Review Article

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Impact of obesity on liver function tests: is nonalcoholic fatty liver disease the only player? A review article

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Abstract

Objectives: Obesity and nonalcoholic fatty liver disease (NAFLD) are common worldwide health problems with a strong relationship in between. NAFLD is currently the most common cause of abnormal liver function tests (LFT) because of obesity pandemic. The question is NAFLD the only player of abnormal LFT in obesity?

Methodology: This article reviews the most important topics regarding the derangements of LFT in obesity through a PubMed search strategy for all English-language literature.

Results: The reported abnormal LFT in obesity were increased serum levels of transaminases (alanine aminotransaminase, aspartate aminotransaminase), gamma glutamyl transferase, and alkaline phosphatase and decreased serum levels of bilirubin and albumin. Besides novel potential hepatic markers of NAFLD/NASH such as triglycerides/high-density lipoprotein cholesterol ratio, sex hormone–binding globulin, fibroblast growth factor 21, and markers of hepatocyte apoptosis i.e. cytokeratin 18 and microribonucleic acids (miRNAs). Beyond NAFLD, there are other underlying players for the abnormal LFT in obesity such as oxidative stress, inflammation, and insulin resistance.

Conclusion: Derangements of LFT in obesity are attributed to NAFLD but also to obesity itself and its related oxidative stress, insulin resistance, and chronic inflammatory state. Abnormal LFT predict more than just liver disease.

Keywords: obesity, nonalcoholic fatty liver disease, liver function tests

Background

Obesity and nonalcoholic fatty liver disease (NAFLD) are common worldwide health problems with a strong relationship in between.[1-3] Traditionally, liver function tests (LFT) including liver enzymes (alanine aminotransaminase [ALT], aspartate aminotransaminase [AST], alkaline phosphatase [AP], and gamma glutamyl transferase [GTT]), serum bilirubin, albumin, and international normalized ratio (INR) are used to guide the diagnosis and management of liver diseases.[4] NAFLD is currently the most common cause of abnormal LFT because of the pandemic of obesity.[5] However, beyond NAFLD, there are other underlying players related to obesity such as oxidative stress, inflammation, and insulin resistance (IR).

The present article reviews the most important topics regarding the derangements of LFT either traditional or novel hepatic markers in obesity with focus on NAFLD and other underlying players related to obesity through a PubMed search strategy for all English-language literature until May 1, 2023 (Fig. 1).

Review

Obesity (body mass index [BMI] ≥30) is a state of excess storage of body fat resulting from a chronic imbalance between energy intake and energy expenditure. Over the last decades, obesity and its consequences have become a major worldwide health problem. According to WHO, approximately 39% of adults are overweight, and 13% are obese.[1] NAFLD is another common worldwide disease; it has emerged as a growing global public health concern with a rising prevalence reaching up to 25%.[2,6] NAFLD is defined as a significant accumulation of lipids (5%–10%) in liver tissue in the absence of a significant chronic alcohol consumption, a viral infection, or any other specific cause of liver disease.[7] It has a wide disease spectrum of histology, ranging from nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), bridging fibrosis, to cirrhosis and hepatocellular carcinoma.[8] NAFLD is redefined in 2020 by an international expert consensus as a metabolic-associated fatty liver disease (MAFLD); MAFLD was diagnosed if there is an evidence of hepatic steatosis by imaging, blood biomarkers/scores or histology, plus one of the three conditions: overweight/obesity or T2D or the presence of metabolic risk abnormalities.[9] Patients with NAFLD, especially those with NASH, carry high risks for hepatic and extrahepatic diseases such as cardiovascular disease (CVD), chronic kidney disease, and endocrine disorders i.e. type 2 diabetes (T2D), metabolic syndrome (MS), IR, and thyroid dysfunction.[2,8,10-12] The strong association between NAFLD and obesity is well established[2,3] which can be explained by increased portal flow of fatty acids,[13] decreased hepatic fatty acid

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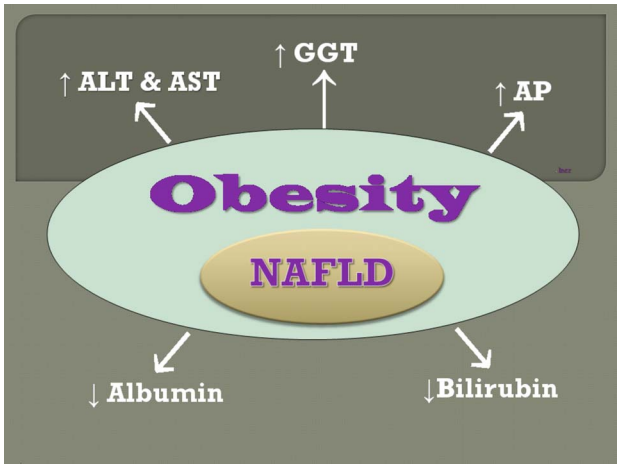

Figure 1. Derangements of liver function tests in obesity. ALT = alanine aminotransaminase; AP = alkaline phosphatase; AST = aspartate aminotransaminase; GGT = gamma glutamyl transferase; NAFLD = nonalcoholic fatty liver disease.

oxidation, increased hepatic lipogenesis,[14] and secretion of proinflammatory cytokines.[15]

Liver is the largest gland in the human body and plays a pivotal role in numerous physiological functions and metabolic homeostasis such as bile production and bilirubin, fat, protein, and carbohydrate metabolism. LFT including liver enzymes (ALT, AST, AP, and GTT), serum bilirubin, albumin, and INR are traditionally used to guide the diagnosis and management of liver diseases.[4] However, abnormal LFT has been found in 7%–9% of asymptomatic healthy adults without identifiable cause.[16] Derangements of LFT have long been noticed in subjects with obesity because of the high prevalence of NALFD and its consequences.[17] Therefore, NAFLD is currently the most common cause of abnormal LFT in particular, increased levels of transaminases.[5]

Liver function tests in obesity

Liver enzymes

ALT and AST. ALT is an enzyme mainly present in hepatocytes and released into the blood stream in response to liver injury, whereas AST is present in the liver and other tissues including the muscles.[18,19] NASH is typically associated with greater ALT than AST levels, and the ALT/AST ratio >1 is an independent predictor of the liver fibrosis in subjects with obesity.[20,21] Moreover, a direct relation between the degree of hepatic steatosis and the alteration in ALT has been detected in a study conducted by Briseño-Bass.[22] In a recent population-based study, the optimal ALT cut-points for diagnosing hepatic steatosis is 24.5 U/L for girls (sensitivity: 55.6%, specificity: 84.0%) and 34.5 U/L for boys (sensitivity: 83.7%, specificity: 68.2%).[23] However, it should be noted that 80% of patients with NAFLD have normal ALT levels.[24] Indeed, other reports have not found any positive association between histological findings of NASH, fibrosis, or cirrhosis and LFT abnormalities.[20,25] Therefore, the estimation of aminotransferase levels lacks sensitivity to detect NASH and specificity to predict liver injury.

Obesity per se may contribute to elevated ALT,[26] which is recognized to be associated with a worse cardiac risk profile and MS.[27] Both overweight and obesity are independent predictors of abnormal LFT in children and young people, irrespective of ALT threshold; however, they are independent predictors of ALT testing in young people but not in children.[28] Furthermore, waist circumference is a strong predictor of liver enzyme levels.[29]

AP. The serum concentrations of hepatic AP are of major clinical relevance as a marker of cholestasis, and it has long been widely used in the diagnosis of hepatobiliary disease. It is worth mentioning that obesity directly affects gall bladder and biliary system as it increases the incidence of cholelithiasis, cholesterolosis, and cholecystitis.[30,31] Excess hepatic secretion of cholesterol and subsequent super saturation of bile[32] are responsible for significant increase in gallbladder volume and decrease contractility in obesity.[33]

Beyond hepatobiliary disease, AP is elevated in NASH and may be considered as a risk factor for hepatic fibrosis.[34] Indeed, AP is often elevated in subjects with obesity, and its levels are decreased after bariatric surgery.[35] Significant correlations between serum AP levels and the whole body fat mass and IR have been also detected.[36] Interestingly, AP may be considered as a marker of visceral obesity and subclinical inflammation.[37] On the other hand, inhibition of AP activity in adipocytes by levamisole reduces lipolysis and expression of various lipogenic genes. Hernández-Mosqueira et al have been suggested that tissue-nonspecific AP activity is involved in lipid and energy metabolism of fat cells, and it may regulate glucose metabolism and insulin sensitivity by adipokine synthesis and secretion.[38] Finally, AP is a strong predictor of poor health outcomes with a greater risk for mortality and CV events in older adults with obesity.[39,40] The atherogenic characteristic of AP is attributed to increased pyrophosphate hydrolysis, a potent inhibitor of vascular calcification, and the induction of subclinical inflammatory state.[41]

GGT. It has long been used as a marker of alcoholism and liver diseases.[42] GGT is also a surrogate marker for NAFLD and often used to monitor the progression of the disease in clinical practice.[43] Increased serum levels of GGT is associated with necroinflammatory activity,[44] and on the other hand, a positive correlation between GGT levels and hepatic histology findings has been found after weight loss.[43,45] In addition, a close association between elevated GGT and obesity has been postulated.[46,47] Recently, a high GGT level has been considered as a sensitive and early biomarker of unfavorable body fat distribution.[48] Elevated GGT is associated with oxidative stress,[49] IR,[50] and markers of chronic inflammation[41,51] which are associated with obesity. GGT is also recognized as a potential predictor of CVD and mortality.[52]

Bilirubin

Bilirubin is the end product of normal heme catabolism. Abnormally elevated serum bilirubin level serves as a marker of hepatobiliary disorders,[53] and it has long been considered as a harmful waste product to the central nervous system.[54] A link between bilirubin and cardiometabolic outcomes has been identified with positive health effects of mild hyperbilirubinaemia.[55] Bilirubin is a strong antioxidant, anti-inflammatory, and immune regulatory product[56] through scavenging reactive oxygen species (ROS).[57]

There is a considerable evidence supporting the association of low bilirubin levels with obesity.[58,59] The reduced bilirubin levels in adiposity state may be due to its increased consumption

to compensate for increased oxidative stress[60]; therefore, bilirubin may be a marker for future CVD in subjects with obesity.[61] On the other hand, hyperbilirubinemia protects against the development of obesity because it reduces visceral obesity and IR by suppression of inflammatory cytokines.[62] Bilirubin directly activates PPARα, which increases target genes to reduce adiposity and decrease de novo lipogenic enzymes.[62] Indeed, intracellular bilirubin inhibits NADPH oxidase activity,[63] the enzyme responsible for increased oxidative stress production from hypertrophied insulin resistant adipocytes.[64] Bilirubin also improves insulin sensitivity at least in part by suppressing endoplasmic reticulum stress and chronic inflammation in adipose tissue and liver.[65] Bilirubin may be a potential target for novel therapies to protect against IR in patients with visceral obesity and diabetes.

In addition, an inverse association between serum bilirubin levels and hepatic steatosis has been previously reported.[66] Beside its antioxidant and anti-inflammatory actions, bilirubin may protect against hepatic steatosis through activation of PPARα and its associated pathways that promote β-oxidation of fatty acids and decrease fatty acid synthesis.[62,67] Recently, it has been demonstrated that the bilirubin nanoparticles significantly reduce hepatic fat, triglyceride accumulation, de novo lipogenesis, AST, and apoB100 through activation of the hepatic β-oxidation pathway by increasing PPARα and acyl-coenzyme A oxidase 1.[68]

Albumin

Albumin concentration and prothrombin time (PT) are other sensitive biomarkers of liver function serving as indices of liver biosynthetic capacity.[69] Lower albumin levels are observed in school students with obesity compared with healthy controls. Albumin levels are also negatively correlated with BMI, mid-upper arm fat area, and body fat percentage.[70] The negative correlation between C-reactive protein (CRP) and albumin levels in subjects with obesity may indicate a low-grade inflammatory state affecting both.[71] Furthermore, obesity-related glomerulopathy may have a nephrotic-range proteinuria with a subsequent hypoalbuminemia.[72] Recently, the decline in serum albumin as a marker of malnutrition after bariatric surgery has been recognized.[73] At last, the presence of hypoalbuminemia (albuminemia <3.00 g/dl), prolonged PT, and hyperbilirubinemia together suggest advanced NASH with impaired hepatic function and liver damage.[74]

Indices used for identifying NAFLD

Although liver biopsy is the gold standard for diagnosis of NAFLD, invasiveness and its complications limit its clinical use, whereas diagnosis based on imaging studies are time-consuming, expensive, and often unavailable in addition to radiation exposure with the use of computed tomography. Therefore, surrogate markers of hepatic steatosis based on laboratory tests and anthropometric measurements have been developed.[75-77]

The fatty liver index

The fatty liver index (FLI) comprises BMI, waist circumference, serum TG, and GGT levels.[76] It has moderate accuracy in diagnosing NAFLD. FLI correlates with IR and predicts liver-related and cancer mortality.[78]

The hepatic steatosis index

The hepatic steatosis index (HSI) comprises AST/ALT ratio, BMI, sex, and presence of T2D. Although HSI was previously reported to have a moderate accuracy to detect NAFLD,[77] this marker was recently validated against magnetic resonance showing a sensitivity of 86% and specificity of 66%.[79] In addition, it has an excellent predictive performance in predicting NAFLD.[80,81]

The NAFLD fibrosis score

NAFLD fibrosis score comprises age, BMI, presence of impaired fasting glucose or T2D, AST/ALT ratio, platelet count, and serum albumin levels. It has been more extensively validated than the other scores.[82] Indeed, it predicts liver decompensation and mortality in patients with NAFLD.[83]

The Fibrosis-4 index

It comprises age, AST, ALT, and platelet count. It has a moderate accuracy in diagnosing NAFLD, whereas it is comparable with the NAFLD fibrosis score.[84]

The BARD score

It comprises BMI, AST/ALT ratio, and presence of T2D. It has a moderate accuracy in detecting F3 fibrosis.[85]

The FibroTest

It comprises serum levels of GGT, total bilirubin, alpha-2 macroglobulin (α2m), apolipoprotein A-I, and haptoglobin.[86] FibroTest was found to be better than BARD and the Fibrosis-4 index (FIB-4) in predicting fibrosis in patients with NAFLD.[87]

The FibroMeter NAFLD

It comprises body weight, prothrombin index, and serum levels of ALT, AST, ferritin, and fasting glucose. The FibroMeter vibration-controlled transient elastography algorithm (combining FibroMeter NAFLD and liver stiffness measurement) might improve the diagnosis of F3–F4 fibrosis versus F0–F2 fibrosis.[88]

Novel potential hepatic markers of NAFLD/NASH

Triglycerides/high-density lipoprotein cholesterol ratio. In the past few years, a close association between triglycerides/high-density lipoprotein cholesterol (TG/HDL-C) ratio and IR has been found even it has been recommended as a surrogate for IR.[89] Recently, an independent association between TG/HDL-C and NAFLD has been also reported, and TG/HDL-C may be considered as a surrogate for NAFLD.[90] TG index-related parameters may be the best choice for NAFLD risk screening in the general population.[91] IR may be responsible for the association between TG/HDL-C and NAFLD; IR promotes the secretion of larger and TG overenriched VLDL particles[92] but decreases the HDL-C. On the other hand, IR promotes NAFLD by inducing lipolysis of the adipose tissue TG and de novo synthesis of TG in the liver.[93] In addition, adiponectin decreases serum TG and increases serum HDL-C[94]; thus, the reduced adiponectin levels in NASH may lead to increased TG/HDL-C ratio.

Sex hormone–binding globulin. Sex hormone–binding globulin (SHBG), a glycoprotein produced by the liver, transports the sex hormones in the blood as biologically inactive forms. Of interest, SHBG is increasingly recognized as a hepatokine related to adverse metabolic and CVD.[95-97] Indeed, it has been recently identified as a marker of increased NAFLD risk.[97,98] The underlying pathogenesis of SHBG as a marker of metabolic alterations is not completely understood; it may be either a cause or a consequence of NAFLD.[96] Experimental overexpression of SHBG in a NAFLD model significantly reduces liver fat accumulation through PPAR$^{\gamma}$ modulation.[99]

Fibroblast growth factor 21. Fibroblast growth factor 21 (FGF-21) is a liver-secret hormone which has beneficial effects on lipid metabolism and hepatic steatosis.[100] Several studies have found an association between FGF-21 and NASH; however, this biomarker is modestly sensitive and specific.[101] Aberrant FGF21 signaling may be responsible for the pathogenesis and progression of NAFLD.[102,103] Pegbelfermin, a pegylated FGF21 analog, administered for 16 weeks to patients with NASH decreases hepatic steatosis evaluated by MRI.[104] Recently, a strong causal effect of FGF21 on improved lipid profile and liver function biomarkers including fibrosis has reported by Larsson et al.[105]

Markers of hepatocyte apoptosis. Cytokeratin 18 (CK18), the major intermediate filament protein within hepatocytes, is cleaved during initiation of cell death leading to extracellular release.[106,107] In patients with NAFLD, serum CK18 correlates with inflammation, ballooning, and histological improvement.[108] Nevertheless, it is not sufficiently accurate for clinical use[109]; therefore, a combination of CK18 with serum levels of apoptosis-mediating surface antigen FAS (sFAS), which is involved in the activation of the extrinsic hepatocyte apoptosis pathway, has been speculated.[110] However, further validation studies are required. More recently, the CK18 fragment has found to be a good predictor for diagnosing NASH in patients with NAFLD. In addition, the combination of the CK18 fragment level and FIB-4 index accurately and noninvasively predicts NASH.[111]

Markers of inflammation. The reported inflammatory biomarkers associated with NASH are interleukin-8 (IL-8), soluble interleukin-1 receptor 1 (sIL-1R-1), total plasminogen activator inhibitor-1 (PAI-1), and activated plasminogen activator inhibitor-1 (aPAI-1); however, aPAI-1 is the only independent predictor of NASH.[112] Ferritin is an acute-phase reactant that is commonly increased in patients with NAFLD. Moreover, an association between increased ferritin and advanced fibrosis in patients with NAFLD has been previously observed.[113] The addition of specific fibrosis biomarkers may increase its diagnostic accuracy for NASH.[114]

The link between NAFLD and chronic inflammation is a well-known issue. NAFLD affects up to 80% of obese subjects.[115] The interplay between inflammation, oxidative stress, and IR is a major characteristic in obesity.[116-118] The increased production of ROS leads to a greater hepatic lipid peroxidation[119,120]; in turn, lipotoxic mediators and intracellular signals activate Kupffer cells, which initiate and perpetuate the inflammatory response and development of fibrosis.[121] On the other hand, impairment of the hepatic insulin signaling pathway occurs as a result of increased hepatocyte apoptosis.[122] Advanced glycation end products (AGEs) abundantly expressed in obesity-related FLD leads to increased secretion of inflammatory cytokines.[123] In the liver, mitochondrial dysfunction, oxidative stress, and hepatocyte apoptosis are the key contributors to hepatocellular injury.

Microribonucleic acids. Circulating microribonucleic acids (miRNAs) are noncoding RNAs which regulate post-transcriptional biological processes such as cell growth, tissue differentiation, and apoptosis.[124] Circulating cell-free miRNAs have been proposed as potential diagnostic and prognostic biomarkers for liver injury. miRNA-21 (miR-21), miR-34a, miR-122, and miR-451 are associated with NAFLD.[125] However, further validation studies are also needed.

Although NAFLD is currently the most common cause of abnormal LFT because of the obesity pandemic, there are other underlying players related to obesity such as oxidative stress, inflammation, and IR beside obesity itself. In fact, these factors are also implicated in the development of NAFLD. Inflammation is among the most important factors which can subsequently lead to IR. Oxidant stress also plays a mediated role in the development of inflammation and IR. Breaking this vicious circle can be achieved by appropriate management of obesity.

Conclusion

Derangements of LFT in obesity are attributed to NAFLD but also to obesity itself and its related oxidative stress, insulin resistance, and chronic inflammatory state. Therefore, abnormal LFT predict more than just liver disease. It is highly important to determine this issue, and clinicians should be aware of it.

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Conflicts of interest

The author declares that she has no competing interests.

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