The Identification of Avoidable Risk Factors for Developing Small for Size Syndrome in Patients Undergoing Major Liver Surgery and Transplantation

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To all those God blessed me with,

My Beloved Wife Fatma,

My Lovely Sons

Khaled and Ali

And

My Great Parents

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Abstract

When a live transplant patient receives a small volume of graft, the postoperative liver function is not optimal. This is described as small-for-size live syndrome (SFSS), SFSS is a recognizable clinical condition after major liver surgery (transplantation & resection), characterised by postoperative liver dysfunction/failure. Overcoming this condition will allow us to transplant smaller livers into larger patients without major complications. This will encourage living donors to donate a smaller part of their liver to their sick relative with less risk to the donor, as well as a good outcome for the recipient. This study aims to understand the mechanism of the condition. This research assesses the relationship between portal pressure and the outcome of major live surgery , which might lead to the modification of surgical techniques in order to overcome SFSS.

Key Words : Liver surgery - Transplant - Dysfunction - Failure.

List of Abbreviations

Alanine aminotransferase (ALT)
Alanine aminotransferase ratio (AAR)
Alcoholic liver disease (ALD)
Apolipoprotein A (apoA)
Asialoglycoprotein (ASGP)
Aspartate aminotransferase (AST)
AST-to platelet ratio index (APRI)
Blood volume (BV)
Body surface area (BSA)
Cardiac output (CO)
Cardiotrophin (CT)
Central venous pressure (CVP)
Chemotherapy associated steatohepatitis (CASH)
Child-Turcotte-Pugh (CTP)
Ciliary Neurotrophic Factor (CNTF)
Cobalt-protoporphyrin (CoPP)
Computed tomography (CT)
Donation after brain death (DBD)
Donation after cardiac death (DCD)
Donor risk index (DRI)
Early growth response one (Egr-1)
Endothelin (ET)
Epidermal growth factor (EGF)
Extended donor criteria (EDC)
Galactosyl-human serum albumin (GSA)
Graft-to-recipient weight ratio (GRWR)
Graft volume (GV)
Graft-to-recipient spleen size ratio (GRSSR)
Heat Shock Protein (HSP)
Heme oxygenase (HO)
Hemiportocaval shunts (HPCS)
Hepatic artery flow (HAF)
Hepatic venous pressure gradient (HVPG)
Hepatocellular carcinoma (HCC)
Hepatocyte growth factor (HGF)
Indocyanine green (ICG)
Intensive therapy unit (ITU)
Interleukin (IL)
King's College Hospital (KCH)
Kupffer cells (KC)
Leukemia Inhibitory Factor (LIF)
Live donor liver transplantation (LDLT)
Liver transplantation (LT)
Magnetic Resonance Imaging (MRI)
Middle hepatic vein (MHV)
Model of End-stage Liver Disease (MELD)
Modified right lobe graft (MRL)
Nitric oxide (NO)
Nitric Oxide (NO)
Non-heart-beating donors (NHBD)
Nuclear factor (NF) –κB
Orthotopic liver transplantation (OLT)
Paracetamol overdose (POD)
Portal hypertension (PHT)
Portal venous flow (PVF)
Portal venous pressure (PVP)
Porto-systemic (PS)
Proliferating cell nuclear antigen (PCNA)
Prostaglandin E2 (PGE2)
Proximal splenic artery embolization (PSAE)
Remnant liver volume (RLV)
Sinusoidal endothelial cells (SEC)
Small for size syndrome (SFSS)
Splenic artery embolization (SAE)
Splenic artery ligation (SAL)
Standard liver volume (SLV)
Superior mesenteric artery (SMA)
Superior mesenteric vein (SMV)
Transjugular intrahepatic portosystemic shunt (TIPSS)
Tumour growth factor (TGF)
Tumour necrosis factor (TNF)
Tumour necrosis factor receptor (TNFR-1)
UK End stage Liver Disease (UKELD)
United network for organ sharing (UNOS)
Vascular endothelial growth factor (VEGF)

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Review of Literature

1. Review of Literature

1.1. Introduction

The liver has a remarkable ability to regenerate following injury or resection. The earliest allusion of the livers regenerative capacity dates back to Greek mythology. Prometheus was punished for stealing the secret of fire from the gods of Olympus and giving it to primitive humans by being chained to a rock and having an eagle of Zeus devour his liver each day. Each night his liver regenerated leaving him fit for the following dates torture. It wasn't until the late 1800s that the regenerative capacity of the liver was documented scientifically. A variety of genes, proteins, cytokines and cells are involved in the initiation and modulation of the liver regeneration. In this review, the cells that participate in the regenerative process in the liver, factors known to influence the regenerative response and the clinical consequence of inadequate parenchymal mass and potential treatment options available, are discussed.

1.2. Liver Histology

Liver parenchyma is divided into hepatic lobules by the connective tissue septa invaginating from its capsule. The lobule is a roughly hexagonal arrangement of plates of hepatocytes, which are the parenchymal cells, radiating outward from a central vein in the center, separated by blood sinusoids. Portal triads, formed from a bile duct and branches of the hepatic artery and hepatic portal vein, are regularly distributed at the vertices of the lobule. The walls of the sinusoids are lined by three different non-parenchymal cell types: sinusoidal endothelial cells (SEC), Kupffer cells (KC), and hepatic stellate cells. Hepatocyte functions are regulated by substances released from neighboring non-parenchymal cells both under physiological and pathological conditions. Kupffer cells secrete potent mediators of the inflammatory response and thus control the early phase of liver inflammation, while stellate cells play a key role in the development of inflammatory fibrotic response following liver injury (1).

Liver regeneration is characterized by the proliferation of all existing cell lines within the liver, including hepatocytes, sinusoidal endothelial cells, Kupffer and stellate cells. Hepatocytes swell due to an increase in intracellular triglyceride, leading to mild hepatic steastosis (2-4). DNA synthesis begins within the first 24 hours after resection and is characterized by an increase in mitotic rate and density of chromatin. Cellular proliferation starts in the periportal areas of the liver and spreads to the pericentral area, resulting initially in the formation of disorganized

clumps of cells, which undergo remodeling after the deposition of collagen types I and IV (2;5).

Histologic features of small for size syndrome include cholestasis with bile plugs, and areas of regeneration and ischaemia with patchy necrosis (6;7). The mechanism by which this occurs following parenchymal resection, is thought to be due to a reduction in the intra-hepatic vascular bed leading to higher portal flow per gram of remnant liver (8;9). It is postulated that the increased hepatic portal pressure leads to transient sinusoidal narrowing, endothelial injury, Kupffer cell activation and release of pro-inflammatory cytokines, and consequently an impairment of liver regeneration (10;11).

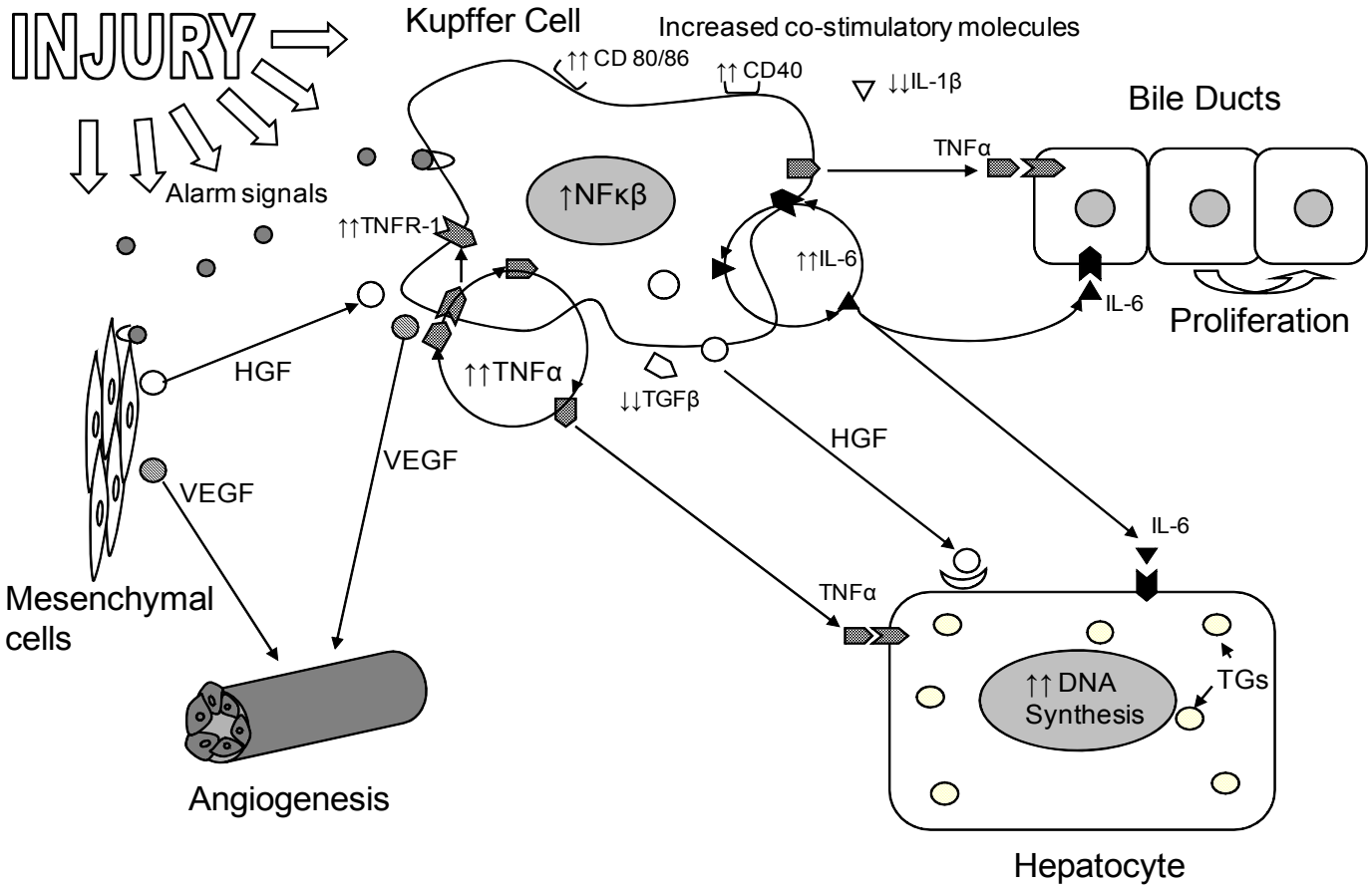
1.3. Liver Regeneration

Liver regeneration after partial hepatectomy is a perfectly calibrated response whose apparent sensor is the body's requirement for liver function (12). The liver regenerates following injury, ischaemia or resection, but resection is the strongest stimulator of hepatic regeneration (13). Regeneration starts approximately 72 hours following tissue loss and is usually complete within 3–6 months (14). Following liver resection, re-growth of the liver remnant occurs by compensatory hypertrophy rather than true regeneration. The regenerative response is proportional to the degree of tissue loss up to 70% of the parenchymal mass, then there is a decline in the intensity of the response (15).

The orchestration of this complex physiological response is dependent on numerous cytokines, growth factors, and metabolic networks (16) [Figure 1]. Liver resection reduces the liver mass, but leaves few injured cells. 'Alarm signals' released by the injured cells are thought to trigger hepatic regeneration and have been the subject of intense investigation, but remain elusive. The liver specific tissue macrophages, Kupffer cells, play a central role in mediating the process. Following liver injury, the Kupffer cells are activated through the binding of tumour necrosis factor (TNF) -α to tumour necrosis factor receptor (TNFR-1), leading to activation of nuclear factor (NF) –κB , and the release of proinflammatory cytokines, including interleukin (IL) -6, and TNF- α. IL-6 is a family of proteins that includes oncostatin M, Leukemia Inhibitory Factor (LIF),

Ciliary Neurotrophic Factor (CNTF), Interleukin 11 (IL-11) and cardiotrophin (CT) (17).

Figure 1: Orchestration of liver regeneration



Non-foreign alarm signals are released from cells injured during hepatectomy and include: mammalian DNA, RNA, heat shock proteins (Hsps), interferon-a, interleukin-1b, CD40-L (a surface molecule on activated platelets and activated T cells), and breakdown products of hyaluron (made when vessels are damaged)(18)

HGF released from mesenchymal cells as well as Kupffer cells after their activation

VEGF released from mesenchymal cells as well as Kupffer cells after their activation

TGF-β, which is an antiproliferative cytokine produced by Kupffer cells, is inhibited [Non-parenchymal cells]

IL-1β, which is an antiproliferative cytokine produced by Kupffer cells, is inhibited [Non-parenchymal cells]

TGs Triglycerides