**Mini review**

**The Relationship between Lipid metabolism and Weight loss of elderly**

Da-Ming Liao1，Chieh Chen 2

Dental Department, Puli Christian Hospital 1

Anxing Clinic2

Corresponding author: Chieh Chen

Address: No. 36, Lane 100, Section 2, Zhongshan Road, Taiping District, Taichung City

Tel: 0928-698950

E-mail: [guppy5230@yahoo.com.tw](mailto:guppy5230@yahoo.com.tw)

\*Corresponding Author: Chieh Chen

Running title : Lipid metabolism Disorder

**Abstract:**

According to the reports, the number of people with fatty liver disease around the world is increasing, and the prevalence of type 2 diabetes in whom is over 18 years old has increased from 4.7% in the 1980s to 8.5% in 2014. Metabolic associated fatty liver disease(MAFLD) is not only affecting the liver but also poses as a serious threat to the entire body, with approximately 25% of the patients suffer from cardiovascular diseases. The literature review adopted perspectives of using databases like PubMed(Medline), UpToDate and Google scholar, searching through MeSH terms for keywords, such as adipokines, metabolic fatty liver disease, microbiota, microbiome, etc., for which articles on the molecular mechanism would be included, along with case-control studies, systematic review or meta-analysis, and randomized control studies to explore the effect of adipokines or myokines on the epidemiology and prevention of MAFLD. This article would investigate the adipokines and its function related to the disease of MAFLD.

**Keywords**: Adipokines; MAFLD; metabolic syndrome; Visfatin; Weight loss.

**Introduction**

This review summarized the current development in association of adipokines and MAFLD, by discussing the therapeutic strategies that target on the modulation of adipokines as a potential tool for the treatment of fatty liver[1]. The Cochrane, Embase, MEDLINE, and PubMed databases were searched. After the term MAFLD was proposed in 1980, the statistics up to year 2021 showed the diseases as a popular topic for research. The proteins that are specifically and abundantly expressed in adipocytes for certain biological functions are called adipokines[2]. The common important examples include leptin, adiponectin, tumor necrosis factor-α, resistin(anti-insulin hormone) and interleukin-6 [3,4]. Studies have shown that TNF-α, IL-6 and resistin can reduce the sensitivity of cells to insulin and cause resistance, while TNF-α and IL-6 are considered as cytokines for inflammation[5]. The major milestone in the research on MAFLD was seen in 2023, as its mechanism was now revised to involve multiple pathogenetic paths. The mechanism of MAFLD also includes inducing systemic inflammation and insulin resistance, not to mention the presence of fat accumulation that eventually leads to hepatic insufficiency, fibrosis, and cancer. Risk factors are medications (such as Renin-angiotensin inhibitor), age, and iron deposition, etc. As time progresses, 25% of the cases will develop into fatty liver disease, and another 6.3% will become metabolic fatty liver disease[6]. Many studies in the past decade have shown that obstructive sleep apnea is almost synonymous with the so-called metabolic dysfunction (i.e obesity, hyperlipidemia and diabetes)[7].

**The role of adipokines in fatty liver disease**

Adipokines are secreted in the adipose tissues; hence, its crucial role in the pathogenesis of the disease, as it produces pro-inflammatory cytokines called adipokines[1,8]. Adiponectin and leptin have been well studied of their actions in terms of MAFLD pathophysiology. Adiponectin deficiency is associated with a pro-inflammatory condition, mostly observed in obesity people or other metabolic disorders. On the other hand, increased level of leptin above the normal may also induce pro-inflammatory state. As for other adipokines such as resistin, visfatin, retinol-binding protein 4, irisin, etc., adiponectin protects cell from TNF-α induced death. So adiponectin is a potent TNF-α-neutralizing adipokine[9].

**Adipokines and metabolic associated fatty liver disease**

Metabolic associated fatty liver disease defined as a metabolic syndrome, runs the risk of inducing insulin resistance. The incidence of the disease is related to ethnicity, dietary habit, genetics (*PNPLA3* gene abnormality), and intestinal flora, etc. As a result, the disease course and the response of individual patient may vary. It was observed that some patients showed more metabolic dysfunction, as well as genetic abnormalities[9,10]. Epidemiological studies have pointed out that the incidence of MAFLD was as high as 22% in the United States and 32% in Asia. Visceral and subcutaneous adipose tissues are the location of most abundant fat deposit with distinct adipokine profile[11].

**Role of adipokines in metabolic associated fatty liver disease**

Adiponectin enhances glucose and fatty acid oxidation, improves insulin sensitivity, attenuates plaque formation, and increases aldosterone production. The hepatoprotective effects of adiponectin, including anti-inflammatory and antifibrogenic effects, have been greatly investigated that the reduced level in individuals with MAFLD was shown to inversely related to the severity of steatosis, inflammation, and fibrosis[12]. Hypoadiponectinemia may play an important pathophysiological role in the progression of condition from fatty liver to metabolic associated fatty liver disease. Adiponectin is an abundant adipocyte-derived protein with well-established anti-atherogenic, anti-inflammatory, and insulin-sensitizing properties[13]. Both serum and hepatic levels of adiponectin expression were decreased in patients with MAFLD. PPAR-γ ligands have been used recently in the treatment of MAFLD and are able to increase serum concentration of adiponectin. Adiponectin may also suppress inflammation and the activities of macrophages by reducing its synthesis, which leads to an imbalance of mediators toward pro-inflammatory condition[13-15]. The elevated production of these adipokines is increasingly considered to be important in the development of diseases linked to the obesity and metabolic disorder. The effective treatment for MAFLD is through weight loss that may halt the progression of the disease and even revert histological changes[16]. The underlying mechanism in all stages of the disease from prevention, early identification, and treatment require an in-depth understanding of the pathogenesis of liver injury in MAFLD.

**Adipokines and the systematic inflammation**

Most adipokines are upregulated in obesity and promote inflammation through leptin, TNFα, IL-6, IL-18, etc., even though adiponectin acts the opposite as an anti-inflammatory modulator [17]. Accumulating evidence has linked the condition of obesity with low-grade inflammation that first originates from adipose tissues, which secrete a plethora of pro- and anti-inflammatory cytokines, all of which being termed adipokines. These molecules have been implicated in initiating and perpetuating the chronic state of inflammation that is observed in obesity and MAFLD. However, more investigation should be conducted to identify the exact role of adipokines derived from intra-abdominal adipose, as these molecules also seem to drive the progression of liver injury in patients with obesity [18]. Given that MAFLD is related to systemic inflammation characterized by disrupted imbalance of adipokines, obesity related digestive diseases, such as gastroesophageal reflux disease, fatty liver disease, cholelithiasis, gallbladder cancer, pancreatic cancer, and others may specifically alter the adipokine in body tissues[19,20]. MAFLD is a chronic liver inflammation affecting 30% of all populations, with 41% to 70% of humans have the disease. MAFLD patients with hepatic fibrosis tend to have worse prognosis and it is recommended to monitor the degree of fibrosis through serum level of AFP and GPT. MAFLD is not an isolated liver problem, but it may affect brain to cause depression, infarction, insomnia, and dementia[21,22]. It is also shown that adipokines in MAFLD are involved in oral cancer, heart diseases (such as arrhythmia and cardiomyopathy), sleep apnea, lung cancer, chronic kidney disease, ovarian cancer, and polycystic ovary syndrome [23,24].

**References**

1. Chang ML, Yang Z, Yang SS. Roles of adipokines in digestive diseases: markers of inflammation, metabolic alteration and disease progression. Int. J. Mol. Sci. 2020; 21(21): 8308.
2. Francisco V, Sanz MJ, Real JT, Marques P, Capuozzo M, Ait Eldjoudi D, Gualillo O. Adipokines in Non-Alcoholic Fatty Liver Disease: Are We on the Road toward New Biomarkers and Therapeutic Targets? Biology 2022; 11(8): 1237.
3. Murray KA, Hoad CL, Garratt J, Kaviani M, Marciani L, Smith JK, et al. A pilot study of visceral fat and its association with adipokines, stool calprotectin and symptoms in patients with diverticulosis. PLoS One 2019; 14(5), e0216528.
4. Méndez-Sánchez N, Chávez-Tapia NC, Medina-Santillán R, Villa AR, Sánchez-Lara K, Ponciano-Rodríguez G, et al. The efficacy of adipokines and indices of metabolic syndrome as predictors of severe obesity-related hepatic steatosis. Digestive diseases and sciences 2006; 51: 1716-22.
5. Morshedzadeh N, Rahimlou M, Asadzadeh Aghdaei H, Shahrokh S, Reza Zali, M., Mirmiran P. Association between adipokines levels with inflammatory bowel disease (IBD): systematic reviews. Digestive diseases and sciences 2017; 62: 3280-6.
6. Aller R, de Luis DA, Fernandez L, Calle F, Velayos B, Olcoz JL, et al. Influence of insulin resistance and adipokines in the grade of steatosis of nonalcoholic fatty liver disease. Digestive diseases and sciences 2008; 53: 1088-92.
7. Tilg H, Hotamisligil GS. Nonalcoholic fatty liver disease: cytokine-adipokine interplay and regulation of insulin resistance. Gastroenterology 2006; 131(3): 934-45.
8. Sahin-Efe A, Katsikeris F, Mantzoros CS. Advances in adipokines. Metab. Clin. Exp. 2012; 61(12): 1659-1665.
9. Kumar R, Prakash S, Chhabra S, Singla V, Madan K, Gupta SD, et al. Association of pro-inflammatory cytokines, adipokines & oxidative stress with insulin resistance & non-alcoholic fatty liver disease. Indian J. Med. Res. 2012; 136(2): 229.
10. Rombouts K, Marra F. Molecular mechanisms of hepatic fibrosis in non-alcoholic steatohepatitis. Digestive diseases 2010; 28(1): 229-35.
11. Batra A, Siegmund, B. The role of visceral fat. Digestive diseases 2012; 30(1): 70-4.
12. Stojsavljević S, Palčić MG, Jukić LV, Duvnjak LS, Duvnjak M. Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease. World J. Gastroenterol.: WJG 2014; 20(48): 18070.
13. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int. J. Mol. Sci. 2014; 15(4): 6184-223.
14. Marra F, Bertolani C. Adipokines in liver diseases. Hepatology 2009; 50(3): 957-69.
15. Jamali R, Razavizade M, Arj A, Aarabi MH. Serum adipokines might predict liver histology findings in non-alcoholic fatty liver disease. World J. Gastroenterol. 2016; 22(21): 5096.
16. Parola M, Marra F. Adipokines and redox signaling: impact on fatty liver disease. ANTIOXID REDOX SIGN 2011; 15(2): 461-83.
17. Marra F, Navari N, Vivoli E, Galastri S, Provenzano A. Modulation of liver fibrosis by adipokines. Digestive diseases 2011; 29(4): 371-376.
18. Aller R, de Luis DA, Fernandez L, Calle F, Velayos B, Olcoz JL, et al. Influence of insulin resistance and adipokines in the grade of steatosis of nonalcoholic fatty liver disease. Digestive diseases and sciences 2008; 53: 1088-1092.
19. Wozniak SE, Gee LL, Wachtel MS, Frezza EE. Adipose tissue: the new endocrine organ? A review article. Digestive diseases and sciences 2009; 54: 1847-56.
20. Nobili, V., Carpino, G., Alisi, A., Franchitto A, Alpini G, De Vito, R., et al. Hepatic progenitor cells activation, fibrosis, and adipokines production in pediatric nonalcoholic fatty liver disease. Hepatology 2012; 56(6): 2142-2153.
21. Nier, A., Huber, Y., Labenz, C., Michel, M., Bergheim, I., Schattenberg, J. M. Adipokines and endotoxemia correlate with hepatic steatosis in non-alcoholic fatty liver disease (NAFLD). Nutrients 2020; 12(3): 699.
22. Ismaiel A, Spinu M, Budisan L, Leucuta DC, Popa SL, Chis BA, et al. Relationship between adipokines and cardiovascular ultrasound parameters in metabolic-dysfunction-associated fatty liver disease. J. Clin. Med. 2021; 10(21): 5194.
23. Waluga M, Hartleb M, Boryczka G, Kukla M, Żwirska-Korczala K. Serum adipokines in inflammatory bowel disease. World J. Gastroenterol. 2014; 20(22): 6912.
24. Kelly AS, Ryder JR, Marlatt, K. L., Rudser, K. D., Jenkins, T., Inge TH. Changes in inflammation, oxidative stress and adipokines following bariatric surgery among adolescents with severe obesity. Int J Obes 2016; 40(2): 275-80.