MEDS Clinical Medicine (2025)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2025.060219
ISSN 2616-1907 Vol. 6 Num. 2

Advances in Uric Acid Metabolism Mechanisms under High-altitude Environments

Yu He[1,a], Hong Liu[2,b,*], Run Ma[1,c], Weiji Yue[1,d]

[1]Clinical Medical College, Dali University, Dali, Yunnan, China
[2]The First Affiliated Hospital of Dali University, Dali, Yunnan, China
[a]3274391174@qq.com, [b]daliliuhong@163.com, [c]marun9851@163.com, [d]2473326859@qq.com
**Corresponding author*

Keywords: High-altitude environments; Hyperuricemia; Uric acid

Abstract: Hyperuricemia (HUA) is a metabolic disease caused by disorders in purine metabolism, and its occurrence and progression are influenced by multiple factors including genetic and environmental factors. This article aims to review the impact of high-altitude environments on uric acid levels and the mechanisms of uric acid metabolism under such conditions.

1. High-altitude Environments

High-altitude regions are defined as areas above 2,400 meters above sea level[1]. China's vast territory encompasses diverse terrains and landforms, with four major plateaus covering a total area of 4.8379 million km ²Currently, approximately 140 million people reside in China's high-altitude regions, including not only indigenous populations but also numerous migrants engaged in education, employment, and tourism. However, a proportion of these migrants fail to acclimatize or adapt to the hypoxic environment, developing acute and chronic mountain sickness that threatens human health and impacts the implementation of the Healthy China Strategy.

The prevalence of hyperuricemia (HUA) among Chinese residents has shown a year-on-year increase. Studies reveal a higher incidence of HUA in high-altitude regions compared to plains, with current research suggesting that the plateau environment alters renal function. Notably, in 2011, scholars proposed defining the combination of polycythemia, systemic hypertension, hyperuricemia, and microalbuminuria observed in high-altitude populations as "high-altitude nephropathy syndrome"[1,2]. This review aims to systematically examine the impacts of high-altitude

environments on serum uric acid (SUA) levels and elucidate the mechanisms underlying uric acid metabolism under hypoxic conditions.

2. Effects of High Altitude on Uric Acid Levels

2.1 Regional Variations in Hyperuricemia Prevalence

The prevalence of HUA among Chinese adults aged 18 years or older has shown sustained growth, reaching 14% by 2019[3]. Significant geographical disparities are observed, with higher rates in urban areas compared to rural regions, coastal zones compared to inland areas, and high-altitude plateaus compared to lowland plains. A meta-analysis across six Chinese regions revealed the following HUA prevalence: Northeast China (24.6%), Central-South China (20.7%), Eastern China (17.3%), Northern China (17.4%), Southwest China (15.8%), and Northwest China (15.5%)[4]. High-altitude regions show higher HUA prevalence than lowland plains, as seen in Xizang (16.86%) [5] and Inner Mongolia (15.6%)[6]. Ethnic disparities in HUA prevalence are evident in high-altitude areas, as exemplified by the disparity between the Mongolian ethnic group in Inner Mongolia (19.74%) and the Zangzu ethnic group in Lhasa (10.9%) [7,8].

2.2 Effects of Altitude Variation on Uric Acid Levels

Research has found that miners working in high-altitude mines (3,990-4,400 meters) exhibit higher SUA levels compared to those in low-altitude mines (100-120 meters), while no significant difference in SUA levels has been observed between surface and underground miners at the same altitude[9]. The prevalence of HUA among Han Chinese populations in the plains is lower than that of Han Chinese populations who migrated to high-altitude regions (4,520 meters)[10].HUA prevalence in high-altitude regions consistently exceeds that in both low-altitude regions and the national average. Examples include 41.31% in the Naxi ethnic group in Yunnan's high-altitude regions[11],48.8% among workers in the Northwest Sichuan Gas Field (2,552 meters), and 37.2% in the Zangzu ethnic group in Sichuan's Garzê region (above 3,500 meters)[12]. HUA interacts with metabolic syndrome, and meta-analyses suggest an inverse correlation between altitude and metabolic syndrome prevalence, potentially linked to genetic and adaptive responses affecting glucose metabolism under hypoxic conditions at high altitudes[13]. This partially explains altitude-related influences on uric acid metabolism. Additionally, research by Tang Z.W. et al. found that HUA prevalence peaked after one year of high-altitude exposure, but showed no significant changes in SUA levels or HUA incidence rates with prolonged exposure[10] .

3. Impact of High-Altitude Environment on Uric Acid Levels and Related Mechanisms

Long-term residence in high-altitude environments characterized by hypobaric hypoxia, cold

temperatures, and intense ultraviolet radiation exerts both detrimental and beneficial effects on the human body. To acclimate to this environment, long-term residents develop various physiological adaptations to counteract hypoxia. The impact of the high-altitude environment on uric acid metabolism results from multiple interacting factors, primarily involving uric acid production and excretion. Based on existing literature, the mechanisms can be summarized as follows:

3.1 Role of Red Blood Cells in Uric Acid Metabolism

Numerous studies have shown that SUA levels are influenced by red blood cells (RBCs). The prevalence of HUA and the SUA levels are significantly higher in polycythemia patients compared to healthy populations[14].

Among the Zangzu ethnic group in China's high-altitude areas (above 3,500 meters), a significant correlation has been observed between SUA levels and red blood cell parameters in males[15]. In Peruvian males with polycythemia (4,300 meters), urate levels were found to correlate with hematocrit [16]. A cohort study in Shigatse, Xizang, demonstrated that polycythemia patients treated with erythrocytapheresis exhibited reduced hemoglobin levels, improved renal function (eGFR, SUA, proteinuria, etc.), and demonstrated a correlation between decreased SUA levels and improved eGFR [17].However, other studies indicate that the Zangzu ethnic group has lower hemoglobin and erythropoietin (EPO) concentrations compared to Andean highlanders at similar altitudes, which may be linked to genetic variations, relatively higher blood flow, and enhanced nitric oxide bioavailability in vascular walls.

Under high-altitude hypoxic conditions, the body upregulates erythropoiesis (red blood cell production) to meet oxygen demands for physiological and metabolic activities. Hypoxia in these environments enhances the expression of hypoxia-inducible factors (HIF-1α and HIF-2α)[17], which promote the transcription of the EPO gene, leading to increased EPO synthesis and subsequent elevation in red blood cell production. Potential mechanisms linking polycythemia to elevated uric acid include: (1) Increased synthesis of RBCs elevates hemoglobin levels, leading to a rise in hematocrit and blood viscosity [16,17]. This reduces renal plasma flow, triggering compensatory mechanisms that increase renal blood flow and glomerular filtration rate (GFR). These hemodynamic adaptations may induce structural and functional alterations in the kidneys, resulting in renal impairment that disrupts uric acid excretion and ultimately elevates serum uric acid levels. (2) Enhanced hemoglobin synthesis and degradation accelerate purine catabolism, thereby increasing uric acid production. These combined effects of elevated urate synthesis and impaired renal excretion drive hyperuricemia in high-altitude populations[16].

3.2 Oxidative Stress and Inflammatory Response

3.2.1 Xanthine Oxidase System

Hypoxia induces the breakdown of adenosine triphosphate (ATP) into adenosine monophosphate (AMP). AMP is subsequently metabolized to hypoxanthine, which is further catalyzed by the xanthine oxidase system—specifically via xanthine dehydrogenase (XDH) and xanthine oxidase (XO)—into xanthine, ultimately generating SUA and other metabolites. Research by Tang Z.W. et al. demonstrated that uric acid levels in high-altitude regions are positively correlated with the activity and concentration of XO[10]. Hypoxia and ischemia-reperfusion injury enhance the transcription of xanthine oxidoreductase (XOR), thereby increasing the activity of both XDH and XO. Additionally, XDH can be converted to XO through the action of proteolytic enzymes, thereby accelerating the decomposition of hypoxanthine into xanthine and uric acid[16,18].On the other hand, under high-altitude hypoxic and low-pressure conditions, the xanthine oxidase system, mitochondrial electron transport chain, and NADPH oxidase system also generate reactive oxygen species (ROS), inducing oxidative stress responses[18-20]. When oxidative stress exceeds a certain threshold, it results in damage to cells, tissues, and organs, triggering ischemia-reperfusion injury. This, in turn, further disrupts the uric acid metabolism process.

3.2.2 TLR/MyD88/NF-κB Pathway

Intermittent exposure to high-altitude hypobaric hypoxic environments triggers inflammatory responses in the body, activating Toll-like receptors. This leads to downstream NF-κB activation and increased expression of inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, TNF-α, and MCP-1 [21,22], thereby promoting inflammatory cascades. Activated NF-κB also drives renal tubular epithelial-mesenchymal transition (EMT), exacerbating renal inflammation and interstitial fibrosis. Multiple studies have demonstrated that diosgenin alleviates inflammatory responses by inhibiting the TLR4/NF-κB signaling pathway, thereby protecting renal tubular epithelial cells. Concurrently, diosgenin upregulates EPHX expression, reduces levels of IL-1, TNF-α, and ROS, mitigates renal inflammation, enhances lipid metabolism, and promotes SUA excretion [23,24].These findings further confirm that the TLR/MyD88/NF-κB pathway influences uric acid metabolism.

3.2.3 Impact of Lactate on Uric Acid

Lactate, a glycolysis-derived metabolite, modulates uric acid metabolism through distinct mechanisms under hypoxic high-altitude conditions: (1) Competitive Inhibition by Lactate. Under hypobaric hypoxia at high altitudes, suppression of aerobic metabolism promotes anaerobic glycolysis. Glucose is sequentially converted to pyruvate through enzymatic reactions and then

reduced to lactate by lactate dehydrogenase (LDH).Although current evidence remains insufficient to conclusively support lactate production occurring exclusively under hypoxic conditions, recent studies indicate that sustained aerobic glycolysis contributes to lactate generation even during high-altitude exposure[25,26].Concurrently, the HIF-1α pathway—activated by hypoxia, ischemia, inflammation, and the Warburg effect—drives glycolytic gene expression and upregulates monocarboxylate transporter 4 (MCT4), synergistically enhancing lactate synthesis and efflux[25,27]. This lactate competitively inhibits renal tubular urate excretion, reducing the fractional excretion of uric acid and elevating SUA levels[1,28]. (2) Lactate-Induced ROS Generation and Lactylation Modifications. Lactate accumulation synergizes with mitochondrial respiration to induce ROS production[25]. Emerging studies reveal that lactate and lactylation modifications modulate the functionality of macrophages, T cells, and B cells[29,30]. These alterations dysregulate inflammatory responses by affecting the expression of cytokines[31]. Such immunometabolic perturbations exacerbate hypoxia-driven inflammation in high-altitude environments, amplifying tissue and organ damage, which ultimately contributes to elevated uric acid levels.

3.3 Impact of Renal Dysfunction on Uric Acid

Approximately two-thirds of uric acid produced in the human body is excreted via the kidneys, with renal structural and functional alterations directly affecting SUA excretion efficiency and capacity. As a metabolically active organ accounting for 10% of total body oxygen consumption, the kidneys exhibit particular sensitivity to hypoxic conditions. Prolonged exposure to high-altitude environments induces structural renal damage to some extent. Studies have shown that low-birth-weight infants at high altitudes exhibit reduced nephron numbers, while children residing in these regions demonstrate enlarged glomeruli compared to their sea-level counterparts[1].Previous studies have identified glomerular hypertrophy in hyperuricemic rats, which progresses to glomerulosclerosis over time. Hypoxia disrupts renal lipid metabolism. A study in the high-altitude Naxi ethnic group of Yunnan Province demonstrated a significant positive correlation between the TG/HDL-C ratio and HUA in middle-aged and elderly individuals[11]. Lipid accumulation triggers inflammatory responses, oxidative stress, and dysregulated autophagy, collectively contributing to renal injury. Additionally, lipid deposition exacerbates glomerulosclerosis and tubulointerstitial damage, impairing both structural and functional integrity of glomeruli and renal tubules, thereby disrupting SUA excretion[11].All SUA (100%) undergoes glomerular filtration. Through subsequent tubular reabsorption and secretion processes, only 6–10% of the filtered SUA is ultimately excreted by the kidneys. Urate transporters play a pivotal role in this regulatory mechanism. Notably, hypobaric hypoxia in high-altitude environments downregulates the expression of key renal urate-handling proteins, including URAT1, GLUT9, and OAT1, thereby disrupting both urate reabsorption and secretion pathways [21].

3.4 Impact of Gut Microbiota on Uric Acid

Approximately one-third of uric acid produced in the human body is excreted through the intestinal tract, which plays a critical compensatory role when renal excretion of uric acid is impaired. While most mammals degrade uric acid via the enzyme uricase, humans lack this enzyme. However, gut microbiota in humans can produce uric acid-degrading enzymes such as urate oxidase and allantoinase, performing a function analogous to uricase to metabolize uric acid. Prolonged residence in high-altitude regions induces adaptive changes in gut microbiota.

Significant differences have been observed in gut microbial communities between the high-altitude Han ethnic group and the high-altitude Zangzu ethnic group[32,33]. Research by Jia et al. demonstrated that as lowland Han individuals experience prolonged exposure to high-altitude environments, their gut microbiota progressively resembles that of the indigenous Zangzu population[34].

The gut microbiota modulates SUA production and excretion through multiple pathways, with mechanisms outlined as follows:(1) Under high-altitude hypoxic and low-temperature environments, the body requires additional energy to maintain body temperature and vital functions[32]. The catabolism of uric acid in the gut produces metabolites such as succinate, lactate, and short-chain fatty acids (SCFAs) during this process. These metabolites participate in energy metabolism, not only providing energy for intestinal epithelial cells but also promoting SUA excretion[35,36]. Additionally, they modulate the expression of uric acid transporters on intestinal epithelium, thereby further influencing systemic SUA levels and excretion efficiency. (2) Under hypobaric hypoxia at high altitudes, the gut microbiota undergoes redistribution and abundance adjustments. Studies indicate that to adapt to the hypoxic environment, intestinal microbial communities reconfigure their composition, with increased abundance of uric acid (UA)-degrading bacteria that reduce intestinal UA levels. The critical remodeling phase for this microbial rewiring may occur approximately one month after exposure[28]. In hyperuricemic mouse models, probiotic strains such as Lactobacillus rhamnosus and Lactobacillus reuteri have been shown to modulate gut microbial abundance, promoting the production of SCFAs by intestinal flora[36,37]. Gut commensal bacteria and their metabolites modulate SUA levels by suppressing the expression of XO.(3) Hypoxia activates inflammatory response-related pathways, leading to elevated levels of inflammatory factors that impair intestinal barrier function and induce gut microbiota dysbiosis. This microbial imbalance compromises intestinal permeability and increases lipopolysaccharide (LPS) levels. On one hand, LPS activates the TLR4/Myd88/NF-κB signaling pathway to exacerbate inflammatory responses. On the other hand, LPS enhances XO activity, thereby promoting uric acid production[35,36].

3.5 The Influence of Age and Gender on Uric Acid

Nephrons are non-renewable and progressively decrease starting from birth, showing a 10% reduction every 10 years after the age of 40. Human renal function gradually declines with age. Multiple studies indicate that the prevalence of HUA follows a U-shaped curve across age groups. Specifically, the prevalence of HUA in males decreases with age, whereas in females, it increases after the age of 40[14,38,39].This phenomenon may be associated with factors such as aging and metabolic disorders. Multiple studies have shown that in individuals aged ≤40 years, males exhibit higher SUA levels and a greater prevalence of HUA compared to females. However, postmenopausal women experience a significant increase in SUA levels, eventually reaching concentrations comparable to those in men. Although a potential association between sex hormones and HUA has been suggested, the exact relationship remains unclear. Based on a review of the literature, the observed sex-based differences in SUA levels may be attributed to the following mechanisms: (1) Activation of the estrogen-related receptor α (ERRα)-organic anion transporter 1 (OAT1) axis can enhance SUA excretion, alleviate renal tubulointerstitial fibrosis, and improve renal function [40]. (2) Current research suggests that estrogen acts through multiple pathways to lower SUA levels: suppressing XO activity to reduce urate production; upregulating intestinal expression of the urate transporter ABCG2 via the PI3K/Akt signaling pathway to enhance urate excretion, thereby decreasing SUA concentrations[41]. However, some studies suggest that in postmenopausal women undergoing sex hormone therapy, the decrease in SUA levels is associated with progesterone, but not with estrogen[42].(3)In diabetic patients, a positive correlation exists between dehydroepiandrosterone (DHEA) and SUA levels in males and postmenopausal females. This may be related to the mechanism by which DHEA activates mineralocorticoid receptors and inhibits glucocorticoid receptors, leading to water and sodium retention and reduced SUA excretion[43,44]. In addition to the aforementioned factors, alcohol consumption and a high-purine diet in males may also influence uric acid levels.

In summary, HUA development in plateau regions is multifactorial, involving altitude-related hypobaric hypoxia, ethnicity, sex, diet, genetics, and socioeconomic conditions. Further research is needed to elucidate these mechanisms and inform targeted interventions in high-altitude populations.

References

[1] Arestegui, A.H., Fuquay, R., Sirota, J., Swenson, E.R., Schoene, R.B., Jefferson, J.A., Chen, W., Yu, X.Q., Kelly, J.P., Johnson, R.J., and Escudero, E. (2011). High altitude renal syndrome (HARS). J Am Soc Nephrol 22, 1963-1968. 10.1681/asn.2010121316.

[2] Wang, S.Y., Liang, J., and Zhao, J.H. (2024). A Case of High-Altitude Renal Syndrome. High Alt Med Biol 25, 149-151. 10.1089/ham.2023.0077.

[3] Zhang, M., Zhu, X., Wu, J., Huang, Z., Zhao, Z., Zhang, X., Xue, Y., Wan, W., Li, C., Zhang, W., et al. (2021).

Prevalence of Hyperuricemia among Chinese Adults: Findings From Two Nationally Representative Cross-Sectional Surveys in 2015-16 and 2018-19. Front Immunol 12, 791983. 10.3389/fimmu.2021.791983.

[4] Huang, J., Ma, Z.F., Zhang, Y., Wan, Z., Li, Y., Zhou, H., Chu, A., and Lee, Y.Y. (2020). Geographical distribution of hyperuricemia in Chinese mainland: a comprehensive systematic review and meta-analysis. Glob Health Res Policy 5, 52. 10.1186/s41256-020-00178-9.

[5] Yuan, Z., Zou, Y., Liu, X., Wang, L., and Chen, C. (2023). Longitudinal study on blood and biochemical indexes of Tibetan and Han in high altitude area. Front Public Health 11, 1282051. 10.3389/fpubh.2023.1282051.

[6] Zhao, W. J., Liu, L. J., Li, X. H., Wang, P. L., Jia, P., and Wang, Y. F. (2022). Epidemiological characteristics and risk factors of hyperuricemia and gout among adults in Inner Mongolia. Journal of Applied Preventive Medicine, 28(05), 421-425, 431.

[7] Zhang, H., Ma, L. F., Zhang, Z. Y., Jiang, Y. Q., Zhao, Y. D., Yang, L. H., Liang, T., Dong, W. X., Liu, L. J., Zhao, F. C., and Kang, L. L. (2020). Distribution characteristics of hypertension, fatty liver disease, and hyperuricemia among adult Tibetan residents: A community-based survey in Lhasa. Journal of Environmental and Occupational Medicine, 37(12), 1182-1187.

[8] Dong, J. H., Pang, H. and Zhao, L. Y. (2022). Status and related factors of hyperuricemia among Mongolian adults in Inner Mongolia from 2018 to 2020. Journal of Health Research, 51(6), 940-946.

[9] Wang, Y., Wang, H., Chen, Y., Xu, N., Lee, W., and Lam, W.K. (2022). Pulmonary Capacity, Blood Composition and Metabolism among Coal Mine Workers in High- and Low-Altitude Aboveground and Underground Workplaces. Int J Environ Res Public Health 19. 10.3390/ijerph19148295.

[10] Tang, Z. W., Liu, F. Y., Xu, G., Jiang, C. H., Guan, L. B., Huang, Q. Y. and Gao Y. Q. (2016). Epidemiological characteristics and genetic susceptibility of hyperuricemia among Han Chinese young males migrating to a plateau (4520 m). Medical Journal of the Chinese People's Liberation Army, 41(10), 859-864.

[11] Han, D., Yao, Y., Wang, F., He, W., Sun, T., and Li, H. (2024). A study on the correlation between hyperuricemia and TG/HDL-c ratio in the Naxi ethnic group at high-altitude regions of Yunnan. Front Med (Lausanne) 11, 1416021. 10.3389/fmed.2024.1416021.

[12] Zhang, X., Meng, Q., Feng, J., Liao, H., Shi, R., Shi, D., Renqian, L., Langtai, Z., Diao, Y., and Chen, X. (2018). The prevalence of hyperuricemia and its correlates in Ganzi Tibetan Autonomous Prefecture, Sichuan Province, China. Lipids Health Dis 17, 235. 10.1186/s12944-018-0882-6.

[13] Zila-Velasque, J.P., Grados-Espinoza, P., Challapa-Mamani, M.R., Sánchez-Alcántara, F., Cedillo-Balcázar, J., Cs, A.D., Hernandez-Bustamante, E.A., Tejada-Flores, J., Piano Suárez, A., Pacheco-Mendoza, J., and Benites-Zapata, V.A. (2024). Prevalence of metabolic syndrome and its components according to altitude levels: a systematic review and meta-analysis. Sci Rep 14, 27581. 10.1038/s41598-024-77928-z.

[14] Gao, C., Chen, Z., Ma, J., Xie, J., Zhang, W., Ren, H., and Chen, X. (2021). Prevalence of and risk factors for high-altitude hyperuricaemia in Bai individuals: a cross-sectional study. J Int Med Res 49, 3000605211028140. 10.1177/03000605211028140.

[15] Cui, D., Huang, R., Yongzong, D., Lin, B., Huang, X., Ciren, Q., and Zhou, X. (2024). Gender-specific association between blood cell parameters and hyperuricemia in high-altitude areas. Front Public Health 12, 1336674. 10.3389/fpubh.2024.1336674.

[16] Jefferson, J.A., Escudero, E., Hurtado, M.E., Kelly, J.P., Swenson, E.R., Wener, M.H., Burnier, M., Maillard, M., Schreiner, G.F., Schoene, R.B., et al. (2002). Hyperuricemia, hypertension, and proteinuria associated with high-altitude polycythemia. Am J Kidney Dis 39, 1135-1142. 10.1053/ajkd.2002.33380.

[17] Ouyang, Y., Zhang, Y., Li, H., Ma, L.B.Z., De Ji, C.R., Qiao, C., Dun, B., Gao, X., Zhu, J., Xu, P., et al. (2024). Effect of therapeutic erythrocytapheresis on outcomes and renal benefit in patients with high-altitude polycythemia: a real-world study. Sci Rep 14, 29081. 10.1038/s41598-024-80609-6.

[18] Sinha, S., Singh, S.N., and Ray, U.S. (2009). Total antioxidant status at high altitude in lowlanders and native

highlanders: role of uric acid. High Alt Med Biol 10, 269-274. 10.1089/ham.2008.1082.

[19] Dong, H. M., Tian, G., Wang, Z. Q. and He, W. Y. (2020). Protective role of Klotho in adaptive responses of cardiomyocytes to chronic hypoxia at high altitude. Journal of Preventive Medicine of Chinese People's Liberation Army, 38(11), 95-97.

[20] Yang, G. Y., Xiong, Y. Z., Li, Y. Y., Ma,Y. C. and Liu, Z. L. (2010). Comparison of gastric mucosal XOD activity between indigenous Han populations in plateau and plain regions. Journal of Clinical Gastroenterology, 22(02), 74-75.

[21] Pu, L., Xu, H., Wang, Z., Li, R., Ai, C., Song, X., Zhang, L., Cheng, X., Wang, G., Wang, X., et al. (2024). Intermittent high altitude hypoxia induced liver and kidney injury leading to hyperuricemia. Arch Biochem Biophys 758, 110078. 10.1016/j.abb.2024.110078.

[22] Liu, H. F., Xia, Y., Xu, Q., Xiong, J. C., Zhao, J. H. and Li, Y. N. (2017). Role of hyperuricemia in inducing epithelial-mesenchymal transition of renal tubular epithelial cells via the TLR4/NF-κB signaling pathway. Journal of the Third Military Medical University, 39(19), 1919-1925.

[23] Dang, W., Li, F., Gao, R., Zhang, C., Cheng, H., Wu, Z., Yang, T., Pan, J., Tang, X., and Gao, Y. (2024). Protective Effects of Dioscin and Diosgenin on Plateau Hyperuricemia by Attenuating Renal Inflammation via EPHX2. Int J Mol Sci 25. 10.3390/ijms252413399.

[24] Miao, C. X., and Leng, J. H. (2024). Research progress on pharmacological effects and mechanisms of dioscin. Chinese Archives of Traditional Chinese Medicine, 42(11), 113-118.

[25] Brooks, G.A. (2020). Lactate as a fulcrum of metabolism. Redox Biol 35, 101454. 10.1016/j.redox.2020.101454.

[26] Dong, S., Qian, L., Cheng, Z., Chen, C., Wang, K., Hu, S., Zhang, X., and Wu, T. (2021). Lactate and Myocardiac Energy Metabolism. Front Physiol 12, 715081. 10.3389/fphys.2021.715081.

[27] Brooks, G.A. (2018). The Science and Translation of Lactate Shuttle Theory. Cell Metab 27, 757-785. 10.1016/j.cmet.2018.03.008.

[28] Su, Q., Li, Y.C., Zhuang, D.H., Liu, X.Y., Gao, H., Li, D., Chen, Y., Ge, M.X., Han, Y.M., Gao, Z.L., et al. (2024). Rewiring of Uric Acid Metabolism in the Intestine Promotes High-Altitude Hypoxia Adaptation in Humans. Mol Biol Evol 41. 10.1093/molbev/msae233.

[29]Zhang, D., Tang, Z., Huang, H., Zhou, G., Cui, C., Weng, Y., Liu, W., Kim, S., Lee, S., Perez-Neut, M., et al. (2019). Metabolic regulation of gene expression by histone lactylation. Nature 574, 575-580. 10.1038/s41586-019-1678-1.

[30] Chen, X., Liu, L., Kang, S., Gnanaprakasam, J.R., and Wang, R. (2023). The lactate dehydrogenase (LDH) isoenzyme spectrum enables optimally controlling T cell glycolysis and differentiation. Sci Adv 9, eadd9554. 10.1126/sciadv.add9554.

[31] Lopez Krol, A., Nehring, H.P., Krause, F.F., Wempe, A., Raifer, H., Nist, A., Stiewe, T., Bertrams, W., Schmeck, B., Luu, M., et al. (2022). Lactate induces metabolic and epigenetic reprogramming of pro-inflammatory Th17 cells. EMBO Rep 23, e54685. 10.15252/embr.202254685.

[32] Lv, J., Qi, P., Yan, X., Bai, L., and Zhang, L. (2023). Structure and Metabolic Characteristics of Intestinal Microbiota in Tibetan and Han Populations of Qinghai-Tibet Plateau and Associated Influencing Factors. Microorganisms 11. 10.3390/microorganisms11112655.

[33] Zhang, X., Xu, W., Zhong, W., Zhang, W., Yang, C., Duan, L., Niu, H., Dong, Y., Liu, T., Xia, S., and Wang, B. (2023). Exploring the links between gut microbiome changes and irritable bowel syndrome in Han populations in the Tibetan Plateau. J Zhejiang Univ Sci B 24, 823-838. 10.1631/jzus.B2200509.

[34] Jia, Z., Zhao, X., Liu, X., Zhao, L., Jia, Q., Shi, J., Xu, X., Hao, L., Xu, Z., Zhong, Q., et al. (2020). Impacts of the Plateau Environment on the Gut Microbiota and Blood Clinical Indexes in Han and Tibetan Individuals. mSystems 5. 10.1128/mSystems.00660-19.

[35] Wang, J., Chen, Y., Zhong, H., Chen, F., Regenstein, J., Hu, X., Cai, L., and Feng, F. (2022). The gut microbiota as a target to control hyperuricemia pathogenesis: Potential mechanisms and therapeutic strategies. Crit Rev Food Sci Nutr 62, 3979-3989. 10.1080/10408398.2021.1874287.

[36] Hussain, A., Rui, B., Ullah, H., Dai, P., Ahmad, K., Yuan, J., Liu, Y., and Li, M. (2024). Limosilactobacillus reuteri HCS02-001 Attenuates Hyperuricemia through Gut Microbiota-Dependent Regulation of Uric Acid Biosynthesis and Excretion. Microorganisms 12. 10.3390/microorganisms12040637.

[37] Ni, C., Li, X., Wang, L., Li, X., Zhao, J., Zhang, H., Wang, G., and Chen, W. (2021). Lactic acid bacteria strains relieve hyperuricaemia by suppressing xanthine oxidase activity via a short-chain fatty acid-dependent mechanism. Food Funct 12, 7054-7067. 10.1039/d1fo00198a.

[38] Shen, Y., Wang, Y., Chang, C., Li, S., Li, W., and Ni, B. (2019). Prevalence and risk factors associated with hyperuricemia among working population at high altitudes: a cross-sectional study in Western China. Clin Rheumatol 38, 1375-1384. 10.1007/s10067-018-4391-9.

[39] Du, Y., Qi, M., Wang, W., and Chen, B. (2022). Effect of High-altitude Hypoxia Environment on Uric Acid Excretion, Desmin Protein Level in Podocytes, and Na+-K+- ATPase Activity. Cell Mol Biol (Noisy-le-grand) 68, 84-91. 10.14715/cmb/2022.68.6.14.

[40] Hu, H., Li, W., Hao, Y., Peng, Z., Zou, Z., Wei, J., Zhou, Y., Liang, W., and Cao, Y. (2024). The SGLT2 inhibitor dapagliflozin ameliorates renal fibrosis in hyperuricemic nephropathy. Cell Rep Med 5, 101690. 10.1016/j.xcrm.2024.101690.

[41] Liu, L., Zhao, T., Shan, L., Cao, L., Zhu, X., and Xue, Y. (2021). Estradiol regulates intestinal ABCG2 to promote urate excretion via the PI3K/Akt pathway. Nutr Metab (Lond) 18, 63. 10.1186/s12986-021-00583-y.

[42] Jung, J.H., Song, G.G., Lee, Y.H., Kim, J.H., Hyun, M.H., and Choi, S.J. (2018). Serum uric acid levels and hormone therapy type: a retrospective cohort study of postmenopausal women. Menopause 25, 77-81. 10.1097/gme.0000000000000953.

[43] Wan, H., Zhang, K., Wang, Y., Chen, Y., Zhang, W., Xia, F., Zhang, Y., Wang, N., and Lu, Y. (2020). The Associations between Gonadal Hormones and Serum Uric Acid Levels in Men and Postmenopausal Women with Diabetes. Front Endocrinol (Lausanne) 11, 55. 10.3389/fendo.2020.00055.

[44] Jiang, Y. M., Qiu, K. L., & Liao, Y. F. (2024). Research progress on the relationship between sex hormones, sex hormone-binding globulin, and hyperuricemia/gout. Journal of Huazhong University of Science and Technology (Medical Sciences), 53(3), 389-393.