

UNDERSTANDING PEDIATRIC NAFLD: A WESTERN AND TRADITIONAL CHINESE MEDICINE PERSPECTIVEZHANG

¹Dr. Xinghua Li, ²Dr. Qian Wang and ³Dr. Ming Zhang

¹Department of Hepatology, the First Clinical Medical College of Shaanxi University of Chinese Medicine, Xianyang, China

²Department of Hepatology, Ankang Hospital of Traditional Chinese Medicine and Seventh Clinical Medical College of Shaanxi University of Chinese Medicine, Ankang, China

³Department of Hepatology, the First Clinical Medical College of Shaanxi University of Chinese Medicine, Xianyang, China

Abstract: *Non-alcoholic fatty liver disease (NAFLD) in children is a growing concern worldwide, marked by chronic fat accumulation in the liver, mainly affecting individuals under 18. This metabolic liver condition is closely linked to genetic susceptibility and insulin resistance. The NAFLD spectrum encompasses nonalcoholic simple fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), and associated liver fibrosis and cirrhosis. The prevalence of NAFLD in children has surged alongside the global rise in obesity and changes in dietary patterns. Recent research indicates that NAFLD affects around 3% to 10% of children worldwide. Obesity is a key risk factor, with NAFLD prevalence reaching as high as 70%-80% in obese children. Children with NAFLD are at a significantly higher risk of end-stage liver disease and mortality. Long-term studies reveal that children with NAFLD face a risk of death or liver transplantation 13.8 times higher than their peers without NAFLD. Compared to adults, children with NAFLD progress to steatohepatitis and liver fibrosis more rapidly, making early intervention and treatment vital to prevent complications. This pressing public health issue underscores the need for effective prevention and treatment strategies for pediatric NAFLD.*

Keywords: *NAFLD, children, obesity, steatohepatitis, liver fibrosis, mortality, prevention, treatment.*

1. The concept and prevalence of children's NAFLD

Non-alcoholic fatty liver disease in children refers to chronic fatty degeneration of the liver in children and adolescents under the age of 18, which involves more than 5% of liver cells, and is a clinical syndrome characterized by chronic fatty accumulation in the liver caused by exclusive drinking and other definite pathogenic factors. It is a metabolic stress liver injury closely related to genetic susceptibility and insulin resistance [1]. Its disease spectrum includes nonalcoholic simple fatty liver (NAFL), nonalcoholic steatohepatitis (NASH) and their related liver fibrosis and cirrhosis [2]. With the development of social economy and the improvement of living standards, people's diet structure has also undergone major changes. So far, metabolic fatty liver disease is one of the most commonly diagnosed liver diseases in the world, which not only occurs in adults, but also increases in children and adolescents.[3,4]. In fact, according to a recent meta-analysis, the

prevalence of children in the general population is 8% [5]. According to research statistics, NAFLD has affected about 3% ~ 10% of children around the world [6]. The prevalence of NAFLD in American children is about 3% ~ 11% [7]. The prevalence rate of children in Asia is about 6.3%, NAFLD that of

children in China is about 3.4% [8]. Obesity is considered as one of the main risk factors of NAFLD in children, and the prevalence rate of NAFLD in obese children may be as high as 70%-80% [9]. An autopsy study found that 9.6% of American teenagers aged 2-19 had NAFLD, and it increased to 38% among obese people [10]. In recent years, with the prevalence of obesity and metabolic syndrome in young people, the high incidence of NAFLD in children has gradually become a hot spot of public and clinical concern [11]. In addition, various studies also show that children with NAFLD have a higher risk of end-stage liver disease and a higher mortality rate [12]. A 20year follow-up survey of 66 children found that 2 cases (3.03%) with fatty liver underwent liver transplantation, and 30.8% of the children underwent liver biopsy again. Compared with the expected survival of the general population of the same age, the risk of death or liver transplantation of children with NAFLD was 13.8 times higher than that of the general population of the same age and gender, and the life span of children with fatty liver was significantly shorter than that of children without fatty liver [13]. In another 15-year-old study, 59 children and adolescents with NAFLD (younger than 25 years old) were compared with 36 ordinary people. The absolute risk of mortality of NAFLD patients was 7.7%. Compared with the control group, the mortality of simple steatosis increased by 5.26 times and NASH increased by 11.51 times [14]. Therefore, compared with adult fatty liver, children's fatty liver develops into steatohepatitis and liver fibrosis much faster than adults, and the risk of end-stage liver disease is higher, and the mortality rate is also high. Therefore, it is more significant for the prevention and treatment of nonalcoholic fatty liver in children, and it is also an urgent social problem to be solved at present.

1.1 Diagnostic criteria for NAFLD in children

According to the expert consensus on the new definition of metabolism-related fatty liver disease (MAFLD) issued by the international expert group in early 2020, the definition and diagnostic criteria of MAFLD were put forward: excluding excessive drinking and other clear pathogenic factors, liver biopsy histology or imaging or even blood biomarker examination suggested the existence of fatty liver, and meeting one of the following three conditions at the same time: overweight/obesity, type 2 diabetes mellitus and metabolic dysfunction [15]. Liver histological examination (liver biopsy) is the most reliable means to diagnose and differentiate NAFLD in children at present, which can accurately judge the degree of fat storage, inflammation and fibrosis in liver tissue. However, due to the complexity, difficulty and trauma of this method, it is greatly limited in practical clinical application.

2. Current treatment of NAFLD in children

2.1 Diet and lifestyle changes

The primary treatment is to intervene the lifestyle, reduce the intake of high-calorie food, increase the amount of exercise, and achieve the expected effect of losing weight. This lifestyle change may have a positive impact on serum transaminase levels and various metabolic parameters (such as insulin resistance, fasting blood glucose and blood lipids) [16].

2.2 Drug treatment of children's NAFLD progress

2.2.1 Metformin

Metformin is an oral insulin sensitizer, which can inhibit the production of glucose in liver and increase the intake of glucose in muscle. A study shows that taking metformin can improve the transaminase level, liver fat content and insulin sensitivity of patients, and has a significant effect on improving the quality of life [17]. In another study on children's NAFLD, it was shown that metformin had no obvious effect on reducing alanine aminotransferase level and liver histology, but it could improve insulin resistance (IR) [18]. At present, in the domestic treatment guidelines, it is suggested that children with NAFLD complicated with diabetes can use metformin. Its contraindication is that it cannot be used in patients with hepatic and renal insufficiency.

2.2.2 Vitamin e

According to the current research, oxidative stress is considered to play an important role in the occurrence and development of NAFLD [19]. As a recognized antioxidant, vitamin E has been widely used in the research of treating NAFLD. Studies have shown that [20] Vitamin E can reduce the ALT level

of patients by inhibiting lipid peroxidation and subsequent oxidative stress. Liu Shenshen and others [21] it is found that vitamin E can significantly improve the ALT level in children with NAFLD. Generally speaking, vitamin E can improve the ALT level of children with NAFLD, but as an auxiliary drug in clinic, a large number of clinical data need to be verified.

2.2.3 **Vitamin d**

The low level of vitamin D in the body is related to obesity and NAFLD [22]. In a study, compared with the control group, NAFLD subjects are 26% more likely to lack vitamin D levels, and vitamin D deficiency is considered to accelerate liver fibrosis and further promote the occurrence of NASH [23]. Jiang Xue et al [24] It is considered that the content of VD in obese children with NAFLD is generally insufficient, and the degree of VD deficiency is positively correlated with the abnormal blood lipid metabolism and the severity of insulin resistance in children. Appropriate VD supplementation can improve the VD level in obese children with NAFLD, and correspondingly improve the liver function, lipid metabolism disorder, insulin resistance and liver steatosis.

2.2.4 **Probiotics**

Studies have shown that intestinal flora plays an important role in the pathogenesis and progress of NAFLD. In recent years, its therapeutic application in NAFLD has been widely concerned by changing the composition of intestinal flora, regulating immunity and intestinal-hepatic circulation. In healthy children, the intestinal flora is mostly Bifidobacterium, while in NAFLD and obese children, it is mostly Lactobacillus [25]. Many studies have shown that probiotics can effectively reduce liver enzymes, reduce waist circumference and improve the levels of total cholesterol, LDL and triglyceride in children with NAFLD [26, 27]. Therefore, probiotics have broad prospects for the treatment of NAFLD.

3. **TCM research progress in children's NAFLD**

At present, there is little research on children's metabolic fatty liver, which can be studied by referring to adult NAFLD and combining with children's physical factors. Fatty liver is a disease of excessive accumulation of liver fat and dysfunction of liver function and metabolism caused by many pathogenic factors. There is no name of NAFLD in Chinese medicine, and the theory of expansion of the spirit axis says: "The liver is swollen, and the hypochondrium is full and the pain leads to less abdomen." According to the classic Chinese medical classics, characteristics and clinical manifestations, it can be classified into diseases such as liver addiction, accumulation, hypochondriac pain, liver stagnation and phlegm turbidity. NAFLD is located in the liver, but it is closely related to the spleen and stomach. In the Theory of Blood Syndrome, "The nature of wood is mainly related to dispersing qi. Eating in the stomach depends on the wood gas of the liver to relieve it, while the water valley is the essence. "It shows that the liver is closely related to the spleen, and the digestion and absorption of food and drink by the spleen and stomach cannot be separated from the liver's catharsis function, and the rise and fall of qi activity of the spleen and stomach depends on the liver. Wan Mizhai, a famous physician in Ming Dynasty, combined Qian Yi's theory of syndrome differentiation of five zang-organs on his own clinical exploration, and put forward the physical characteristics of children: "There is excess of liver in five zang-organs, deficiency of spleen and deficiency of kidney, the theory that heart heat is fire and liver is the same, and jiao lung is hard to heal after being injured". This requires us to pay more attention to protecting stomach qi in the treatment of fatty liver in children.

3.1 **Treatment of NAFLD in Children with Traditional Chinese Medicine**

Traditional Chinese medicine (TCM) has obvious advantages and curative effects in preventing and treating children's metabolic diseases. A study showed that TCM can effectively reduce alanine aminotransferase (ALT) and improve liver steatosis, with a certain curative effect and few side effects [28]. However, according to the investigation and study, at present, the vast majority of treatments are western medicine combined with traditional Chinese medicine, which cannot clearly highlight the characteristics and advantages of traditional Chinese medicine in treating this disease, and further retrieval of relevant clinical research at home and abroad on the treatment of children's NAFLD with traditional Chinese medicine is also in a blank stage.

Chief physician Cui Xiang studied the treatment theories and experiences of many famous traditional Chinese medicine practitioners. Through continuous summary and further innovative summary in clinical practice, he proposed that the onset of NAFLD lies in the liver, and its origin lies in the spleen. The pathogenesis of NAFLD is "spleen deficiency, disturbed gasification, and fatigue in dispersing essence". Based on the treatment principle of "invigorating the spleen to promote yang, reducing turbidity and reducing fat", the prescription of invigorating the spleen to eliminate turbidity and eliminate fat was made according to the pathogenesis and the idea of treatment from the spleen^[29]. Dialectical addition and subtraction of this prescription has a good effect on improving adult NAFLD liver dysfunction and regulating blood lipid. Based on the treatment of more than 10,000 cases in the past three years, it is found that this prescription has remarkable effects of "protecting liver, resisting inflammation and lowering enzymes", "improving metabolic disorders" (blood sugar, blood lipid, uric acid, etc.), "reversing liver pathological changes" (fatty lesions, liver fibrosis/early cirrhosis) and reducing weight.

Compared with adults, the etiology of children's NAFLD is relatively simple, and children's physiological characteristics, such as "the body is not full, the viscera function is fragile, and the spleen is often insufficient", coupled with improper diet and a preference for fat and sweetness, should start with the spleen, strengthen the spleen and replenish qi, and eliminate turbidity and reduce blood fat. Cui Xiang, the chief physician, used pure Chinese medicine to follow up more than 60 children with NAFLD for 3 months. After treatment, most of the children's liver enzymes decreased to normal, and fatty liver was reversed under CT. Therefore, this prescription is more suitable from the idea of treating according to the cause. Coupled with the high degree of self-discipline of children and the careful cooperation of parents, the effect is outstanding in a short period of time, reaching the recovery standard in 12 weeks. Starting from the overall concept, traditional Chinese medicine has a good curative effect in the treatment of metabolic fatty liver disease, which is not only manifested in protecting liver, lowering enzymes, regulating sugar and lipid disorders, lowering blood uric acid level, but also showing outstanding curative effect in improving liver steatosis, which deserves further study. To sum up, the incidence of nonalcoholic fatty liver in children is getting higher and higher, which has great harm to children and adults. Unfortunately, there is a lack of a safe and effective drug at present, and there is even less experience in clinical research and medication of children's MAFLD in traditional Chinese medicine. Chief physician Cui Xiang has achieved good results by using the self-made recipe of Jianpi Huazhuo Xiaozhi in a large number of clinical practices in the early stage, laying a foundation for the treatment of children's MAFLD in the future.

References

- Zhou Xuelian & Fu Junfen. (2018). Expert consensus on the diagnosis and treatment of nonalcoholic fatty liver disease in children. *China Journal of Practical Pediatrics* (07), 487-492. DOI: 10.19538/J. EK 20187060. 20010000001
- Vos, M. B., Abrams, S. H., Barlow, S. E., Caprio, S., Daniels, S. R., Kohli, R., Mouzaki, M., Sathya, P., Schwimmer, J. B., Sundaram, S. S., & Xanthakos, S. A. (2017). *NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)*. *Journal of pediatric gastroenterology and nutrition*, 64(2), 319–334. <https://doi.org/10.1097/MPG.0000000000001482> [3] Weiß, J., Rau, M., & Geier, A. (2014). Non-alcoholic fatty liver disease: epidemiology, clinical course, investigation, and treatment. *Deutsches Arzteblatt international*, 111(26), 447–452. <https://doi.org/10.3238/arztebl.2014.0447>

- Younossi, Z. M., Stepanova, M., Afendy, M., Fang, Y., Younossi, Y., Mir, H., & Srishord, M. (2011). Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*, 9(6), 524–e60. <https://doi.org/10.1016/j.cgh.2011.03.020>
- Anderson, E. L., Howe, L. D., Jones, H. E., Higgins, J. P., Lawlor, D. A., & Fraser, A. (2015). The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis. *PloS one*, 10(10), e0140908. <https://doi.org/10.1371/journal.pone.0140908>
- Nobili, V., Alisi, A., Newton, K. P., & Schwimmer, J. B. (2016). Comparison of the Phenotype and Approach to Pediatric vs Adult Patients with Nonalcoholic Fatty Liver Disease. *Gastroenterology*, 150(8), 1798–1810. <https://doi.org/10.1053/j.gastro.2016.03.009>
- Welsh, J. A., Karpen, S., & Vos, M. B. (2013). Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. *The Journal of pediatrics*, 162(3), 496–500. e1. <https://doi.org/10.1016/j.jpeds.2012.08.043>
- Zhang Wei, Wei Lai. Prevalence of nonalcoholic fatty liver disease in Asia [J]. *Chinese Journal of Hepatology*, 2013, 21(11):801-804.
- Mencin, A. A., & Lavine, J. E. (2011). Nonalcoholic fatty liver disease in children. *Current opinion in clinical nutrition and metabolic care*, 14(2), 151–157. <https://doi.org/10.1097/MCO.0b013e328342baec>
- Schwimmer, J. B., Deutsch, R., Kahen, T., Lavine, J. E., Stanley, C., & Behling, C. (2006). Prevalence of fatty liver in children and adolescents. *Pediatrics*, 118(4), 1388–1393. <https://doi.org/10.1542/peds.2006-1212>
- Atsawarungrangkit, A., Elfanagely, Y., Pan, J., Anderson, K., Scharfen, J., & Promrat, K. (2021). Prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the United States' adolescent population. *World journal of hepatology*, 13(7), 790–803. <https://doi.org/10.4254/wjh.v13.i7.790>
- Allen, A. M., Hicks, S. B., Mara, K. C., Larson, J. J., & Therneau, T. M. (2019). The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity - A longitudinal cohort study. *Journal of hepatology*, 71(6), 1229–1236. <https://doi.org/10.1016/j.jhep.2019.08.018> [13] Feldstein, A. E., Charatcharoenwittaya, P., Treeprasertsuk, S., Benson, J. T., Enders, F. B., & Angulo, P. (2009). The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. *Gut*, 58(11), 1538–1544. <https://doi.org/10.1136/gut.2008.171280>
- Simon, T. G., Roelstraete, B., Hartjes, K., Shah, U., Khalili, H., Arnell, H., & Ludvigsson, J. F. (2021). Non-alcoholic fatty liver disease in children and young adults is associated with increased longterm mortality. *Journal of hepatology*, 75(5), 1034–1041. <https://doi.org/10.1016/j.jhep.2021.06.034> [15] Eslam, M., Newsome, P. N., Sarin, S. K., Anstee, Q. M., Targher, G., Romero-Gomez, M., ZelberSagi, S., Wai-Sun Wong, V., Dufour, J. F., Schattenberg, J. M., Kawaguchi, T., Arrese, M., Valenti, L.,

Shiha, G., Tiribelli, C., Yki-Järvinen, H., Fan, J. G., Grønbaek, H., Yilmaz, Y., Cortez-Pinto, H., George,

J. (2020). A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *Journal of hepatology*, 73(1), 202–209. <https://doi.org/10.1016/j.jhep.2020.03.039>

Utz-Melere, M., Targa-Ferreira, C., Lessa-Horta, B., Epifanio, M., Mouzaki, M., & Mattos, A. A. (2018). Non-Alcoholic Fatty Liver Disease in Children and Adolescents: Lifestyle Change - a Systematic Review and Meta-Analysis. *Annals of hepatology*, 17(3), 345–354. <https://doi.org/10.5604/01.3001.0011.7380>

Spahis, S., Alvarez, F., Ahmed, N., Dubois, J., Jalbout, R., Paganelli, M., Grzywacz, K., Delvin, E., Peretti, N., & Levy, E. (2018). Non-alcoholic fatty liver disease severity and metabolic complications in obese children: impact of omega-3 fatty acids. *The Journal of nutritional biochemistry*, 58, 28–36. <https://doi.org/10.1016/j.jnutbio.2018.03.025>

Lavine, J. E., Schwimmer, J. B., Van Natta, M. L., Molleston, J. P., Murray, K. F., Rosenthal, P., Abrams, S. H., Scheimann, A. O., Sanyal, A. J., Chalasani, N., Tonascia, J., Ünalp, A., Clark, J. M., Brunt, E. M., Kleiner, D. E., Hoofnagle, J. H., Robuck, P. R., & Nonalcoholic Steatohepatitis Clinical Research Network (2011). Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA*, 305(16), 1659–1668. <https://doi.org/10.1001/jama.2011.520>

Tilg, H., & Moschen, A. R. (2010). Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology (Baltimore, Md.)*, 52(5), 1836–1846. <https://doi.org/10.1002/hep.24001>

Phung, N., Pera, N., Farrell, G., Leclercq, I., Hou, J. Y., & George, J. (2009). Pro-oxidant-mediated hepatic fibrosis and effects of antioxidant intervention in murine dietary steatohepatitis. *International journal of molecular medicine*, 24(2), 171–180. https://doi.org/10.3892/ijmm_00000220

Liu Shenshen, Xing Yiqing, Wang Ning, Yu Qiaoling & Zeng Leping. (2020). Meta-analysis of the effect of vitamin E on nonalcoholic fatty liver disease in children. *Journal of Clinical Hepatobiliary Diseases* (07), 1545-1550.

Hourigan, S. K., Abrams, S., Yates, K., Pfeifer, K., Torbenson, M., Murray, K., Roth, C. L., Kowdley, K., Scheimann, A. O., & NASH CRN (2015). Relation between vitamin D status and nonalcoholic fatty liver disease in children. *Journal of pediatric gastroenterology and nutrition*, 60(3), 396–404. <https://doi.org/10.1097/MPG.0000000000000598>

Eliades, M., Spyrou, E., Agrawal, N., Lazo, M., Brancati, F. L., Potter, J. J., Koteish, A. A., Clark, J. M., Guallar, E., & Hernaez, R. (2013). Meta-analysis: vitamin D and non-alcoholic fatty liver disease. *Alimentary pharmacology & therapeutics*, 38(3), 246–254. <https://doi.org/10.1111/apt.12377> [24] Jiang Xue, Gao Jian, Hong Ze & Zhou Wendi. (2022). Clinical study of vitamin D in the treatment of obese children with nonalcoholic fatty liver disease. *China Journal of Child Health* (09), 970-974. [25] Nobili, V., Putignani, L., Mosca, A., Del Chierico, F., Vernocchi, P., Alisi, A., Stronati, L., Cucchiara, S., Toscano, M., & Drago, L. (2018). Bifidobacteria and lactobacilli in the gut microbiome of children with non-alcoholic fatty liver

disease: which strains act as health players? *Archives of medical science : AMS*, 14(1), 81–87. <https://doi.org/10.5114/aoms.2016.62150>

- Çakır, M., Aksel İşbilen, A., Eyüpoğlu, İ., Sağ, E., Örem, A., Mazlum Şen, T., Kakhkkaya, N., & Kaya, G. (2017). Effects of long-term synbiotic supplementation in addition to lifestyle changes in children with obesity-related non-alcoholic fatty liver disease. *The Turkish journal of gastroenterology: the official journal of Turkish Society of Gastroenterology*, 28(5), 377–383. <https://doi.org/10.5152/tjg.2017.17084>
- Gao, X., Zhu, Y., Wen, Y., Liu, G., & Wan, C. (2016). Efficacy of probiotics in non-alcoholic fatty liver disease in adult and children: A meta-analysis of randomized controlled trials. *Hepatology research: the official journal of the Japan Society of Hepatology*, 46(12), 1226–1233. <https://doi.org/10.1111/hepr.12671>
- Shi, K. Q., Fan, Y. C., Liu, W. Y., Li, L. F., Chen, Y. P., & Zheng, M. H. (2012). Traditional Chinese medicines benefit to nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Molecular biology reports*, 39(10), 9715–9722. <https://doi.org/10.1007/s11033-012-1836-0>
- Hua Peng, Guo Wei, Xue Jingdong, Li Fenping & Cui Xiang. (2020). Clinical evaluation of Jianpi Huazhuo Xiaozhi recipe in treating nonalcoholic steatohepatitis. *Journal of Integrated Traditional Chinese and Western Medicine Liver Disease* (05), 408-410.
- Cui Xiang, Liu Linglan & Zhang Fengyuan. (2022). Objectives and advantages of TCM in treating metabolic fatty liver disease. *Dr. Gan* (04), 50.
- Xiang C, Zhang F Y, Li L. Experience of successfully treating a child with severe metabolic associated fatty liver disease in 12 weeks using traditional Chinese medicine alone[J]. *Gastroenterol Hepatol Res*, 2021, 3(2): 4.