Iron overload in chronic liver disease Update in pathogenesis and management

Essay

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بسم الله الرحمن الرحيم

ربى أوزعنى

أن أشكر نعمتك التى أنعمت على

وعلى والدى و أن أعمل صالحا

ترضاة و أدخلني برحمتك في عبادك

الصالحين

صدق الله العظيم

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List of abbreviations

ABCG2 ..... ATP binding cassette protein G2

ALD ..... alcoholic liver disease

ALT……alanine aminotransferase

ATF6 ..... activating transcription factor 6

BIP…… binding immunoglobulin protein

BMP ..... bone morphogenitic protein

CHC …….. chronic hepatitis c

CLDS……..chronic liver diseases

DCYT B ..... duodenal cytochrome B

DMT1 ..... divalent metal iron transporter 1

ER..... endoplasmic reticulum

FLVCR..... feline leukemia virus C receptor

FPN ..... ferroportin

GDF15 ..... growth defrentiation factor 15

HCC…… Hepatocellular carcinoma

HCP1..... heme carrier protein 1

HCV…….. hepatitis c virus

HIC ..... hepatic iron concentration

HJV…… hemjuvlin

IRE1 ..... inositol requiring enzyme 1

IRE1-XBP1 ..... inositol requiring enzyme 1-x box DNA binding protein 1

IREs**.....** iron responsive elements

IRPs**.....** iron regulatory proteins

INOS..... isoform of nitric oxide synthase

JAK-STAT….. janus kinase/signal transducers and activators of transcription

NAFLD..... non alcoholic fatty liver disease

NASH..... non alcoholic steatohepatitis

NS3 ..... non structural **3**

NS5A…… non structural 5A

MRI…….. magnetic resonance imaging

PCT ..... porphyria cutanea tarda

PERK ..... double stranded RNA- activated protein like ER kinase

ROS..... reactive oxygen species

TNFα ..... tumor necrosis factor α

TFR1 ..... transferrin receptor 1

TFR2 ..... transferrin receptor 2

UPR..... unfolded protein response

USF2…… upstream stimulatory factor2

UTR..... untranslated region

VHL/HIF..... von hippel lindau/hypoxia inducible factor

8-OH-DG ..... 8 hdroxy 2 deoxyguanosine

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Introduction

Iron is an essential element necessary for multiple cellular processes. However, excess free iron is toxic and can also produce reactive oxygen species that can contribute to cellular injury. (**Nagashima and Kudo, 2006**)

Many diseases arise from imbalances in iron homeostasis. In addition,iron represent akind of oxidative stress contributing to development of hepatocellular damage in chronic hepatitis C (CHC).(**Fujita et al ., 2007**)

Serum ferritin and hepatic iron concentrations are frequently elevated in chronic hepatitis C (CHC) patients and may be associated with more aggressive disease and decreased responsiveness to interferon therapy.(**Bertino et al ., 2007**)

Phlebotomy therapy normalizes serum alanine aminotransferase (ALT) levels in chronic hepatitis C (CHC) patients further suggesting that excess iron plays a pivotal role in hepatocellular damage. (**Kawamura et al ., 2005**)

With respect to non-alcoholic steatohepatitis, data are contradictory. An association between unexplained, mixed and mild hepatic iron-overload and various metabolic abnormalities including

moderate overweight with visceral distribution of fat, high blood pressure, dyslipidemia and abnormal glucose metabolism, has been described under the name of insulin resistance-associated iron-overload or dysmetabolic iron-overload syndrome.(**Deugnier et al ., 2008**)

In recent years, the major contributions to our understanding of iron overload pathogenesis have been centered around hepicidin which is apeptide hormone made in the liver as a homeostatic regulator of Iron metabolism. (**Domenico et al ., 2007**)

The identification of hepcidin raised the possibility of diagnostic and therapeutic applications. The ability to measure plasma or urinary hepcidin could potentially become the single most important test for monitoring iron status. However, progress in developing a simple, inexpensive and widely available hepcidin assay has been slow. (**Kemna et al ., 2007**)

Magnetic resonance imaging assessment of liver iron is becoming increasingly important in the management of iron overload because it is noninvasive, relatively widely available. (**Charatcharoenwitthaya and Lindor , 2007**)

Aim of work

The aim of this review is to discuss update in pathogenesis and management options in iron overload in chronic liver diseases

Introduction

Iron is an essential element used by living organisms in redox enzymes, oxygen carriers, and oxygen-storage proteins for examples Components of the mitochondrial electron-transport chain, the enzyme ferrochelatase and haemoglobin, which are indispensable for bioenergetics, haem synthesis and oxygen transport **(Ajioka et al ., 2006).**

Enzymes that are involved in DNA synthesis, replication, repair and transcription, including ribonucleotide reductase4, pirin5, DNA primase6 and the DNA helicases7, bind iron, and the ATPase which is needed for mRNA translation, incorporates iron as shown in fig(1) (**Rudolf** et al ., 2006)

Viruses depend on cells for their continued existence. Virus replication is associated with enhanced cellular metabolism, as viral genomes are copied and viral proteins are synthesized. Because these processes require iron, for a virus to efficiently propagate in its cellular host, that host must be replete in iron. Therefore, one might expect an increase in iron bioavailability to be accompanied by an expansion in virus populations (**Drakesmith** et al ., 2008).

The human iron economy is based on iron conservation and recycling as the excretion of iron is poorly regulated and there is no specific mechanism of its removal so that only approximately 1/2000 of the total iron (1–2 mg) needs to be replaced daily by absorption from the diet.(**Anderson et al ., 2009).**

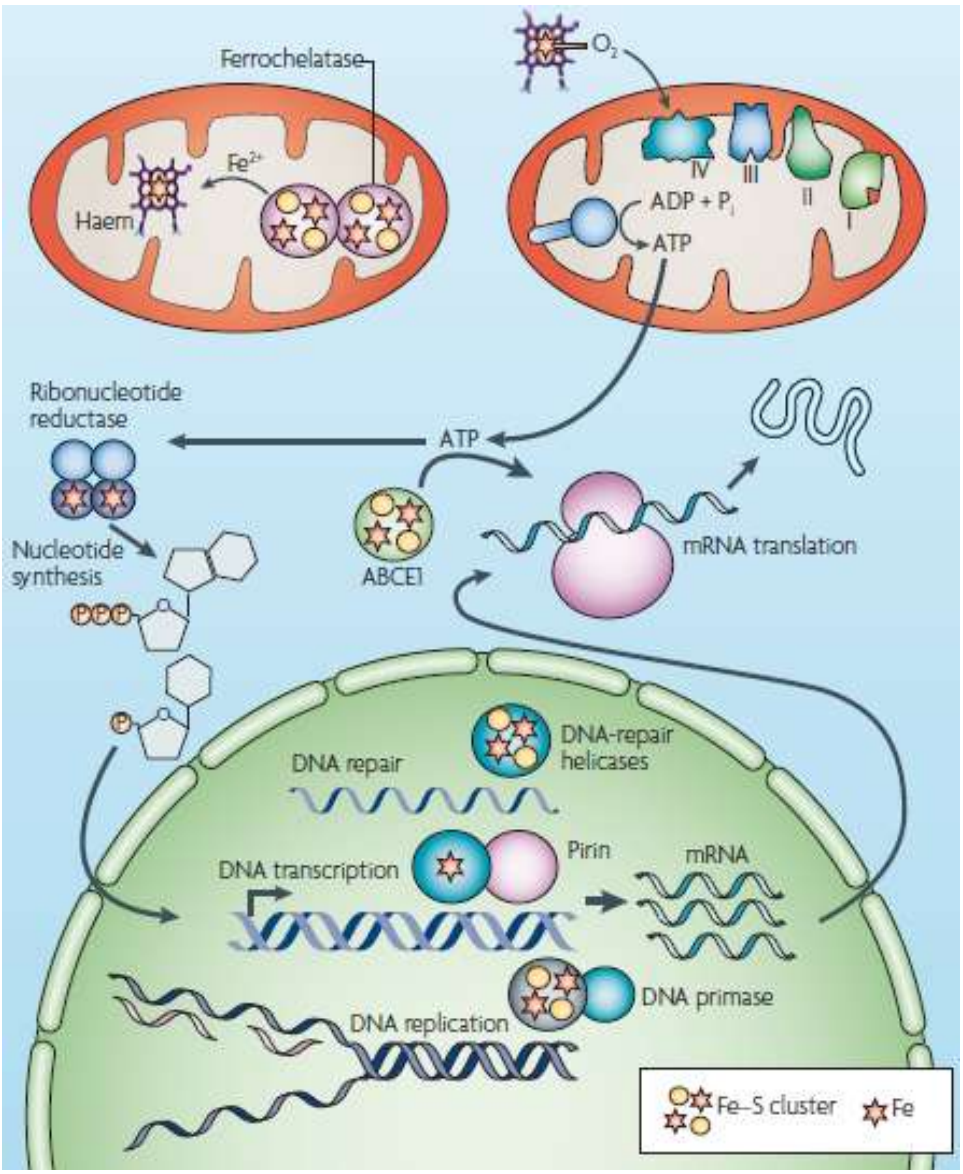

Figure (1) Fundamental aspects of cellular function are dependent on iron

(Rudolf . et al 2006)

Iron transport across the intestinal enterocytes

Iron in the diet is usually considered to be in either the heme or nonheme form and both can be utilized by the intestinal epithelium. Nonheme iron crosses the apical brush border of enterocytes through the ferrous iron (Fe2) transporter divalent metal ion transporter 1 (DMT1). As most dietary iron is in the ferric or Fe3 state, it must first be reduced before it can be utilized, and a candidate iron reductase is the brush border protein duodenal cytochrome B **(Anderson , 2007).**

Once within the enterocyte, iron has two basic fates depending on iron requirements. If iron demand is low, it will remain in the enterocyte sequestered by the iron storage protein ferritin and will be lost when the enterocytes are sloughed from the villus tip several days later . If iron is required by the body, it will cross the basolateral membrane through the iron export protein ferroportin (FPN) and enter the circulation in which it binds to plasma transferrin. The efflux of iron from enterocytes also requires the iron oxidase hephaestin as shown in fig (2).(**Anderson et al ., 2009).**