Management of Diabetes Mellitus in patient with decompensated liver disease

Essay

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By

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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Contents

List of Figures

LIST OF ABBREVIATIONS

APC	Antigen presenting cells
CVD	Cardiovascular disease
CLD	chronc liver disease
CKD	Chronic kidney disease
DM	Diabetes mellitus
FFAs	Free fatty acids
GAD	Glutamic acid decarboxylase
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
HVPG	Hepatic venous pressure gradient
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HCC	Hepatocellular Carcinoma
HOMA	Homeostasis model assessment
HRS	Hepatorenal syndrome
IA2	islet antigen 2
IDDM	insulin-dependent diabetes mellitus
IR	Insulin resistance
MHC	Major histocompatibility complex
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
ORFs	open reading frames
PPAR	Peroxisome proliferator-activated receptor
PTPN22	Protein tyrosine phosphatase, non-receptor type 22
SGLT2	Sodium glucose co-transporter 2
TZDs	Thiazolidinediones

T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
FXR	Farnesoid X receptor
OCA	Obeticholic acid
ZnT8	Zinc transporter 8

Abstract

Diabetes mellitus (DM) is considered to be one of the most common chronic diseases and a growing public health challenge globally, where an estimated 382 million people, corresponding to 8.3% of the world's adult population, has diabetes.

DM was found to be an important cause of liver disease, where patients with diabetes were found to have a spectrum of liver diseases, ranging from abnormal liver enzymes, nonalcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure, all associated with the increased prevalence of hepatic complications including liver cirrhosis and portal hypertension.

DM and insulin resistance are common in cirrhosis.The prevalence of diabetes is up to 30% in cirrhotic patients and prevalence increases with the severity of liver disease**.**

Key words:

Diabetes Mellitus in patient with decompensated liver disease.

Introduction

Diabetes mellitus (DM) is considered to be one of the most common chronic diseases and a growing public health challenge globally, where an estimated 382 million people, corresponding to 8.3% of the world's adult population, has diabetes**(Guariguata et al., 2013).**

DM was found to be an important cause of liver disease, where patients with diabetes were found to have a spectrum of liver diseases, ranging from abnormal liver enzymes, nonalcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure, all associated with the increased prevalence of hepatic complications including liver cirrhosis and portal hypertension**(Blachier et al., 2013).**

DM and insulin resistance are common in cirrhosis.The prevalence of diabetes is up to 30% in cirrhotic patients and prevalence increases with the severity of liver disease**(Garcia-Compean et al., 2009).**

A positive association between hepatitis C virus (HCV) infection and DM has been reported in a number of clinical studies. In a recent publication, data from the third National Health and Nutrition Examination Survey provided compelling evidence for the unique association between HCV infection and DM **(Mehata et al., 2000).**

Type 1 diabetes is often associated with other autoimmune diseases as primary biliary cirrhosis. Furthermore, type 1 diabetes and primary biliary cirrhosis may share similar pathogenic pathways. Identification of markers for associated autoimmune diseases may permit earlier diagnosis and more effective treatment**(Carmine et al., 2003).** Diabetes has been associated with a higher risk of biliary stones **(Festi et al., 2008).**

Most interventions evaluated for the treatment of NAFLD are those commonly used for the treatment of Type 2 diabetes –thiazolidinedione, metformin, incretinmimetics, insulin, weight loss, exercise and diet – and exert a rather indirect effect through improvement in insulin resistance and glycaemia. Other treatments tested – such as antioxidants, probiotics, statins and ARBs **(John Richard and IldikoLingvay, 2011).**

Therefore, the purpose of this study was to highlight the pathophysiological aspects of diabetes mellitus in decompensated liver disease patient and to provide recommendations for the management of this potentially dangerous condition..

Aim of the study

To highlight the pathophysiological aspects of Diabetes Mellitus in decompensated liver disease patient and to provide recommendations for the management of this potentially dangerous condition.

Pathophysiology of Diabetes Mellitus

Diabetes mellitus (DM) is rapidly becoming one of the most common non-communicable diseases globally. In 2013 there were 382 million people with diabetes, which quantity is expected to increase to592 million by 2035. Population growth, aging of population and urbanization with associated lifestyle change is likely to lead to a 55% increase in worldwide figures with diabetes by 2035 (**Li et al., 2015**).

A newly released nationwide diabetes epidemiological study indicated that prevalence of DM and pre-diabetes has increased to 9.7% and 15.5 %, translating into 92. 4 million adults with diabetes (**Yang et al., 2010**).

There are two main types of diabetes mellitus:

- ***Type 1*** (Insulin dependent) or Juvenile onset.
- ***Type 2*** (Non insulin dependent). It could also result from pregnancy and this is referred to as Gestational diabetes mellitus. This can result in increase in both perinatal and maternal morbidity and mortality. Some complications of diabetes mellitus include diabetic foot infections, retinopathy, nephropathy, gastroparesis, NAFLD, erectile dysfunction and many others. (**Mazen et al., 2008**).

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue. Consequently, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. The body obtains glucose from: the digestive tract absorption of food, the breakdown of glycogen, the storage form of blood sugar found in the liver and gluconeogenesis, the generation of glucose from non-

carbohydrate substrates in the body. Insulin plays a critical role in balancing blood sugar levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transportation of glucose into fat and muscle cells, and it can stimulate the storage of glucose as glycogen (**Shoback et al., 2011**).

Insulin is released into the blood by beta cells(β-cells), presented in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin can be used by about two-thirds of the human body's cells to absorb glucose from the blood for use as energy, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and the breakdown of glycogen to glucose. This kind of process is principally handled by the hormone glucagon, which acts in the reverse manner to insulin (**Barrett et al., 2012**).

If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis (**Shoback et al., 2011**).

If the blood sugar concentration in blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be passed in the urine (glycosuria) (**Murray et al., 2012**). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, leading to increase in urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water

held in body cells and other body compartments, creating dehydration and increased thirst (polydipsia) (**Shoback et al., 2011**).

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a relative common disease, currently affecting about 0.3% of the population in developed countries. It has a prevalence that increases with around 3% annually and produces sometimes disabling micro- and macrovascular complications. Thus, T1DM represents a great financial burden to the world. The condition recognizes two major subtypes: 1A (autoimmune) and 1B (idiopathic). Once considered a disease of acute onset, it is now generally accepted that 1A subtype is a genetically determined chronic immune-mediated disorder that causes selective reduction of pancreatic insulin-secreting beta -cells. It starts with a long subclinical prodromal stage that lasts for years and it is associated with several immunologic abnormalities **(Vlad and Timar, 2012).**

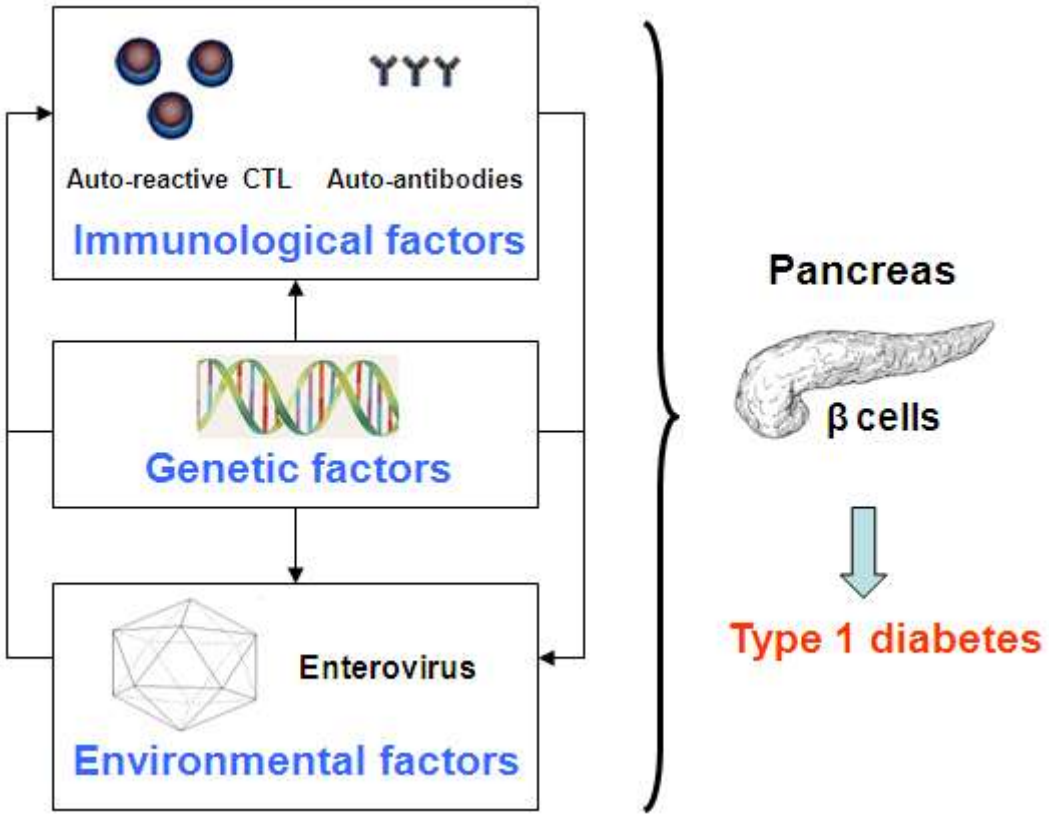

Figure 1: *Pathogenesis of Type 1 Diabetes (**Hober and Sane, 2010**)*

- ***Genetics***:

T1D does not fit any simple pattern of inheritance and is considered a multifactorial disease (**Noble and Erlich 2012**). The first T1D susceptibility locus recognized, the Human Leukocyte Antigen (HLA) complex, provides the greatest contribution (i.e., 60%) to the overall genetic susceptibility. Three classes of HLA genes were discovered with class II gens having the strongest relationship with T1D. Because category II HLA genes encode for molecules that take part in antigen presentation, the impact of Major histocompatibility complex(MHC) allelic variability on T1D risk may, for example, be described by dissimilarities in the presentation of beta-cell antigens,