**Metabolic Fatty Liver Disease is also a Metabolic Disease of the Heart**

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:970 No. 198, Minde 1st Street, Hualien city

Tel: 0928-698950

E-mail: guppy5230@yahoo.com.tw

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**Abstract**

According to the WHO’s report, the number of people with diabetes worldwide is increasing, and the prevalence of type 2 diabetes in adults who is over 18-year-old has risen from 4.7% in the 1980s to 8.5% in 2014. Among them, the prevalence of diabetes in low- and middle-income countries has even reached as high as 9.3% over the decades. Metabolic associated fatty liver disease (MAFLD) is not only affecting the liver but is also considered a problem for the heart, as there is about 25% of the patients suffering from cardiovascular syndrome.

Keyword: metabolic syndrome; cardiovascular disease; metabolic fatty liver disease; low-density cholesterol; insulin resistance.

**Introduction**

Metabolic fatty liver disease is one of the common clinical diseases, with its incidence on the rise on an annual basis, especially observing a dramatic increase since 1980s when Ludwig and his colleagues first reported an unknown non-alcoholic fatty liver disease to be a risk factor for cardiovascular problems. The disease affects as many as 25% of the adult population in the world. It is often associated with obesity, type 2 diabetes mellitus, atherosclerotic dyslipidemia, and metabolic syndrome. Metabolic fatty liver often develops into metabolic steatohepatitis (NASH), cirrhosis or even cancer, making it a primary root to many other liver diseases; for example, patient in the end-stage of the disease needs liver transplantation or may die from cancer development1-5. The hypothesis is that metabolic fatty liver disease shares common risk factors with some of cardiovascular problems, such as atherosclerotic dyslipidemia, hypertension, type 2 diabetes, and metabolic syndrome, all of which can be attributed to insulin resistance, since it is closely related to the accumulation of fats outside the liver in a body. The fat accumulation, such as at the epicardial adipose tissues, is known to exacerbate the development of cardiovascular diseases, supporting the notion that patients with metabolic fatty liver are at an increased risk of cardiovascular diseases. The disease will therefore require interventive treatment at medical institution. To diagnose the disease, biopsy of liver tissues is needed, which makes the process a bit more difficult to proceed, even though laboratory test and abdominal ultrasound are available to “observe” the condition, especially the invasive procedure is likely to aggravate the liver condition and increase the risk of cardiovascular event at the same time. But nevertheless, to diagnose the liver disease and determine its severity, biological indicator via ultrasound and histopathological examination to identify fibrosis in the liver will help to evaluate the risk of atherosclerosis and the likelihood to develop into cardiovascular disease, as well as helping to identify the presence of metabolic fatty liver or steatohepatitis in patients6,7.

**Clinical Features of Metabolic Fatty Liver**

The common causes of metabolic fatty liver include obesity, hypertriglyceridemia, abnormal blood sugar metabolism (diabetes), overnutrition, etc. The disease has no specific clinical symptom and there is no subjective complaint that anyone can put into words to describe, but it is mostly discovered during annual general medical examination. Metabolic fatty liver can only be defined as a condition where various hepatic indices are elevated but without the presence of hepatitis B, hepatitis C, viral infection, drug use, alcohol consumption, or other known causes of chronic liver diseases8-10. Also, metabolic fatty liver can be identified as lean when BMI is less than 23kg/m2. This will contrast with the healthy population and the overweight population in terms of metabolic profile, as the patients of metabolic fatty liver disease will show different body composition than others11,12.

**How Metabolic Fatty Liver Affects Cardiovascular Health** Hormones secreted by fat cells, primarily by white adipose tissues (WAT) and brown adipose tissues (BAT), are known to exert different effects on organs and tissues. Adiponectin, which is an essential compound for maintaining the glucose homeostasis, insulin sensitivity and organ function during chronic inflammation, is downregulated in obesity. The hormonal axes that are in charge of suppressing appetite, improving peripheral insulin resistance, increasing body temperature, and circulating levels of leptin will regulate the total adipose tissue mass. Adipsin is an important protein of adipose cells and functions in an alternative complementary pathway to stimulate insulin secretion through C3a receptors on β-cells. Elevated plasma level of the lipid chaperone fatty acid-binding protein 4 (FABP4), as a result of obesity, will increase hepatic gluconeogenesis, peripheral insulin resistance, and arterial plaque formation. On the other hand, the level of anti-inflammatory palmitoleate is reduced in obesity13-16.

**Diagnosis of Metabolic Fatty Liver Disease**

Patients of metabolic fatty liver disease and coronary heart disease may also suffer from chronic inflammation. The high sensitivity c-reactive protein (hs-CRP) can be used clinically to predict the risk of cardiovascular disease or serves as an index of severity for metabolic fatty liver disease. Several clinical studies have already proven that hs-CRP is an independent risk predictor of myocardial infarction, ischemic cerebral infarction or peripheral arterial disease. However, when screening for cardiovascular diseases in the healthy population using hs-CRP, the result was the opposite, showing no correlation between the two, as the later studies eventually proved that the correlation between hs-CRP and cardiovascular diseases would vary among the categories of population, specifically indicating the protein to be used only for people with high risk of cardiovascular conditions, such as myocardial infarction, arrhythmia, diabetes, hypertension and installment of pacemaker, rather than being used as a general screening tool. The process of atherosclerosis involves a low-grade systemic inflammatory response; thus, it is speculated that inflammatory compounds may well play a role in predicting the risk of cardiovascular diseases. The American Heart Association and the US Center for Disease Control and Prevention (AHA/CDC) jointly published a report, recommending three categories of hs-CRP as low, medium and high (respectively, with value of <1, 1-3, and >3mg/L) in terms of risk of cardiovascular diseases17-20.

**Non-drug Treatment of Metabolic Fatty Liver**

Losing weight and increasing physical exercise are currently the only effective treatment for fatty liver because it turns out to be a reversible condition. Regular physical exercise not only burns calories but will also increase the sensitivity of body tissues to insulin and reduce insulin resistance. Moreover, empirically, there is just no specific drug for targeting metabolic fatty liver21.

**The Prognosis**

Cardiovascular disease is the leading cause of death in Europe and the United States, not to mention other parts of the world, too. Potentially modifiable risk factors of cardiovascular diseases include smoking, sedentary lifestyle, high blood pressure, elevated LDL/cholesterol, and other metabolic risk factors. By realizing the relationship of metabolism with cardiovascular events, the focus on eliminating metabolic disorders has significantly reduce the mortality rate. However, the majority of the world population has yet to control the related risk factors, despite that they have been well recognized by the public, especially the increasing prevalence of obesity and type 2 diabetes have actually undermined the effort to promote health around the world. In fact, in the United States alone, approximately two-thirds of adults are overweight or obese when we already know that even moderately overweight is associated with a significantly increased risk of cardiovascular disease-related death. Intervention by changing the lifestyle to lose weight can truly reduce the risk of cardiovascular diseases, but it is often quite difficult for people to maintain the habit in long-term22-24. The increased prevalence of obesity has also led to a marked increase in the prevalence of other important cardiovascular risk factors, including hypertension, dyslipidemia, insulin resistance, and type 2 diabetes. Pharmacotherapies are currently available to address each risk factor, such as endocannabinoid receptor antagonists, inhibitors of peroxisome proliferator-activated receptor subtypes alpha and gamma, and several other drugs that modulate the activities of glucagon-like peptide-1. These new drugs have the potential to significantly improve several cardiovascular risk factors25,26.

**Conclusion**

Because non-alcoholic fatty liver disease, by definition, must exclude other possibilities that are attributable to alcohol consumption and liver conditions, this type of disease is not easy to diagnose. Recently, some experts proposed a new concept of diagnostic standard, placing an emphasis on the presence of a “fatty” liver with any one of the following conditions, including overweight/long waistline, type 2 diabetes, or evidence of metabolic abnormalities, such as high blood pressure, high triglycerides, low high-density cholesterol, pre-diabetic condition, insulin resistance and increased C-reactive protein. Since most patients with fatty liver are asymptomatic, which makes it difficult to detect the condition, physician can only observe through abnormal liver function, blood routines and abdominal ultrasound. Plus, liver fibrosis scan, abdominal magnetic resonance imaging and other examinations can also assist in the diagnosis. Currently, the gold standard for diagnosis is still the liver biopsy.

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