**The Relationship between Adipokines, Lipid metabolism Disorder and Weight loss of elderly**

Running title : Adipokines, Lipid metabolism Disorder

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**Abstract:**

According to the WHO’s reports, the number of people with fatty liver disease around the world is increasing, and the prevalence of type 2 diabetes in adults who 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. One of the health issues associated with aging is the cardiovascular diseases. This literature review adopted perspectives of using databases like Cochrane library, PubMed (Medline), UpToDate and Google scholar, searching through MeSH terms for keywords, such as adipokines, digestive disease, metabolic fatty liver disease, microbiota, microbiome, etc., for which articles on the molecular biological mechanism would be included, along with case-control studies, systematic review and meta-analysis, analytical research, 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; Digestive disease; Visfatin; Weight loss.

**Introduction**

This review summarized the current development in association of adipokines and MAFLD, by discussing the therapeutic strategies that target the modulation of adipokines as a potential tool for the treatment of MAFLD[1]. The Cochrane, Embase, MEDLINE, PEDro, 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, anti-insulin hormone (resistin) and interleukin-6 (IL-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 important 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 sleep apnea is almost synonymous with the so-called metabolic dysfunction (i.e obesity, hypertension, hyperlipidemia and diabetes)[7].

**The role of adipokines in fatty liver**

Adipokines are secreted in the adipose tissues; hence, its crucial role in the pathogenesis of the disease, as it produces and secretes 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 people with obesity 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, chemerin, 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**

MAFLD, 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 course of the disease 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 21.9% in the United States and 31% in Asia. Visceral and subcutaneous adipose tissues are the location of most abundant fat deposit with distinct adipokine profile[11].

**Role of adipokines 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 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 MAFLD. 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 tissue and 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 diseases. 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/diagnosis, 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 fat, as these molecules also seem to drive the progression of liver injury in patients with severe 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, cholangiocarcinoma, pancreatic cancer, and others may specifically alter the adipokine profile in body tissues[19,20]. MAFLD is a chronic liver inflammation affecting 30% of all populations, with 40% 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), apnea, lung cancer, gastrointestinal tract tumors, chronic kidney disease, cervical cancer, ovarian cancer, and polycystic ovary syndrome[23,24].

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