Review Article

Biomarkers, Biocatalysts, or Pathology Conditions to Evaluate Potential History of Liver Disease such as Cancer

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Abstract

Previous publications reported that around 1.5 million individuals suffer from chronic liver disease. Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of related death worldwide. A recent study in Isfahan province, Iran confirmed a period prevalence (2013-2015) of 18.5 per 100000 persons associated with liver cancer (comprise of 20.9 for males and 16.8 for females). It is well known that different available screening methods could reduce the burden of liver disease and liver cancer. This is a focused literature review with the keywords relevant to; *Biomarkers*" *" Biocatalyst " "Pathology" "Potential History*" *"Liver Disease*" and *"Liver Cancer*", based on the search associated with the topic of interest in; Pubmed, Scopus, and Web of Science. For hepatocellular carcinoma, early detection ultrasound-based surveillance was reported as 45%. Alpha-fetoprotein-Lens culinaris-agglutinin-reactive and des-gamma-carboxy prothrombin with abdominal ultrasound could increase the sensitivity of early detection in patients with hepatocellular carcinoma. A raised neutrophil-to-lymphocyte ratio is considered a prognostic indicator for patients with cancer. Serum alanine *aminotransferase* for predicting progression associated with chronic liver disease was reported as a more sensitive and robust marker. For estimating the overall mortality, serum alanine *aminotransferase*, aspartate transaminase, and γ-glutamyl transpeptidase confirmed clinically economic markers. High-quality imaging, MRI, and in some patients guided biopsy proposed. For early prevention of liver disease, regional anthropometric measures based on the; fat index (arm, hip, and waist circumference) besides body mass index, age, and *alanine aminotransferase suggested values*. Further evidence-based pharmacotherapy studies are recommended to be advantageous.

Keywords: *Biomarkers, Biocatalyst, Pathology, Liver disease, Liver cancer*

Introduction

The burden of liver disease in Iran is increasing, as about 5400 deaths were reported due to chronic liver disease in 2017.[1] Publications confirm that 1.5 billion persons have a chronic liver disease which accounted for 62% of death in 2015 in the Asia Pacific region.[2, 3] Metabolic liver disease also defined as fatty liver disease, is associated with inborn metabolism faults that involve hepatomegaly or hepatic dysfunction. Due to inadequate investigations, poor awareness, and lack of definitive diagnostic tests, its' identification is difficult.[4] In all types of human liver disease, hepatocyte death is evident in the form of apoptosis, necrosis, necroptosis, autophagy, pyroptosis, and ferroptosis displayed by inflammation, fibrosis cirrhosis, and hepatocellular carcinoma.[4, 5] Indeed apoptosis is the shared topographies of fatty liver disease that is extremely prearranged by a biochemical process such as aspartate-specific proteases identified as caspases. Intrinsically or extrinsically, apoptosis is triggered by the killer caspases 3 and 7.[6] Destruction of DNA, starvation, or oxidative stress can stimulate the entire apoptotic lining. The noninvasive detection methods for non-alcoholic fatty liver disease (NAFLD) involved the measurement of biomarkers in samples or physical approach by ultrasound or magnetic resonance-based elastography methods.[7] As a result, biomarkers such as serum alanine *aminotransferase* (ALT), in addition to liver-specific mortality, exhibited as a sensitive marker in the prediction of progression associated with chronic liver disease and cardiovascular disease. Aspartate transaminase (AST) and γ-glutamyl transpeptidase (GGT) are connected with overall mortality but do not precisely imitate liver-linked deaths.[8] This review aimed to investigate economic and reliable biochemical, biocatalyst, or pathologic conditions to evaluate the potential history of liver diseases such as

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NAFLD and cancer.

Materials and Methods

This is a targeted, focused review of the literature. Any disturbance of the liver, such as tumors (benign or malignant), cirrhosis (scarring), inflammation (hepatitis), metabolic disorders (such as NAFLD), and any other reasons that affect the function of the liver could cause liver disease. A biomarker is an indicator of normal biological or pathogenic processes and a biocatalyst is an enzyme that could initiate or intensify the rate of reaction.

Therefore, we searched databases to locate all existing articles associated with biomarkers, biocatalysts, or pathology conditions to evaluate the potential history of liver disease published between 1998 and 2021 in electronic form. Excerpta Medica (EMBASE), Google Scholar, Pubmed (NLM) (article attributed to associated data), Scopus (title, abstract, keywords), and Web of Science (basic search, topic) were searched. With the keywords relevant to; " *Biomarkers*" *" Biocatalyst " "Pathology" "Potential History*" *"Liver Disease*" *"Liver Cancer*", the exact search questions were; 1) evaluation of potential history of Liver Disease (Pubmed; 37694 articles, June 2021 to July 2011) (Scopus; 317 articles, June 2021 to 2003) and (Web of Science; 148 articles, July 2021 to October 1998), 2) biomarkers for evaluation potential history of liver disease (Pubmed; 13117 articles, June 2021 to July 2011) (Scopus; 29 articles, June 2021 to 2009) (Web of Science; 9 articles, April 2021 to March 2013), 3) biocatalyst for evaluation potential history of liver disease (Pubmed; 10785 articles, June 2021 to July 2011) (Scopus; no documents were found) (Web of Science; no documents were recorded), 4) pathology conditions to evaluate potential history of liver disease biomarkers (Pubmed; 2951 articles, June 2021 to July 2011) (Scopus; 4 articles, June 2020 to December 2015) (Web of Science; no documents were recorded), 5) biomarkers, biocatalyst or pathology conditions to evaluate potential history of liver disease (Pubmed; 80965 articles, June 2021 to July 2011) (Scopus; no documents were found) (Web of Science; 21 articles, October 2020 to May 2014). In the next step, 38 knowledgeable assortments of relevant, high-quality manuscripts on the topic of thought were selected.

Results and Discussion

(Figure 1) shows biomarkers, biocatalysts, or pathologic conditions for evaluating potential history associated with liver disease such as cancer. A shared pathological progression of all chronic liver diseases is fibrosis. Regarding various liver diseases, pathological progressions could be due to oxidative stress, apoptosis, steatosis, necroinflammation, and fibrosis.[9] Extremely stimulated neddylation and vastly expressed NAE1, UBC12 and ROC1 have been detected in the tissues of liver cancer patients.[1] Pathologic conditions of the excess production of the extracellular matrix could lead to fibrosis and cirrhosis. Fibrosis is related to liver sinusoidal endothelial cells that produce large amounts of anti-inflammatory cytokines, such as transforming growth factor-beta. In cirrhosis, liver sinusoidal endothelial cells regularly alter to a vascular sort with a basement sheath, which restricts the bidirectional exchange of molecules.[10] The first sign of the liver disease is associated with pathologic progression and pattern of the underlying disease process that could be seen in abnormal laboratory results. Under pathological conditions, the hypoxic status might promote lipid synthesis by increasing the levels of lipogenic enzymes such as fatty acid synthase, glucose-6-phosphate dehydrogenase, and acetyl-CoA carboxylase. This process may reveal a state of metabolic stress in the adipocytes. De novo lipogenesis (DNL) is the primary metabolic pathway synthesizing fatty acids from carbohydrates, protein, or alcohol. The generation of fatty acids, recognized as a biocatalyst through lipogenesis, from carbohydrate, alcohol, or protein (fatty acid synthase), that is accompanied by a multi-enzyme protein. In fact, in hepatic steatosis but not inflammation its' transcriptional induction is impaired.[11] In an animal model, tritiated water over a short period was associated with incorporating the labeled water into newly generated cholesterol and fatty acids.[12]

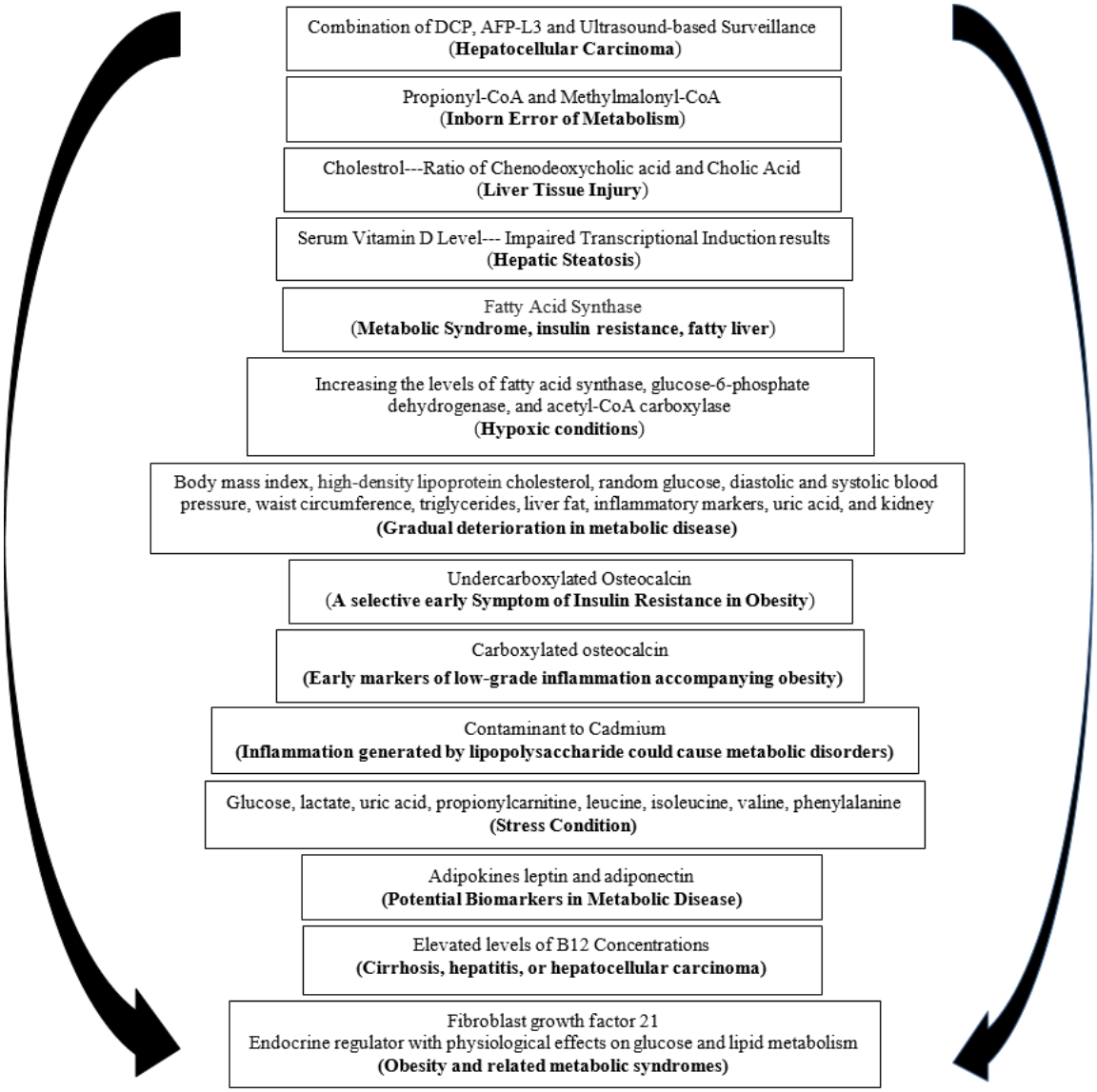

Figure 1. Biomarkers, Biocatalysts, or pathologic conditions to Evaluate Potential History of Liver Disease.

Another pathologic state is the situation that causes an undercarboxylated form of osteocalcin (which takes part in energy metabolism) to increase as carboxylated osteocalcin. Reduced blood concentration of the undercarboxylated form may be a selective early symptom of insulin resistance in obesity. In contrast, the decreased level of carboxylated form seems to be associated with initial signs of low-grade inflammation accompanying obesity.[13] Stress condition as a pathologic condition could cause cellular senescence and growth arrest strongly associated with aging that is aberrantly activated by obesity.[14] For liver pathologies and liver damage such as hepatocellular carcinoma, cirrhosis, and hepatitis, elevated vitamin B_{12} concentrations have been reported as another biomarker.[15]

The deficiency of biomarkers such as methylmalonyl-CoA mutase or propionyl-CoA carboxylase could cause inborn errors of metabolism.[16] In animal models with liver injury, serum histone levels were reported to be raised significantly. Then the released histone bind to toll-like receptors that hastens inflammatory responses. [17, 18] Another biomarker for early detection of metabolic liver disease is the cholesterol ratio of chenodeoxycholic acid or cholic acid.[19, 20] In addition, serum vitamin D levels as another biomarker that could connect to a lower risk of metabolic syndrome, insulin resistance, and fatty liver; however, was reported a higher risk of coronary artery calcification in men and not in women.[21] An abnormal protein called DCP that is produced due to insufficient vitamin K has a sensitivity of around 50% for early detection of hepatocellular carcinoma. The combination of DCP and AFP could increase the sensitivity to 80%. Relevancy, feasibility, and economic tackles included; body mass index, high-density lipoprotein cholesterol, random glucose, diastolic and systolic blood pressure, waist circumference, triglycerides, liver fat, inflammatory markers,

uric acid, and kidney function that gradually deteriorate in patients with metabolic disease.[2, 13, 14, 18, 22] Due to the secretion of many adipokines, such as inflammatory and anti-inflammatory cytokines, adipose tissue could be considered a critical regulator of systemic metabolism. Environmental factors for the detection of metabolic disorders are contaminants of cadmium. That could be linked to metabolic complaints associated with inflammation generated by lipopolysaccharide.

Biomarkers such as glucose, lactate, uric acid, propionyl carnitine, leucine, isoleucine, valine, and phenylalanine are potential molecular markers in plasma/serum and urine that change in patients with metabolic disease. Certain hormones released by the adipose tissue, such as the adipokines leptin and adiponectin, interact in modulating T_2D risk. However, adiponectin is more closely associated with T_2D risk. [23-25] Fibroblast growth factor 21 (FGF21) is a potent endocrine regulator with physiological effects on glucose and lipid metabolism. It thus saves much attention for its translational potential for the management of obesity and related metabolic syndromes. FGF21 is mainly expressed in several metabolically active tissue organs, such as the liver, adipose tissue, skeletal muscle, and pancreas, with profound effects and therapeutic relevance.[24] To detect stage 1 and 2 fibrosis in overweight patients with non-alcoholic fatty liver disease; BMI (BMI≥28 = 1 point), age at liver biopsy (≥50 years=1 point), ALT (≥2 =1 point and serum triglycerides (≥1.7 mmol/L =1 point).[26]

In the year 2018, an estimated 782,000 deaths were reported worldwide due to liver cancer.[3] With an estimated prevalence of 25%, NAFLD is a growing global public health that is connected with the disease of the liver and cancer. The highest prevalence rates of NAFLD are reported in the Middle East (31.8%), and South America (30.4%), and the lowest is in Africa.[15] Insulin resistance and systemic hypertension independently were associated with the advanced forms of NAFLD.[26] There is a link between NAFLD and the risk of colorectal adenomas and cancer, intrahepatic and extrahepatic cholangiocarcinoma, and prostate, gastric, breast, pancreatic, and esophageal cancer.[27] In those with chronic hepatitis B virus infection, a baseline level of greater than 100,000 copies/mL increases the risk of (hepatocellular carcinoma) HCC 10-fold.[28]

In association with detection methods, circulating keratine 18 fragments could be considered as a direct hepatocellular damage measurer' for diagnosing or grading steatosis fatty liver index and staging NAFLD disease fibrosis score (NFS).[8] There is a strong pathogenic link between NAFLD and central obesity. The pro-inflammatory adipokine (leptin) secreted by visceral fat is related to increased blood pressure, dyslipidemia, and insulin resistance. Metabolic disorders in obese patients are associated with high pro-inflammatory adipokine (leptins) and reduced levels of anti-inflammatory adipokine (adiponectin). Waist circumference, waist-to-height ratio, and waist-to-hip ratio are the surrogate markers of abdominal obesity.[29, 30] Several studies have shown that metabolic syndrome can be predicted using these anthropometric indices.[31, 32]

A regional study of 5023 adult individuals showed that the prevalence of NAFLD and metabolic syndrome was 43.8% and 29.6%, respectively. Both diseases were significantly more prevalent in women. The strongest predictors of NAFLD in men were waist circumference>102 cm, serum ALT ≥40 (U/L), and the age group of 40-60 years. The waist circumference was greater than 88 cm in women, and the age groups of 40-60 and >60 years were the most common.[33-35] In children, a single report suggested that 41 million obese children under the age of 5 and about 340 million children and adolescents aged 5-19 reported being overweight.[19] In advanced fibrosis with portal hypertension, thrombocytopenia and high levels of aspartate aminotransferase may be used as indirect markers of non-alcoholic fatty liver disease. Other groups reported that cytokeratin 18 could be used as a direct biomarker of severity and liver fibrosis. However, it has a low sensitivity and specificity.[31] Obesity, lack of physical activity, low consumption of fruits and vegetables, and diets rich in carbohydrates and fats play a vital role in developing hepatic steatosis. Moreover, as metabolic syndrome components, hypertension, and diabetes mellitus exhibit a significant association with non-alcoholic fatty liver disease. In addition, arm fat index, visceral fat, and total body fat show that regional anthropometric measures are associated with the severity of non-alcoholic fatty liver disease in a sex-specific manner. Men and women with lower arm fat and women with a bigger waist circumference could have a greater likelihood of liver injury.[14, 26, 36]

Conclusion

AFP-L3 (Alpha-fetoprotein-Lens culinaris-agglutinin-reactive) and des-gamma-carboxy prothrombin (DCP) with abdominal ultrasound could increase the sensitivity of early detection in patients with hepatocellular carcinoma. In addition to the development of novel biomarkers, contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and contrast liver ultrasound recommended for early detection in which ultrasound-based surveillance were reported as 45%. A raised neutrophil-to-lymphocyte ratio is considered a prognostic indicator for patients with cancer. Regarding the development of hepatocellular carcinoma, screening for hepatitis B and C is recommended to be important. In overweight patients, fat index (body mass index, arm, hip, and waist circumference), age and *alanine aminotransferase should be considered valuable markers.* Education and awareness among clinicians and pharmacists concerning the screening methods and evidence-based pharmacotherapy are required in future guidance for early recognition and management of liver disease and liver cancer.

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Conflict of interest

None.

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Ethics statement
None.

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