**Adipokines and fatty liver disease**

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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.

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