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Review Article

Physiological Effects of Liver Cirrhosis on Abdominal Adipose Tissue

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Abstract: Peripheral metabolic tissues such as abdominal fat cells are highly physiologically dysfunctional in liver cirrhosis, a progressive and irreversible disease with hepatic fibrosis and deformation of the liver architecture. Visceral adipose tissue (VAT) communicates with the liver bidirectionally through adipokines and free fatty acids (FFAs), and is implicated in systemic metabolism. Metabolic disturbance in the development of cirrhosis disrupts normal function of adipocytes, which is characterized by insulin resistance, on-going inflammation and perturbation in secretion pattern of various adipokines. Hepatic fat accumulation and fibrogenesis are promoted by elevated levels of circulating FFAs, enhanced lipolysis and an inflamed adipose microenvironment. Two major adipokines, leptin and adiponectin, are dysregulated that also impinge on the activation of hepatic stellate cells and add to the rate of fibrosis progression. Moreover, portal hypertension induced by cirrhosis and nutrient deficiency compound the remodeling of adipose tissue, causing fat wasting and sarcopenia. In order to identify additional metabolic targets for therapy and prevention of advance hepatic disease it is important that the interactions between the alterations induced in cirrhotic livers and the activities of abdominal fat cells be better understood.

Keywords: *Liver Cirrhosis, Abdominal Fat Cells, Visceral Adipose Tissue (VAT), Hepatic Fibrosis.*

Introduction

The whole body metabolic condition is severely disturbed by functioning hepatocyte loss and portal hypertension,15 the latter increasing in time [1]. Abdominal (especially visceral) fat is among the affected tissues through endocrine and metabolic signaling pathways, which are relevant to cirrhosis development and severity. VAT is biologically distinct from subcutaneous fat in that it functions as an endocrine organ by releasing bioactive adipokines and cytokines such as leptin, adiponectin, resisting (resistance to insulin action), IL 6, and TNF α besides being a site of energy storage as triglycerides. This circulating profile of adipokines is significantly altered in cirrhosis (leptin, a known hepatic stellate cell activator implicated in fibrosis, becomes more profibrogenic and the anti-fibrotic hormone adiponectin tends to be dysregulated) 2. In addition, cirrhosis is often associated with hyperinsulinemia and insulin resistance that disturb the normal regulation of lipolysis in the white adipose tissue. A loss of inhibitory control on fatty acid mobilization from belly fat store led to a exaggerated release of FFA. These FFAs via the portal circulation promote hepatic fat accumulation as well as inflammation steatosis and ultimately exacerbate liver disease [3]. Wasting of LBM and ABM often occur concomitantly in cirrhotic patients with portal hypertension and malnutrition. Hemodynamic changes are indeed important in driving adipose tissue dynamics, since trans jugular intrahepatic portosystemic shunts (TIPS), an intervention that reduces portal pressure, may result in weight gain, increased fat free mass and even increased muscle strength [4]. Finally, independent of insulin resistance and total body adiposity, the area of visceral fat is directly related to the magnitude of liver inflammation and fibrosis. Elevated IL 6 is linked to both adipose and hepatic disease, and with each additional unit of intraabdominal fat there is further added likelihood for steatohepatitis or fibrosis [5].

Methodology

- Patient cohort and imaging: CT scans were reviewed for studies of cirrhosis patients that had reported distributions of VAT-to-SAT ratio across Child-Pugh classifications. The variable in advanced illness which best defined redistribution as compared to the control group was the visceral-to-subcutaneous ratio (VSR) [6].
- Insulin resistance protocols: Patients with chronic liver disease, i.e., for instance those suffering from HCV-related fibrosis, also had adipose tissue-specific insulin resistance (adipo IR = FFA × insulin) or systemic

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HOMA IR measured using efforts to standardize chromatography–mass spectrometry together with metabolomic/lipidomic profiling [7].

- In vitro/ex vivo lipolysis assays: To assess depot-specific lipolytic responsiveness, fat samples (visceral and subcutaneous) were obtained from obese individuals and exposed to a lipolytic stimulus (e.g. noradrenaline), and the glycerol and free fatty acid release was measured [8].
- Adipokine analysis: Cirrhosis and metabolic indices were associated with serum and tissue levels of adipokines, leptin, adiponectin, resisting, visfatin as well as inflammatory cytokines TNF α IL 6 in cirrhotics compared to controls [9].

Results

- Redistribution of visceral fat Deposits The VSR was significantly greater among patients with Child-Pugh class C cirrhosis compared to those with less advanced disease, independent of the BMI Variable (BMI had a weak correlation to VAT%) [10].
- Adipose insulin resistance and fibrosis severity: Next, higher stages of liver fibrosis (F3–F4) as well as specific lipidomic changes such as altered ceramides and lysophosphatidylcholine levels were significantly associated with higher Adipo IR in patients with CLD/HCV [11].
- Depot-specific lipolysis: In comparison with SAT, visceral adipocytes from subjects with 'high' liver fat content exhibited nearly two-fold higher peak glycerol and FFA release levels in response to lipolytic agents, indicating enhanced visceral lipid mobilization during liver fat deposition [8].
- Adipokine alterations: Patients with cirrhosis displayed perturbed adipokine patterns, as evidenced by enhanced leptin and pro-inflammatory cytokines (which drive fibrogenic signaling) and reduced levels of adiponectin in advanced disease; visfatin showed variations by etiologies, which were overall linked to HSC activation and hepatic inflammation [12].

Discussion

- Hepatic pathophysiology versus VAT: a mechanism-based relationship Replacement of the liver with non-parenchymal connective tissue in patients with cirrhosis is thought to result from direct detrimental effects of fatty acids and toxic inflammatory substances carried by the portal vein system (the ‘portal overflow’ theory) [9].
- Altered metabolism and insulin resistance in adipose tissue: The inability of adipose tissue to suppress lipolysis by insulin is accompanied by increased Adipo IR and can lead to hepatic and systemic metabolic abnormalities. The severity of fibrosis is also associated with lipidomic markers [13].
- Adipocytokine-induced hepatic stellate cell (HSC) activation: leptin induces HSC activation and proliferation and the perpetuation of pro-fibrogenic matrix; whereas adiponectin inhibits these effects via a pro-apoptotic pathway and matrix degradation, which in imbalance accelerates HFs [14].
- Adipose depot relocalization independent of BMI increase: In end-stage cirrhosis, visceral adiposity increases without an accompanying gain in total fat, reflecting a preferential VAT accretion and selective hypertrophy in the context of modified metabolic signaling and systemic inflammation [10].
- Complexities of visfatin: Circulating visfatin offers paradoxical results Even though elevated levels of circulating visfatin promote HSCs supporting inflammation and fibrogenesis in HBV-related disease, other findings show that it is lower in cirrhosis independent of the cause [12].

Conclusion

Dramatic body fat redistribution from subcutaneous to omental depot is induced by established liver cirrhosis: visceral adipocytes hypertrophy, becoming insulin-resistant and hyper-lipolytic, resulting in FFA release that ultimately increases hepatic FFA uptake; moreover dysregulated production of adipokines promote hepatic inflammation and fibrosis directly activating stellate cells. By this inter-tissue cross-talk a vicious cycle of disrupted metabolism and worsening liver injury is established.

Recommendations

1. Clinical implication: For assessing body fat distribution in cirrhotics, one should use imaging-based indices such as VSR (by CT/MRI) instead of BMI.
2. Targeting adipose dysfunction with therapy:

a. The hepatic fat burden could potentially be alleviated by agents that are designed to inhibit lipolysis in visceral adipocytes (e.g. pharmaceutical interventions targeting the lipolytic cascade and/or hepatokines like Activin E.

b. Fibrogenesis may be retarded by means of restoration of the balance of adipokine profiles (e.g., enhancing adiponectin activity or inhibiting leptin/visfatin signaling).

3. Metabolomic biomarkers: adipo-IR, ceramide species and lysophosphatidylcholine in chronic liver disease can be used as noninvasive markers of the extent of fibrosis and metabolic risk.

4. Comprehensive metabolic management: The primary focus of any therapy for cirrhosis should be on holistic, multimodality treatment, which should aim for integrated targeting at inflammation, GLA signaling, insulin sensitivity and nutrition.

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