**Adipokines and fatty liver disease**

Da-Ming Liao1，Chieh Chen 2

Dental Department, Puli Christian Hospital 1

Division of family medicine, Hualien Armed Forces General Hospital 2

Corresponding author: Chieh Chen

guppy5230@yahoo.com.tw

Address: No. 198, Minde 1st Street, Hualien city, Hualien County, Taiwan (R.O.C.)

Tel: 0928-698950

E-mail: guppy5230@yahoo.com.tw

Running title: adipokines and disease

**Abstract**

According to the WHO’s report, the number of people with fatty liver disease worldwide is increasing, and the prevalence of type 2 diabetes in adults who is over 18 years old has risen from 4.7% in the 1980s to 8.5% in 2014. Metabolic-associated fatty liver disease (MAFLD)is not only affecting the liver but is also considered a problem of whole body, as there is about 25% of the fatty liver disease patients suffer from cardiovascular diseases. One of the health issues associated with aging is the population with cardiovascular disease. This review adopts perspectives from literature reviews using databases such as Cochrane Library, PubMed (Medline), UpToDate, and Google scholar using three main methods: search for keywords adipokine, digestive disease, metabolic fatty liver diseases, gestational disease, microbiota microbiome, etc.; search for related articles on adipokine and fatty liver disease, molecular biology, etc.; combined with case-control studies, systematic review and meta-analysis, analytical research, and randomized control studies to explore the effects of adipokine or myokine and the fatty liver diseases on the epidemiology, prevention of MAFLD. This article aims to propose adipokine in metabolic fatty liver disease and understanding adipokine function related to the disease of people with MAFLD.

**Keywords**: Adipokine; MAFLD; digestive metabolic disease; **Visfatin**; myokine.

**Introduction**

After the term NAFLD was proposed in 1980, there will be an article statistics by 2023, and there will be a lot of related topics being popularly researched, which means that NAFLD is a very popular topic. These biologically functional proteins that are specifically or abundantly expressed in adipocytes are called adipokines. The most important of which include leptin, adiponectin, tumor necrosis factor-α, anti-insulin hormone(resistin) and interleukin-6[1-3], studies have shown that TNF-α, IL-6 and resistin can reduce the sensitivity of cells to insulin and cause insulin resistance, among which TNF-α and IL-6 are considered to be important cells that cause immune inflammation in the body hormone. The milestones of research in the past 30 years can be seen that after MAFLD was proposed[4-7], it was initially considered as two-hit pathogenesis, and then revised as multiple parallel hits, the mechanism of multiple etiologies. The etiology of MAFLD also includes systemic inflammatory reactions caused by insulin resistance and fat accumulation, and finally hepatic insufficiency, liver fibrosis, and liver cancer; risk factors such as drugs (Renin-angiotensin system inhibitor, RAS inhibitor), age, and iron deposition. As time progresses, 25% will become fatty liver each year, and 6.3% will become metabolic fatty liver disease. Many medical studies in the past decade have shown that sleep apnea is almost synonymous with the so-called metabolic syndrome (i.e obesity, hypertension, hyperlipidemia and diabetes)[8-13].

**The role of adipokine in the digestive system**

Adipokines are polypeptides secreted in the adipose tissue. Adipose tissue plays crucial roles in its pathogenesis, as it produces and secretes pro-inflammatory cytokines called adipokines. Adiponectin and leptin have well determined actions in terms of MAFLD pathophysiology. Adiponectin deficiency is associated with a pro-inflammatory condition, as it is observed in obesity and other metabolic disorders. On the other hand, increased leptin levels, above the normal levels, act as a pro-inflammatory stimulus[14-17]. Regarding to other adipokines such as resistin, visfatin, chemerin, retinol-binding protein 4, irisin, etc., adiponectin protects hepatocytes from TNF-α induced death; specifically, adiponectin is a potent TNF-α neutralizing adipokine. Bile acid synthesis and serum bile acid levels are directly correlated with disease severity in NAFLD, while the adiponectin level is inversely correlated with this parameter. Data about their contribution to MAFLD pathogenesis and progression are inconclusive[18-21].

**Adipokine and non-alcoholic fatty liver disease**

It was recently replaced by the term metabolic association MAFLD, defined as patients with metabolic syndrome and the presence of risk factors such as high insulin resistance. The occurrence of MAFLD is related to race, diet, alcohol, genes (*PNPLA3* gene abnormality), and intestinal flora. As a result, the course of disease and the response to treatment of MAFLD patients are very different. It can be seen that some patients have a higher proportion of metabolic abnormalities, and some patients have a higher proportion of genetic abnormalities. Epidemiological studies have pointed out that the incidence of MAFLD can reach 21.9% in the United States and 31% in Asia. The incidence of slice-proven MAFLD can reach 61% in the United States, but liver slices are rarely performed in Asian patients. Visceral and subcutaneous adipose tissues are the most abundant fat depots with distinct adipokine profiles[22-25].

**Role of Cytokines and Apoptosis in MAFLD**

Adiponectin enhances glucose and fatty acid oxidation, improves insulin sensitivity, attenuates plaque formation, and increases aldosterone production. The hepatoprotective effects of adiponectin, including its antisteatotic, anti-inflammatory, and antifibrogenic effects, have been widely investigated. Adiponectin levels are reduced in individuals with MAFLD and are inversely related to the severity of steatosis, necroinflammation, and fibrosis. Hypoadiponectinemia may play an important pathophysiological role in the progression from non-alcoholic fatty liver to NASH. Adiponectin is an abundant adipocyte-derived protein with well-established anti-atherogenic, anti-inflammatory, and insulin-sensitizing properties. Both serum levels and hepatic adiponectin expression are decreased in patients with MAFLD[26-30]. *PPAR-γ* ligands have been used recently in the treatment of MAFLD and are able to increase tissue and serum concentrations of adiponectin. Adiponectin might play a role in suppressing inflammation and macrophage activity, and its reduced synthesis as observed in MAFLD might lead to an imbalance in favor of proinflammatory mediators.

**Visceral Fat and MAFLD**

The elevated production of these adipokines is increasingly considered to be important in the development of diseases linked to obesity and the metabolic syndrome. Disordered cytokine production is likely to play a role in the pathogenesis of MAFLD. There is no effective treatment for MAFLD, though weight loss may halt disease progression and revert histological changes, the underlying mechanism remaining elusive. All stages of the disease pathway from prevention, early identification/diagnosis, and treatment require an understanding of the pathogenesis of liver injury in MAFLD[12,31].

**Adipose tissue, adipokines and inflammation**

Most adipokines are upregulated in obesity and promote inflammatory(Leptin, TNFα, IL-6, and IL-18), others may act as anti-inflammatory modulators (e.g., adiponectin). Accumulating evidence links obesity with low-grade inflammation which may originate from adipose tissue that secretes a plethora of pro- and anti-inflammatory cytokines termed adipokines. Adipokines secreted by adipose tissue have recently been implicated in initiating and perpetuating the chronic inflammatory state observed in obesity and MAFLD. Studies should be undertaken to examine the exact role of adipokines derived from intra-abdominal fat as these appear to be the main drivers for the development of progressive liver injury in patients with severe obesity[32-35].

**Conclusion**

Non-alcoholic fatty liver disease is related to systemic inflammation characterized by disturbing of adipokine homeostasis on human bodies. Obesity related digestive diseases, such as gastroesophageal reflux diseases, Barrett’s esophagus or esophageal cancer, colon polyps, non-alcoholic fatty liver disease, cholelithiasis, gallbladder cancer, cholangiocarcinoma, pancreatic cancer, and could cause specific alterations in adipokine profiles. MAFLD is a chronic liver disease affecting 30% of the general population and 40% to 70% of individuals. Liver fibrosis in MAFLD patients will have a worse prognosis. The degree of liver fibrosis can be monitored through hyaluronic acid serum markers. MAFLD is not only a liver problem, but also brain diseases such as depression, cerebral infarction, insomnia, dementia; oral cancer, heart disease like arrhythmia, cardiomyopathy, apnea, lung cancer, gastrointestinal tract tumors, chronic kidney disease, cervical cancer, ovarian cancer, and polycystic ovary syndrome. This review summarizes the current developments in the association between adipokines and MAFLD, and discusses therapeutic strategy that targeting the modulation of adipokine as a potential tool for the treatment of MAFLD.

**Reference**

1. Chang, M. L., Yang, Z., Yang, SS. Roles of adipokines in digestive diseases: markers of inflammation, metabolic alteration and disease progression. International Journal of Molecular Sciences 2020, 21(21), 8308.
2. 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.
3. Aller, R., de Luis, D. A., Fernandez, L., Calle, F., Velayos, B., Olcoz, J. L., 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.
4. Wozniak, S. E., Gee, L. L., Wachtel, M. S., Frezza, E. E. (2009). Adipose tissue: the new endocrine organ? A review article. Digestive diseases and sciences, 54, 1847-1856.
5. Aller, R., de Luis, D. A., Fernandez, L., Calle, F., Velayos, B., Olcoz, J. L., 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.
6. Marra F, Navari N, Vivoli E, Galastri S, Provenzano A. Modulation of liver fibrosis by adipokines. Digestive diseases 2011, 29(4), 371-376.
7. 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.
8. Murray, K. A., Hoad, C. L., Garratt, J., Kaviani, M., Marciani, L., Smith, J. K., 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.
9. Al-Azzawi, H. H., Wade, T. E., Swartz-Basile, D. A., Wang, S., Pitt, H. A., Zyromski, N. J. Acute pancreatitis in obesity: adipokines and dietary fish oil. Digestive diseases and sciences 2011, 56, 2318-25.
10. Scarpellini E, Tack J. Obesity and metabolic syndrome: an inflammatory condition. Digestive diseases 2012, 30(2), 148-53.
11. Kerem, M., Ferahkose, Z., Yilman, U., PAŞAOĞLU, H., Ofluoglu, E., Bedirli, A.,et al. Adipokines and ghrelin in gastric cancer cachexia. World journal of gastroenterology 2008, 14(23).
12. Dalbec, K. M., Max Schmidt, C., Wade, T. E., Wang, S., Swartz-Basile, D. A., Pitt, H. A., et al. Adipokines and cytokines in human pancreatic juice: unraveling the local pancreatic inflammatory milieu. Digestive diseases and sciences 2010, 55, 2108-2112.
13. Batra A, Siegmund, B. The role of visceral fat. Digestive diseases 2012, 30(1), 70-4.
14. Waluga, M., Hartleb, M., Boryczka, G., Kukla, M., Żwirska-Korczala, K. Serum adipokines in inflammatory bowel disease. World journal of gastroenterology: WJG 2014, 20(22), 6912.
15. Méndez-Sánchez, N., Chávez-Tapia, N. C., Medina-Santillán, R., Villa, A. R., 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.
16. Wong, V. W. S., Wong, G. L. H., Yu, J., Choi, P. C. L., Chan, A. W. H., Chan, H. Y., et al. Interaction of adipokines and hepatitis B virus on histological liver injury in the Chinese. Official journal of the American College of Gastroenterology| ACG 2010, 105(1), 132-8.
17. Sahin-Efe, A., Katsikeris, F., Mantzoros, C. S. Advances in adipokines. Metabolism-Clinical and Experimental 2012, 61(12), 1659-1665.
18. 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. International journal of obesity 2016, 40(2), 275-80.
19. Chandar, A. K., Devanna, S., Lu, C., Singh, S., Greer, K., Chak, A., Iyer, P. G. Association of serum levels of adipokines and insulin with risk of Barrett's esophagus: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 2015, 13(13), 2241-2255.
20. Russo, F., Chimienti, G., Clemente, C., D’Attoma, B., Linsalata, M., Orlando A, et al. Adipokine profile in celiac patients: differences in comparison with patients suffering from diarrhea-predominant IBS and healthy subjects. Scandinavian Journal of Gastroenterology 2013, 48(12), 1377-85.
21. Fasshauer, M., Blüher, M. Adipokines in health and disease. Trends in pharmacological sciences 2015, 36(7), 461-470.
22. Polyzos, S. A., Kountouras, J., Mantzoros, CS. Adipokines in nonalcoholic fatty liver disease. Metabolism 2016, 65(8), 1062-79.
23. Stojsavljević, S., Palčić, M. G., Jukić, L. V., Duvnjak, L. S., Duvnjak, M. Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease. World journal of gastroenterology: WJG 2014, 20(48), 18070.
24. Behrouz, V., Jazayeri, S., Aryaeian, N., Zahedi, M. J., Hosseini F. Effects of probiotic and prebiotic supplementation on leptin, adiponectin, and glycemic parameters in non-alcoholic fatty liver disease: a randomized clinical trial. Middle East journal of digestive diseases 2017, 9(3), 150.
25. Rombouts, K., Marra, F. Molecular mechanisms of hepatic fibrosis in non-alcoholic steatohepatitis. Digestive diseases 2010, 28(1): 229-35.
26. 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. International journal of molecular sciences 2014, 15(4), 6184-223.
27. Jamali R, Razavizade M, Arj A, Aarabi MH. Serum adipokines might predict liver histology findings in non-alcoholic fatty liver disease. World journal of gastroenterology 2016, 22(21), 5096.
28. Marra F, Bertolani C. Adipokines in liver diseases. Hepatology 2009, 50(3), 957-69.
29. 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. The Indian journal of medical research 2012, 136(2), 229.
30. Parola M, Marra F. Adipokines and redox signaling: impact on fatty liver disease. Antioxidants & redox signaling 2011, 15(2), 461-83.
31. Wong, V. W. S., Hui, A. Y., Tsang, S. W. C., Chan, J. L. Y., Tse, A. M. L., Chan, K. F., et al. Metabolic and adipokine profile of Chinese patients with nonalcoholic fatty liver disease. Clinical Gastroenterology and Hepatology 2006, 4(9), 1154-1161.
32. Tilg H, Hotamisligil GS. Nonalcoholic fatty liver disease: cytokine-adipokine interplay and regulation of insulin resistance. Gastroenterology 2006, 131(3), 934-45.
33. Francisco, V., Sanz, M. J., Real, J. T., 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.
34. 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.
35. Ismaiel, A., Spinu, M., Budisan, L., Leucuta, D. C., Popa, S. L., Chis, B. A., et al. Relationship between adipokines and cardiovascular ultrasound parameters in metabolic-dysfunction-associated fatty liver disease. Journal of Clinical Medicine 2021, 10(21): 5194.