eventually leading to gout. Liu (36) fed 50-day-old male Roman chicken high-protein and -calcium diet (35% basal diet, 15% stone meal and 50% soybean meal) alongside 100 ml water limit and observed that the blood uric acid levels increased on day 42, the levels of blood uric acid reached 681.68±508.76 μmol/l, which was significantly higher than that in normal group. Multi-pathway induction models of poultry HUA and gout are summarized in Table III.

Other induction techniques

Fat-rich diet. Epidemiological and clinical studies have shown a pathological link between abdominal obesity, hyperlipidemia and HUA (61,62). Purine-rich foods may contribute to development of HUA, hypertriglyceridemia and abdominal obesity (63). Lin *et al* (64) fed Difak quails high-fat diet (85% regular diet, 14% cooked lard and 1% cholesterol) and suggested that a high-fat diet may lead to increased adenosine deaminase and xanthine oxidase activity, activate purine metabolism and significantly increase serum uric acid levels. High-fat diet may induce changes in adenosine deaminase and xanthine oxidase activity and increase uric acid production. Simultaneously, lipoprotein lipase, hepatic lipase and total esterase activity increased and lipid metabolism was abnormal.

Induction via injectable drugs and high-fat diet. A quail model of HUA was created by Ma *et al* (65) via high-fat diet combined with adenine (50 mg) gavage for 7 days. Following modeling, serum uric acid, creatinine and urea nitrogen levels increased, joints were enlarged, and kidneys were damaged. It is also associated with dyslipidemia, with an increase in triglyceride, low-density lipoprotein and xanthine oxidase, and a decrease in serum total cholesterol, lipoprotein esterase, adenosine deaminase and high-density lipoprotein. Zhang *et al* (66) reported that blood uric acid levels quickly increase and remain high for 4 weeks when the quails are fed high-fat and -hypoxanthine food (8% soybean meal, 50% corn meal, 16% flour, 10% cooked lard, 1% cholesterol, 5% whole egg powder, 9% sugar and 1% hypoxanthine; 419 kcal/100 g)

and subcutaneously administered potassium oxazepate (200 mg/kg). After 8 weeks, the high-fat diet only could not sustain elevated uric acid levels.

High-calcium and low-phosphorus diet. According to Chen and Fan (67), gout in chickens can be caused by high-calcium and low-phosphorus feeds, as well as high-calcium and normal-phosphorus feeds. Visceral urate deposition and urolithiasis are observed, with high calcium serving a key role and low phosphorus promoting occurrence of gout. The kidneys were pale in color and patterned, with varying degrees of enlargement or atrophy; the ureter was thickened and contained white urate crystals. After 50 days, 16 chickens died of gout (10 in the high-calcium and low-phosphorus group; six in the high-calcium and normal-phosphorus group).

Induced by toxins. Viruses and toxins cause of avian gout (68). Renal excretory dysfunction is associated with pathophysiology of gout produced by ovine toxin poisoning, according to Pegram and Wyatt (69). The virus causing chicken infectious bronchitis can multiply in renal epithelial cells, impairing renal function and triggering visceral gout (70). The goose-derived astrovirus (GoAstV) has been suggested to be the cause of renal disease and visceral gout (71,72), as discovered by Yin *et al* (73) through oral and subcutaneous injection of GoAstV and observation of dynamic distribution of the virus in chicks. The virus could replicate in tissues and cause pathological damage, particularly in the kidney, liver, heart and spleen, and typical visceral gout (74). Ali *et al* (75) added 2.5 and 5.0% sodium bicarbonate to drinking water, causing gout in 72-day-old broiler chickens. Biochemical analyses in week 3 revealed significant elevation of blood (hemoglobin, stacked cell volume, total erythrocyte and leukocyte count and heterophilic granulocytes) and biochemical parameters (aspartate and alanine transferase, uric acid, urea nitrogen, creatinine, total protein and albumin levels) in the sodium bicarbonate group, along with renal damage. In addition to hepatotoxicity and nephrotoxicity, acetyl chloride phenolic acids induce visceral gout in laying hens (76). A previous study also revealed that diclofenac sodium results in uric acid crystal deposition, necrosis of hepatocytes and myocytes, leukocyte infiltration of the liver and heart parenchyma and visceral gout in male broiler chickens (77). Using diclofenac sodium, Jiao (78) developed a model of chicken gout with visceral-type gout lesions. Methods of inducing avian HUA and gout are summarized in Table IV.

4. Metrics from post-model induction assays

To assess whether animal models of HUA have been established, it is important to detect related indices. Animal models of HUA are generated by various methods but there is no unified method of evaluation. Of 281 HUA models, 98.22% examined biochemical indicators, 48.75% assessed pathological indicators and 18.15% investigated epigenetic indicators (79).

General observation indicators. Body mass, joint swelling, mental state, changes in activity, food and water intake, diarrhea, pain and other bodily changes have been observed in animal models since they are the common indicators of HUA and gout (29,54,60,80). However, because researchers may introduce subjective elements (such as human error in observing and recording indicators), these alone cannot be used to evaluate models but must be used in conjunction with other methods of evaluation (79).

Biochemical indices. Biochemical markers serve as key indicators for tracking alterations in tissue and organ function since they demonstrate the degree of the pathological change at the molecular level. The most common method to assess the success of modeling is dynamic measurement of blood uric acid levels (31,57,59,81). Development of gout due to high blood uric acid levels is associated with inflammation and oxidative stress damage (82). The excretion of uric acid could be indicated by the amount of uric acid in the feces and urine of birds, owing to their unique physiology, including the ureter, reproductive ducts and digestive tract converging at the end of the cloaca (59). The primary clinical biochemical markers of HUA include alterations in the activity of XOD, adenosine deaminase and guanosine deaminase, which impact uric acid metabolism. Aspartate and alanine aminotransferase are markers of liver function and urea nitrogen and creatinine levels indicate renal impairment associated with HUA (82). Both the degree of modeling and therapeutic and adverse effects of medication can be assessed through kidney and liver function (83). Blood glucose, blood lipids, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol are indicators that can be used to observe HUA combined with metabolic syndrome. They are also commonly tested clinical indicators in patients with gout (82). Oxidative stress-induced variations in the capacity of the body to scavenge free radicals and repair damage can be inferred from changes in the activity of glutathione peroxidase and reductase, reduced glutathione, malondialdehyde and peroxide dismutase (84). The increase in lactic acid affect the excretion of uric acid (85). Additionally, the pathophysiology of HUA is connected to inflammatory factors, uric acid transporter protein levels, pathways and changes in gene expression. Monitoring these indicators may contribute to research on the mechanism of decreasing uric acid and serve as targets for research on drug interventions.

Signs of pathology. X-ray examination is a common examination of gout in humans. It can show changes in the bones and joints of gout and the presence or absence of urate deposits. Ma *et al* (65) examined the swollen toes of HUA quails by X-ray and histomorphology. X-ray results show decreased toe bone density, osteolytic articular surface destruction and soft tissue changes of the toe, which can be combined with biochemical indexes as a method to establish the detection model. Hong *et al* (35) used X-rays to examine joints and phalanges of chickens with high-protein diet-induced HUA and discovered that the structure of joint sections was unclear, similar to images of joints of patients with mild gout, while urate crystals in synovial fluid of chicken joints were detected by optical microscopy, which is also used as a test for human gout. Furthermore, the damage induced by modeling was primarily assessed by examining morphological changes, inflammatory cell infiltration, urate deposition and organelle changes in the heart, liver, kidney and joints (85). Furthermore, pathological section directly reflects the extent of target organ damage. In experimental investigations, the modeling is

Table III. Summary of hyperuricemia and gout models multi-pathway induction.

Model animal	Modeling method	Time to increased uric acid, days	Experiment duration, days	Performance	(Refs.)
1-day-old male Hl-line brown chicken	High-protein and -calcium feed (protein, 30%; calcium, 3.0%)	8	40	Increased levels of UA and activity of XOD; notable symptoms of gout, such as urate deposition on the surface of viscera, enlargement of the ureter and kidney; kidney damage	(53)
35-day-old chicken	High-calcium and -protein diet (245 g/kg protein; 36.8 g/kg calcium)	30	30	Increased levels of plasma uric acid, calcium and sodium; kidney injury-induced visceral gout; increased urine volume and 24 h urinary acid, calcium, magnesium, inorganic phosphorus and potassium excretion; decreased 24 h urinary sodium excretion	(54)
1-day-old Yangzhou White Goose (male:female, 1:1)	High-protein and -calcium diet (22% protein, 3% calcium)	15	21	Increased levels of UA, CR and Bun and activity of XOD; kidney damage; increased abundance of harmful flora such as *Enterococcus* and *Proteus*	(48)
1-day-old male Magang geese	High-calcium and -protein diet (24.03% protein, 3.04% calcium)	28	28	HCP diet interfered with intestinal flora via intestinal/hepatic/renal axis, which induced systemic inflammation	(55)
40-day-old male Dafak quails	High-purine and -calcium diet (basic feed:yeast powder: bovine bone powder, 5:2:3) and water limit 150 ml/day	10	40	Visceral gout in quails was induced by increase of UA, CR and BUN levels, ADA activity and renal urate deposition in renal tubules	(57)
21-day-old male Lingnan chickens	High-protein and -calcium feed (50% corn powder, 30% soybean meal, 6% imported fish powder, 7% calcium powder, 7% calcium phosphate powder), water limit 50 ml/day	7	105	Gout arthritis diagnosed after 3 weeks of poor general condition, elevated serum uric acid, rapid weight gain and increased tarsus ankle circumference in chickens with uric acid >476.57 μmol/l	(31)
50-day-old male in Huainan hemp chickens	High-protein and -calcium diet (35% basic diet, 15% calcium powder, 50% soybean meal) + water limit 100 ml/day	17	42	Poor general condition; increased blood uric acid levels; loose feathers, decreased eating, water-like stool, joint swelling, pain	(37)
30-day-old male Xiang Yellow chickens	High-protein diet (50% protein, 9.17% calcium), limited drinking water (100 ml/day)	7	21	Poor general condition, ankle swelling, elevated serum uric acid levels, synovial inflammation of the ankle joint	(60)

Table III. Continued.

Model animal	Modeling method	Time to increased uric acid, days	Experiment duration, days	Performance	(Refs.)
50-day-old, male Roman egg chickens	High-calcium and -protein feed (35% basal diet, 15% calcium powder, 50% soybean meal) and limited water (100 ml)	28	42	UA increased slightly on the 42nd day, the level of serum uric acid reached 681.68±508.76 μmol/l, which was much higher than normal group; whole blood viscosity, hematocrit, ESR and erythrocyte aggregation increased, erythrocyte deformability decreased	(36)

UA, uric acid; XOD, Xanthine Oxidase; CR, creatinine; BUN, blood urea nitrogen; ADA, Adenosine Deaminase; HUA, Hyperuricemia; ESR, Erythrocyte Sedimentation Rate.

mostly assessed through biochemical and pathological indicators (29,35,54). Chu *et al* (57) fed the quails with a high purine diet and induced quail HUA. Biochemical tests showed that the levels of creatinine, urea nitrogen and adenosine deaminase activity were increased. The renal histopathology was observed, it was found that black urate crystals were deposited in the renal tubules in the model group, and both proximal and distal tubules were distributed. Renal tubular obstruction can aggravate uric acid excretion disorders, and eventually induce the occurrence of gout. In order to evaluate the renal injury of this model more comprehensively. Meng *et al* (86) combined conventional renal function indexes: increased levels of creatinine and urea nitrogen, and early markers of kidney injury: elevated levels of kidney injury molecule 1(KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL); pathological indices: congestion of the kidney, dilation of the renal tubules, epithelial cell shedding; The accumulation of urate in the kidney was observed by inflammatory cell infiltration and fibrosis, and by renal examination with silver staining.

Intestinal flora indicators. Numerous studies have shown that development of HUA and gout is directly associated with alteration of the gut microbiota and decreased gut barrier function (87,88). The human body obtains a notable amounts of uric acid from the intestinal microflora. The intestine excretes approximately one-third of uric acid and bacteria such as *Lactobacillus*, *Bacteroides* and *Bifidobacterium* are key to this process. Changes in the relevant intestinal microbiological indices may provide new targets and approaches for the treatment of HUA (89,90). Guo *et al* (91) reported a decrease in *Lactobacillus* and *Pseudomonas* among the intestinal flora of patients with gout and diagnosis via 17 gout-associated bacteria reached 88.9% accuracy. Compared with serum uric acid as a reference index, this method is more sensitive in the diagnosis of gout As well as structural alterations in intestinal flora, Huang *et al* (92) found that a quail model of high-purine diet-induced HUA was associated with ~3 times the level of lipopolysaccharide (LPS) in peripheral blood compared with that in quail fed normal diet. LPS is considered to be responsible for metabolic disorders and elevated XOD activity, which may increase uric acid levels (93,94). According to Xi *et al* (95), geese with gout have considerably higher serum levels of LPS and increased loss of intestinal barrier as a result of gut dysbiosis causes the translocation of gut-derived LPS, may put chicks at risk for developing gout.

Traditional Chinese Medicine (TCM) indicators. TCM emphasizes the relationship between 'disease' and 'evidence'. From this perspective, gout belongs to the categories of 'paralysis' 'dampness, heat and steam embedded in the meridians' and 'paralyzing disease' (96,97). Lin *et al* (98) used a high-purine diet to induce HUA in quail and measured the indices of questioning, smelling and looking, observed changes in the shape of urine and feces, along with changes in the tongue. Certain pathological changes such as stool is loose and greasy were similar to the symptoms of 'spleen deficiency, phlegm and dampness' triggered by poor diet.

5. Issues in the modeling of gout and HUA in poultry

Methodology for model selection. The ideal HUA and gout model should show stability, repeatability, applicability and affordability. The model should mimic the progressive pathological process of gout and should be able to be replicated in a short time. Moreover, the state of HUA should be maintained, whereas tissue damage unrelated to HUA and gout should be decreased (99).

Current models of HUA and gout focus on rodents, which have urate oxidase that break down uric acid into more water-soluble allantoin (90,100-102). Mice are unlikely to undergo the persistent, progressive pathological changes that lead to gout when high uric acid levels arise in the body. Mouse models of HUA are primarily divided into environment-(drug- or diet-induced) and gene-induced (103). The use of urate Oxidase (UOX) inhibitors, such as potassium oxazate, is a common method of modeling since they block the further metabolism

Table IV. Summary of other methods to induce avian hyperuricemia and gout models.

Model animal	Modeling method	Time to increased uric acid, days	Experiment duration, days	Performance	(Refs.)
Male Difak quails	High-fat diet (85% common diet, 14% cooked lard, 1% cholesterol)	7	14	Increased ADA and XOD activity, purine metabolism and UA levels and activities of LPL, HL; abnormal lipid metabolism	(64)
30-day-old male Diphac quails	High-fat diet (54% corn, 2% bran, 7% fish meal, 30% soybean meal) and adenine suspension (50 mg/kg) by gavage	11	22	Increased UA, CRE, BUN, TG and LDL levels and XOD activity; decreased CHO, LPL, ADA and HDL levels; joint swelling; decreased toe bone density; synovial hyperplasia; uric acid deposition in kidney; lipid metabolism disorder	(65)
5-week-old Chinese white-feathered quail (male:female, 1:1)	High-fat and -hypoxanthine diet (8% soybean meal, 50% corn meal, 16% flour, 10% cooked lard, 1% cholesterol, 5% whole egg meal, 9% sugar, 1% hypoxanthine) combined with subcutaneous injection of potassium oxazate (200 mg/kg)	7	63	Increased levels of UA, TG, insulin, AlT, AST, BUN and CRE and peak blood glucose; liver, kidney and aorta damaged	(66)
21-day-old Hessex and Roth hybrid chicken	High-calcium and low-phosphorus diet (3.1% calcium and 0.19% absorbable phosphorus). High calcium and phosphorus (containing 3.1% calcium and 0.39% absorbable phosphorus)	21	91	Uric acid salt with visceral deposition and urolithiasis; kidney pale and patterned; thick ureter; white uric acid salt crystals; death due to gout	(67)
72-day-old broiler chickens	2.5 and 5.0% sodium bicarbonate in drinking water	7	21	Significantly increased hemoglobin, AST, ALT, UA, BUN, CRE, TP and ALB levels, packed cell volume, total red and white blood cells and heterophils; renal damage	(75)
357-day-old White Leghorn chickens (The sex of the animal is not stated)	Sodium diclofenac (300, 500 and 700 mg/kg) in basal feed	1	7	Poor general condition; visceral uric acid deposition, including the kidney, liver, heart, pericardium, mesentery	(78)

ADA, adenosine deaminase; XOD, Xanthine oxidase; UA, uric acid; LPL, Lipoprotein lipase; HL, Hepatic Lipas; CRE, creatinine; BUN, blood urea nitrogen; TG, Triglyceride; LDL, ow density lipoprotein; CHO, Total cholesterol; LPL, lipoprotein lipase; HDL, High-density lipoprotein; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TP, Total Protein; ALB, albumin.

of uric acid (104). However, in rodents, uricase exists, which breaks down uric acid into allantoin and excretes it. Uric acid rarely accumulates in the body; therefore it is difficult to replicate a sustained model of HUA in experiments (105,106).

Concentration of uric acid is much lower in mice than that in human. In addition, drugs can cause renal functional damage unrelated to gout (30,107,108). Uricase-deficient mice developed by gene knockout, abrogated a major difference in

the inability of uric acid to accumulate *in vivo* due to the presence of uricase in mice, more in line with the human uric acid metabolic pathway; however, complex techniques and high animal mortality suggest that the model is less economically viable for basic research (100,109).

The pathway of purine nucleotide metabolism in birds is similar to that in humans. Purine nucleotides are metabolized, and uric acid is excreted as an end product. When purine content in the diet is too high, it can lead to an increase in uric acid production in the body, which can accurately reflect the metabolic levels of purine nucleotides (66). Notably, similar to in humans, birds lack uricase and uric acid is the end product of their purine metabolism. When birds are selected to generate a model of HUA, there is no need to use an inhibitor of uricase, which can decrease the visceral damage caused by inducers (such as a high purine diet). Studies have shown that stable yet persistent serum uric acid levels and mild renal lesions in avian models of HUA are required to observe the effects of drug therapy for a long time (42,85). Compared with mouse models, avian models of gout have a longer survival time and are considered more suitable for long-term observation of drug effects (30,52). Furthermore, gout in poultry is affected by genetic factors, dietary changes and environmental factors, similar to the etiology of gout in humans, and the joint symptoms of gout in poultry are akin to those in humans (18). Therefore, due to physiological and pathological characteristics, birds may be a suitable model for exploring human HUA and gout since they simulate the whole pathological process from HUA to gout onset in the human body (9,57,110).

Animal selection for poultry models. In terms of HUA models, factors such as incidence of gout in poultry, feeding management and experimental feasibility should be considered. Medium and small-sized poultry, such as chickens, pigeons and quails, are easy be raise and manage in large quantities. The large size of chickens, ducks and geese is convenient for experimental observation and observation of experimental indexes. Poultry have a short growth cycle, hatching can be controlled and they are low cost. Common species of experimental poultry include chickens, ducks, quails, pigeons and geese; however, only specific pathogen-free (SPF) chickens and ducks have been developed. Other species of birds have not yet been standardized, making it difficult to use them in laboratory studies. Notably, the avian model of HUA requires further exploration.

To the best of our knowledge, there is no uniform conclusion regarding the effect of sex on modeling. The sex of most animal models of HUA has been male, with fewer studies using female HUA models (79,110,111).

6. Conclusion

In conclusion, the most common approach to induce avian HUA and gout is diet. The majority of researchers induce HUA by increasing uric acid production and inhibiting uric acid excretion, because preparing the model is easy, affordable and it produces a stable model that is convenient to operate and allows for the dynamic observation of blood biochemical indices. The progression of human gout and its etiology is similar to that in avian models. Nevertheless, the applicability of these models is restricted by the strains, species and feeding circumstances of experimental animals. Evaluation indexes include apparent index, biochemical index, pathological index and intestinal microflora index; however, there is no consistent standard for creation and assessment of animal models of HUA in gout research.

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Availability of data and materials

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Authors' contributions

QH and WJ conceived the study and revised the manuscript. WL and WB wrote manuscript. LJ and YX reviewed the manuscript. Data authentication is not applicable. All authors read the final version of the manuscript.

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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