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# Inflammation and Hypoglycemia: The Lipid Connection

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## 1. Introduction

Patients can be exposed to a variety of potentially life threatening acute inflammations mainly sepsis, which accounts to 9% of all death in the US. The prevalence of non-alcoholic fatty liver disease (NAFLD) is about 30% in the general population. Fatty liver is known to be more sensitive to endotoxins. It has been reported that metabolic aspects of sepsis and endotoxemia are suppression of the fatty acid beta-oxidation pathway and severe hypoglycemia. This can be due to lipotoxic effects following accumulation of free fatty acids in the liver and suppression of gluconeogenesis. In this chapter we will review the published facts about the development of hypoglycemic effects during sepsis and the possible connection of such an effect to the dysregulation of lipid metabolism. Secondly a possible redox related antilipotoxic cellular mechanism will be suggested. Such mechanism can alleviate the endotoxic hypoglycemic effect and is related to nitric oxide signaling. Nitric oxide signaling has been demonstrated to regulate the metabolic status of cells including upregulation of mitochondrial biogenesis, promoting liver glucose production and depending on the biological setting to protect cells against accumulation of oxidative damage, all possibly protect against development of hypoglycemia following liver injury.

## 2. Non-alcoholic fatty liver disease

### 2.1 Introduction

Non-alcoholic fatty liver disease NAFLD comprises a spectrum of hepatic pathology, ranging from simple steatosis (SS), in which there is an increase of fat accumulation in hepatocytes, through steatohepatitis to cirrhosis (Farrell, GC et al., 2008). Primary NAFLD is associated with obesity, insulin resistance and metabolic syndrome, diabetes and dyslipidemia, while secondary NAFLD is associated with all forms of liver damage including viral infections autoimmune and hereditary disease, drugs, toxins and nutrition (parenteral nutrition, B12/folic acid deficiency etc.) (Musso, G et al., 2010) (Figure 1). Nonalcoholic steatohepatitis (NASH) is a progressive lesion in which steatosis is accompanied by hepatocyte injury and death, as well as hepatic infiltration by inflammatory cells. NASH-related liver damage often triggers liver fibrosis. In severe cases, NASH may progress to cirrhosis and possibly hepatocellular carcinoma (Lim, JH et al., 2006). NAFLD is one of the most common liver diseases worldwide, affecting all racial, ethnic, and age

groups without sex predilection. The prevalence of NAFLD is around 30 % of the general population (Musso, G et al., 2009; Musso, G et al., 2010), NASH affects about 3 percent of the lean population (those weighing less than 110 percent of their ideal body weight), 19 percent of the obese population, and almost half of morbidly obese people. It is estimated about that 8.6 million obese adult Americans may have NASH and about 30.1 million may have the simple steatosis. Thus, the very high prevalence of fatty liver means that this disorder will contribute significantly to an increased burden of ill-health at the present and in the future (Farrell, GC et al., 2008).

NAFLD refers to the presence of hepatic sterosis not associated with a significant intake of alcohol (Adams, LA & KD Lindor, 2007) and its incidence is paralleling the increasing numbers of overweight and obese individuals worldwide (Yan, E et al., 2007). When fat accounts for more than 10% of liver's weight, then the condition is called fatty liver and it can develop more serious complications (American Liver Foundation). Fatty liver may cause no damage, but the excess fat leads to inflammation causing liver damage is referred to as steatohepatitis (American Liver Foundation). The term nonalcoholic steatohepatitis (NASH) was first coined by Ludwig et al at 1980 (Ludwig, J et al., 1980) describing the pathology of 20 patients histologically similar with alcoholic hepatitis but without the history of alcohol abuse. Sometimes, inflammation from a fatty liver is linked to alcohol abuse; this is known as alcoholic steatohepatitis (ASH). Otherwise the condition is called NASH (American Liver Foundation). NAFLD comprises a spectrum of liver pathology including bland steatosis, steatohepatitis, cirrhosis (Yang, L & A Diehl, 2007) and hepatocellular carcinoma (Angulo, P, 2007) where most liver related morbidity and mortality occur. The histological damage in NAFLD is very similar to that seen in patients with alcoholic liver disease (ALD), but NAFLD is by definition not alcohol induced (Angulo, P, 2007).

NAFLD is the most common chronic liver disease in the western world (Adams, LA & KD Lindor, 2007). Sedentary lifestyle and poor dietary choices are leading to a weight gain epidemic in westernized countries, subsequently increasing the risk for developing the metabolic syndrome and NAFLD (Rector, RS et al., 2008). Although, NAFLD may be categorized as primary and secondary depending on the underlying pathogenesis both type of NAFLD can be interrelated (Figure 1).

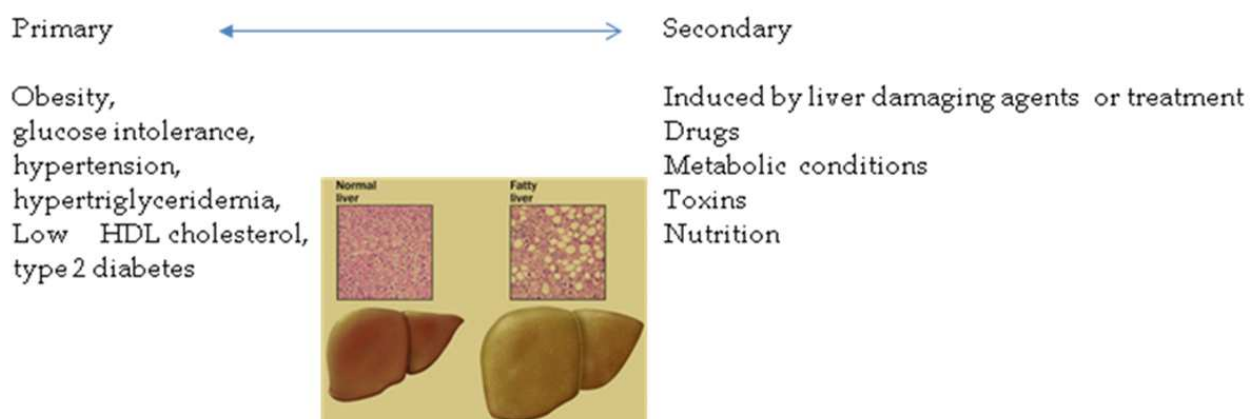


Fig. 1. Type and causes of NAFLD. Primary and secondary NAFLD may be interrelated. Induction of liver damage with may lead to fat accumulation in the liver may exacerbate primary NAFLD under conditions of hyperlipidemic, on the other hand primary NAFLD can increase the vulnerability of the liver to different kind of stressors and damaging agents.

## 2.2 Epidemiology

NAFLD is increasingly being recognized as an important and common condition, affecting approximately 20-45% of the general population (Joy, D et al., 2003) in different countries. It is estimated to affect approximately 30% of the general US population and is considered the hepatic manifestation of the metabolic syndrome (Rector, RS et al., 2008; Zivkovic, AM et al., 2007). According to (Angulo, P, 2007), NAFLD affects one in three adults and one in 10 children in the United States. Although NAFLD typically occurs between the fourth and six decades of life (Targher, G et al., 2007; Zhou, YJ et al., 2007), it is known to affect children as well as adults and is not considered discriminatory to age (Imhof, A et al., 2007; Zhou, YJ et al., 2007). Many studies have found a wide discrimination of NAFLD between the sexes (Amarapurkar, D et al., 2007; Zelber-Sagi, S et al., 2006).

Among different ethnic groups, however, the picture becomes a bit more complicated. Browning et al (Browning, JD et al., 2004) reported that the prevalence of fatty liver was highest in Hispanics (45%) compared to Caucasians (33%) or African Americans (24%) which introduced the possibility of race related variability in the susceptibility to NAFLD. Furthermore, within specific race, such as Caucasians, sex-related differences in the presence of fatty liver (42% in men and 24% in women) had been observed, which indicates the risk factors for NAFLD may vary depending on ethnicity and sex (Browning et al, 2004). Among 3543 peoples, surveyed in South China, 609 (17.2%) were diagnosed having fatty liver disease (FLD, 23.0% in urban and 14.5% in rural) out of which prevalence of NAFLD was 15.5% (Zhou, YJ et al., 2007). In the same study, prevalence of FLD among the children at the age of 7-18 years was 1.3% with all having NAFLD. The prevalence and incidence of NAFLD is expected to increase worldwide as the global obesity epidemic spreads and the trend in developing countries toward the western lifestyle continues (Angulo, P, 2007).

## 2.3 Clinical aspects of NAFLD

Most patients with NAFLD have no symptoms or signs of liver disease at the time of diagnosis (Angulo, P & KD Lindor, 2002). NAFLD has been characterized with asymptomatic elevation of aminotransferases, radiological findings of fatty liver or unexplained persistent hepatomegaly (Angulo, P & KD Lindor, 2002). NAFLD patients may be complaint of fatigue or a sensation of fullness or discomfort in the right upper abdomen . Hepatomegaly is one of the more consistent physical findings, described in up to 75% of patients with NAFLD (Yan, E et al., 2007). Other findings on physical examination that may suggest NAFLD as the cause of liver abnormalities include those characterizing insulin resistance and metabolic syndrome, such as central obesity, hypertriglyceridemia, and hypertension (Yan, E et al., 2007).

The most common and often the only laboratory abnormality found in NAFLD patients, is mild to moderate elevation of liver enzymes (Angulo, P, 2007; Angulo, P & KD Lindor, 2002) alanine aminotransferase (ALT) and aspartate aminotransferase (AST): defined as ALT>45 U/L, AST>45 U/L or  $\gamma$  Glutamyl transferase (GGT) >50 U/L (Hickman, I et al., 2008) In the patients with FLD, AST/ALT ratio is usually less than one, but this ratio increases as fibrosis advances (Angulo, P, 2007). A study on Japanese adults showed that triglycerides, total protein albumin, AST and ALT were all significantly higher while high density lipoprotein (HDL) cholesterol and AST/ALT ratio were significantly lower in subjects with NAFLD than those without fatty liver (Jimba, S et al., 2005).

### 3. Association of fatty liver with hypoglycemia

#### 3.1 Fatty acid oxidation defects

Adipocytes have the unique capacity to store excess fatty acids in the form of TGs in lipid droplets. Non-adipose tissues, such as hepatocytes, cardiac myocytes and pancreatic beta-cells, have a limited capacity for lipid storage. In hyperlipidemic states, the accumulation of excess lipid in non-adipose tissues can lead to cellular dysfunction and/or cell death, a phenomenon known as lipotoxicity (Listenberger, LL et al., 2003; Unger, RH, 1995; Weinberg, JM, 2006). Most studies attribute strong lipotoxic effects to free fatty acids (FFAs). Lipotoxic effects in the liver include disruption of liver-cell function (Alkhoury, N et al., 2009).

The connection between increased levels of fatty acids to hypoglycemia is known in genetic diseases of fatty acid oxidation defects (Figure 2). Inherited defects in mitochondrial fatty-acid beta-oxidation comprise a group of at least 12 diseases characterized by distinct enzyme or transporter deficiencies. Most of these diseases have a variable age of onset and clinical severity. Symptoms are often episodic and associated with mild viral illness, physiologic

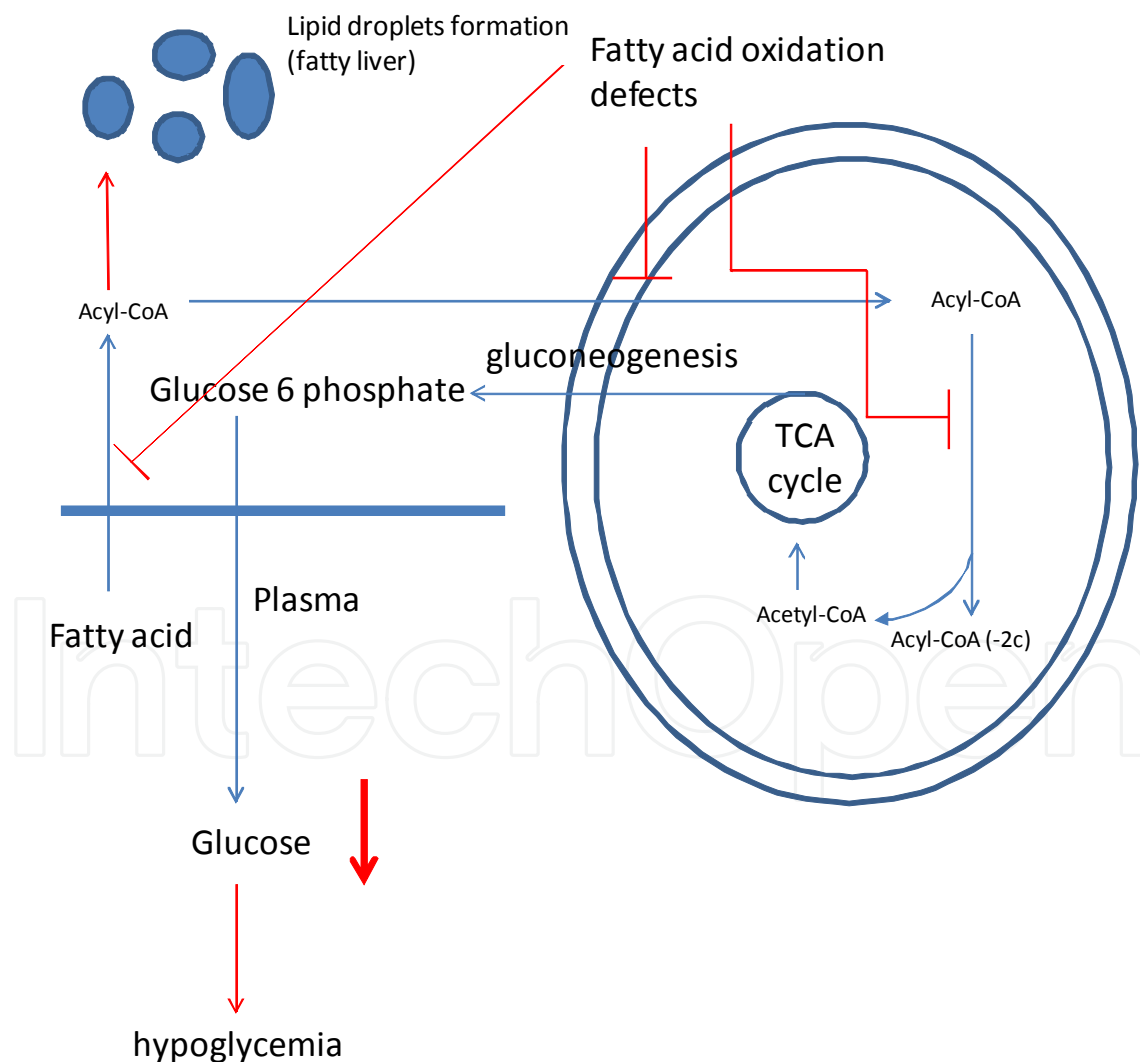


Fig. 2. Classical theory of how biochemical fatty acid oxidation defects generate hypoglycemic phenotype



stress, or prolonged exercise that overwhelms the ability of mitochondria to oxidize fatty acids. Depending on the specific genetic defect, patients develop fasting hypoketotic hypoglycemia, cardiomyopathy, rhabdomyolysis, liver dysfunction, or sudden death (Kompore, M & WB Rizzo, 2008). Medium-chain acyl-CoA deshydrogenase (MCAD) deficiency is the most frequent disorder of mitochondrial fatty acid oxidation (Baruteau, J et al., 2009). The pathophysiology of these diseases is still not completely understood, hampering optimal treatment (Houten, SM & RJ Wanders). Hypoglycemia as one major clinical sign in all fatty acid oxidation defects and occurs due to a reduced hepatic glucose output and an enhanced peripheral glucose uptake (Spiekerkoetter, U & PA Wood). A connection of such disorders-phenotype with metabolic derangement that are not necessarily related to genetic defect has been demonstrated recently via the Sirtuins. Sirtuin 3 (SIRT3) is localized in the mitochondrial matrix, where it regulates the acetylation levels of metabolic enzymes, including acetyl coenzyme A synthetase 2. Mice lacking SIRT3 exhibit hallmarks of fatty-acid oxidation disorders during fasting (Hirschey, MD et al.).

### 3.2 Liver regeneration

The liver is known for its regenerative capacity. It is now well accepted that there are two physiological forms of regeneration in the liver as responses to different types of liver injury. The first line for regeneration are mature, normally quiescent adult hepatocytes. During mild liver injury due to drugs, toxins, resection, or acute viral diseases, hepatocytes are the main cell type to proliferate and regenerate the liver. The mature hepatocytes have relatively low proliferative capacity. The second line of defense are the progenitor cell population, that are activated when injury is severe, or when the mature hepatocytes can no longer regenerate the liver due to senescence or arrest (Riehle, KJ et al., 2011). The metabolic requirements of the generating liver form Partial hepatectomy (PH) of from liver damage are impressive. There is a need to activate Kupffer cells in order to initiate the regenerating cascade. For these reasons increased accumulation of insulin independent glucose utilization is needed which may cause plasma glucose utilization due to the high metabolic demand. Impaired regenerative capacity of fatty livers might promote the progression of nonalcoholic fatty liver disease (NAFLD). Partial hepatectomy (PH) activates oxidant-sensitive, growth-regulatory kinase cascades which is abnormal in fatty hepatocytes. The normal coordinated induction of Jun N-terminal kinases (Jnks) and extracellular regulated kinases (Erks) does not occur after PH in ob/ob mice. This is associated with enhanced activation of Akt, which inhibits phosphoenolpyruvate carboxykinase (PEPCK) induction, causing severe hypoglycemia and increased lethality in the ob/ob group (Yang, SQ et al., 2001).

## 4. Alcoholic liver injury

### 4.1 Introduction

The liver breaks down alcohol so that it can be eliminated from our body. When alcohol is over consumed than the liver can process, the resulting imbalance can injure the liver by interfering with its normal breakdown of proteins, fats, and carbohydrates (American Liver Foundation). ALD is a common consequence of long term alcohol abuse (Zeng, MD et al., 2008) and represents a major cause of mortality and morbidity worldwide (Albano, E, 2008; Bergheim, I et al., 2005). ALD encompasses a broad spectrum of morphological features ranging from simple steatosis with minimal injury to more advanced stage liver injury, including alcoholic steatohepatitis, alcoholic fibrosis and alcoholic cirrhosis (Albano, E, 2008;

Zeng, MD et al., 2008). The risk of steatosis, inflammation and fibrosis are more common in alcoholics and increases with time and the amount of ethanol consumed (Vidali, M et al., 2008).

#### 4.2 Clinical aspects of ALD

Fatty liver, the most common syndrome of ALD, is characterized by the excessive accumulation of fat inside hepatocytes (Adachi, M & DA Brenner, 2005). Indeed the excessive fat accumulation in the hepatocytes is the most common and earliest response of the liver to chronic alcohol consumption (Song, Z et al., 2008). Morphological criteria of steatohepatitis are steatosis, ballooning of hepatocytes, pericellular fibrosis and inflammation (Denk, H et al., 2005). In an animal model of ALD, rats exposed 4 weeks to alcohol exhibited a significant increase in liver to body weight ratio, serum ALT levels and hepatic TNF-  $\alpha$  compared to control group (Song, Z et al., 2008). Tabassum, F et al. (Tabassum, F et al., 2001) found that the levels of alkaline phosphate, ALT, protein and globulin were significantly increased in alcoholic males compared to control subjects. The AST/ALT ratio is significantly higher in ALD patients sometimes even higher than two (Adachi, M & DA Brenner, 2005).

#### 4.3 Ethanol metabolism and role of acetaldehyde

There are multiple mechanisms for the development and progression of ALD (Figure 3) and many of these mechanisms interact to each other (Barve, A et al., 2008).

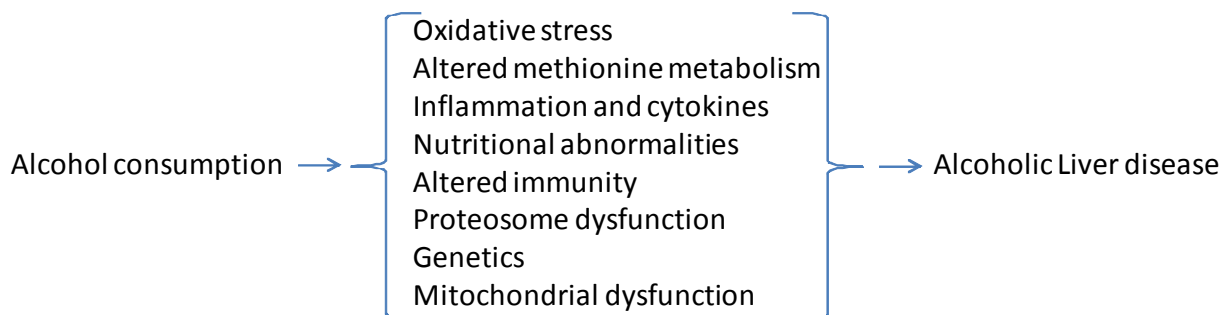


Fig. 3. Mechanisms for the development of non-alcoholic fatty liver disease

ALD has a complex pathogenesis, in which acetaldehyde; the major ethanol metabolite plays a central role (Lieber, CS, 1997). Alcohol is primarily metabolized by the successive oxidative activities of alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH), Figure 4, (Hasse, J & L Matarese, 2004; Lumeng, L & DW Crabb, 2001). Ethanol is metabolized mainly in the hepatocytes in three different sites: cytosol, endoplasmic reticulum, peroxisome and mitochondria (De Minicis, S & DA Brenner, 2008). According to (Lieber, CS, 1997) the main pathway involves cytoplasmic ADH which catalyzes the oxidation of ethanol to acetaldehyde then oxidized to acetate by the mitochondrial ALDH. Most of acetate is released into the blood (Hasse, J & L Matarese, 2004). According to Novitskiy, G *et al* (Novitskiy, G et al., 2006) acetaldehyde enhances the formation of ROS. According to (Lieber, CS, 1997), sever toxic manifestations are produced by an accessory inducible pathway, the microsomal ethanol-oxidizing system (MEOS) in endoplasmic reticulum involving an ethanol-inducible CYP2E1 in which the oxidation of ethanol to acetaldehyde and acetate also leads to generation of ROS [hydroxyethyl free radicals,

hydrogen peroxides ( $H_2O_2$ ) and super oxide anion ( $O_2^-$ )]. High reduced nicotinamide adenine dinucleotide (NADH) is produced due to alcohol metabolism leading to high NADH/NAD<sup>+</sup> ratio which overrides the cell's ability to maintain normal redox state (Hasse, J & L Matarese, 2004).

The lactic acid cannot be converted into pyruvate due to lack of NAD<sup>+</sup> leading to hyperlacticacidemia (Hasse and Matarese, 2004). They also reported that tricarboxylic acid cycle (TCA) is also diminished because; in one hand it requires a lot of NAD<sup>+</sup> and on the other hand the excess NADH inhibits two regulatory enzymes isocitrate dehydrogenase and  $\alpha$ -ketoglutarate dehydrogenase, as a consequence acetyl coenzyme A (CoA) is accumulated. The mitochondria in turn use hydrogen produced from the ethanol metabolism as a fuel source and all these activities lead to decreased fatty acid oxidation and accumulation of triglycerides in the hepatocytes (Hasse, J & L Matarese, 2004). They also reported that malnutrition can also occur in early alcoholic liver disease due to the suppression of TCA cycle coupled with decreased gluconeogenesis due to ethanol.

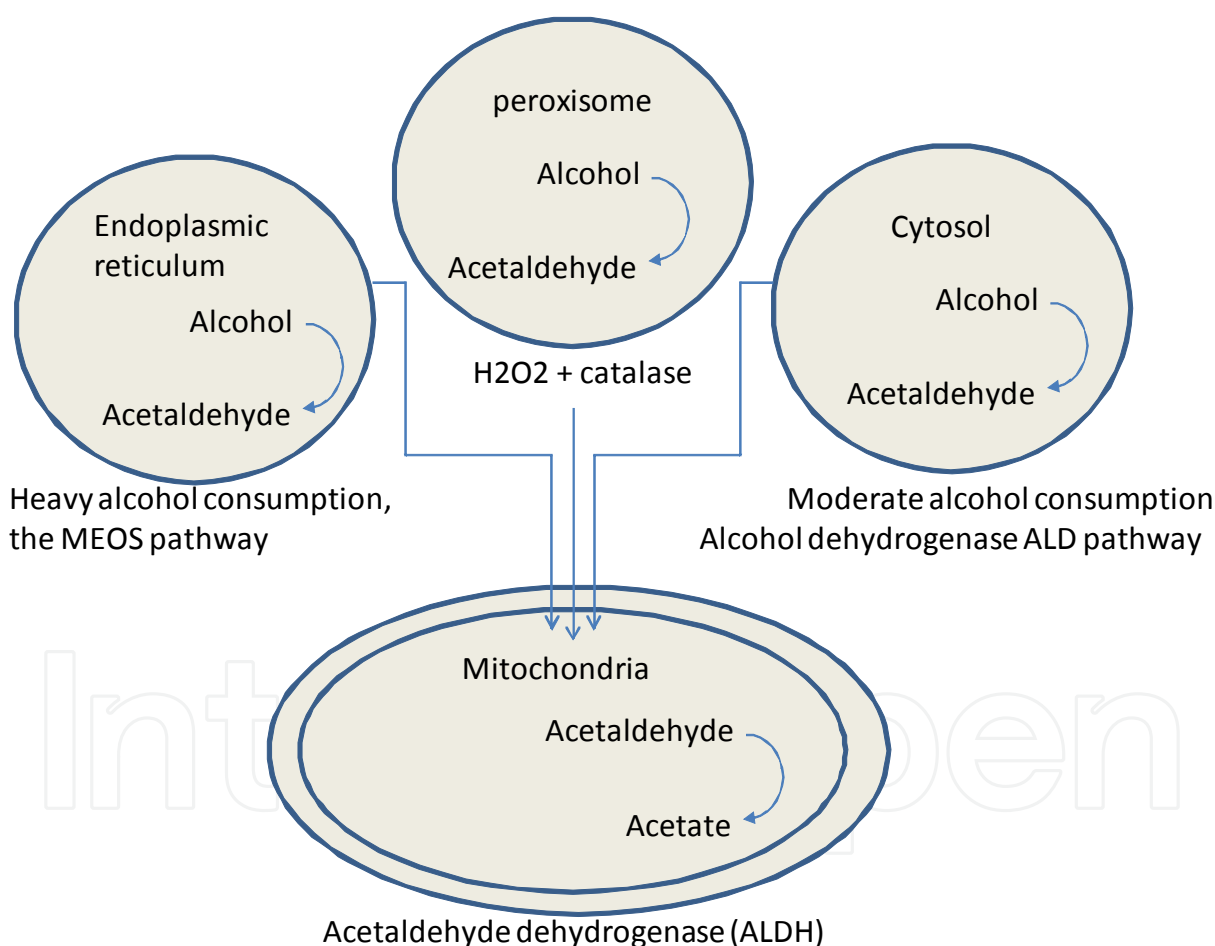


Fig. 4. Ethanol metabolism in hepatocytes. These mechanisms are potentially involved in oxidative stress production. Ethanol is metabolized in acetaldehyde and then transformed into acetate, as shown.

Chronic ethanol consumption increases fatty acid synthesis by inducing the expression of lipogenic enzymes which are regulated by transcription factor SREBP (Adachi, M & DA Brenner, 2005). Chronic ethanol consumption significantly inhibits mitochondrial ALDH



activity while the rate of ethanol oxidation to acetaldehyde is even enhanced, resulting in striking increase in tissue and plasma levels of acetaldehyde which results in metabolic disturbances, such as hyperlactacidemia, acidosis, hyperglycemia, hyperuricemia and fatty liver (Lieber, CS, 1997). However, in many cases Alcohol consumption can generate a life threatening hypoglycemia.

## 5. ALD and hypoglycemia

Alcohol consumption may have beneficial as well as deadly consequences. It is generally considered that alcohol consumption interferes with all three glucose sources and with the actions of the regulatory hormones. Chronic heavy drinkers often have insufficient dietary intake of glucose. Without eating, glycogen stores are exhausted in a few hours (Gordon, GG & CS Lieber, 1992). In addition, the body's glucose production is inhibited while alcohol is being metabolized (Sneyd, JGT, 1989). The combination of these effects can cause severe hypoglycemia 6 to 36 hours after the drinking episode (1). Even in well-nourished people, alcohol can disturb blood sugar levels. Acute alcohol consumption, especially in combination with sugar, augments insulin secretion and causes temporary hypoglycemia (O'Keefe, SJ & V Marks, 1977). In addition, studies in healthy subjects and insulin-dependent diabetics have shown that acute alcohol consumption can impair the hormonal response to hypoglycemia. Alcohol consumption can be especially harmful in people with a predisposition to hypoglycemia, such as patients who are being treated for diabetes. Alcohol can interfere with the management of diabetes in different ways. Acute as well as chronic alcohol consumption can alter the effectiveness of hypoglycemic medications. Treatment of diabetes by tight control of blood glucose levels is difficult in alcoholics, and both hypoglycemic and hyperglycemic episodes are common. In a Japanese study, alcoholics with diabetes had a significantly lower survival rate than other alcoholics (Judith Fradkin, MD, 1994). A recent meta analysis indicated beneficial effect of moderate alcohol consumption reduces the incidence of type 2 diabetes (T2D), however, binge drinking seems to increase the incidence. Acute intake of alcohol does not increase risk of hypoglycemia in diet treated subjects with T2D, only when sulphonylurea is co-administered. Long-term alcohol use seems to be associated with improved glycemic control in T2D probably due to improved insulin sensitivity (Pietraszek, A et al., 2010). The capacity of alcohol to shift its activity from beneficial to deleterious could be related to other factors that are related to impairment in lipid metabolism.

ALD has been suspected known to generate the sudden death syndrome in alcoholic individuals. Two major factors have been considered contributory to ethanol-induced hypoglycaemia (Arky, RA & N Freinkel, 1966; Madison, LL, 1968) suppression of hepatic gluconeogenesis resulting from an increase in the NADH/NAD<sup>+</sup> ratio accompanied by enhanced ethanol metabolism, and depletion of hepatic glycogen storage secondary to starvation. In cases of alcohol-related sudden deaths hydroxybutyrate levels are significantly elevated. Platia and Hsu (Platia, EV & TH Hsu, 1979) described five non-diabetic alcohol abusers with hypoglycaemic coma and ketoacidosis and contended that the combination of alcohol-related hypoglycaemia and ketoacidosis may be common.

Part of the pathogenesis of the widely known syndrome of sudden death with hepatic fatty metamorphosis observed in alcohol abusers was described by Yuzuriha *et al.* (Yuzuriha, T et al., 1997), 11 subjects who died under such circumstances between 1987 and 1993 were scrutinized both for clinical and pathological data. Death occurred followed several days of

uninterrupted drinking often with little dietary intake. Most of these individuals suffered from severe hypoglycemia. The common hepatic pathology was the extensive appearance of numerous microvesicular fatty droplets in the hepatocytes together with varying degrees of macrovesicular fatty change; four subjects had an underlying cirrhosis. Death undoubtedly results from a variety of metabolic disturbances triggered by the combination of massive ethanol intake and starvation. The appearance of extensive microvesicular fatty change superimposed on macrovesicular fatty change was considered to be an associated phenomenon. The most striking findings in the liver were extensive microvesicular fatty change within hepatocyte and the presence of megamitochondria.

## 6. Ischemic hepatitis

Ischemic hepatitis also known Hypoxic hepatitis or shock liver, can be characterized by necrosis of the zone 3 hepatocytes and significant increase in serum aminotransferase levels. It is the consequence of multiorgan injury. Outcome is influenced by the severity of liver impairment and the etiology and severity of the basic disease (Fuhrmann, V et al., 2009). The syndrome occurs under conditions of clinical setting of cardiac, circulatory or respiratory failure. It is recognized as the most frequent cause of acute liver injury with a reported prevalence of up to 10% in the intensive care unit (Fuhrmann, V et al., 2010). Patients with ischemic hepatitis and vasopressor therapy have a significantly increased mortality risk in the medical intensive care unit population. Ischemic hepatitis causes several complications including spontaneous hypoglycemia which can be considered secondary to impairment of gluconeogenic response in the exhausted liver (Fuhrmann, V et al., 2010; Fuhrmann, V et al., 2009; Nomura, T et al., 2009).

## 7. Sepsis

### 7.1 Introduction

Definition "Systemic Inflammatory Response Syndrome or (**SIRS**) is evidence of the body's ongoing inflammatory response. When SIRS is suspected or known to be caused by an infection, this is sepsis. Severe sepsis occurs when sepsis leads to organ dysfunction, such as trouble breathing, coagulation or other blood abnormalities, decreased urine production, or altered mental status. If the organ dysfunction of severe sepsis is low blood pressure (hypotension), or insufficient blood flow (hypoperfusion) to one or more organs (causing, for example, lactic acidosis), this is septic shock. Sepsis can lead to multiple organ dysfunction syndrome (MODS) (formerly known as multiple organ failure), and death. Organ dysfunction results from local changes in blood flow, from sepsis-induced hypotension (< 90 mmHg or a reduction of  $\geq 40$  mmHg from baseline) and from diffuse intravascular coagulation, among other things.

Sepsis can be defined as the body's response to an infection. An infection is caused by microorganisms or bacteria invading the body and can be limited to a particular body region or can be widespread in the bloodstream. Sepsis is acquired quickest with infections developed in surgery and physical contact with someone with sepsis.

Bacteremia is the presence of viable bacteria in the bloodstream. Likewise, the terms viremia and fungemia simply refer to viruses and fungi in the bloodstream. These terms say nothing about the consequences this has on the body. For example, bacteria can be introduced into the bloodstream during toothbrushing. This form of bacteremia almost never causes problems in normal individuals. However, bacteremia associated with certain dental

procedures can cause bacterial infection of the heart valves (known as endocarditis) in high-risk patients. Conversely, a systemic inflammatory response syndrome can occur in patients without the presence of infection, for example in those with burns, polytrauma, or the initial state in pancreatitis and chemical pneumonitis" (wikipedia).

Severe sepsis is a significant cause of mortality worldwide. Current research estimates that more than 9% of all deaths in the US can be attributed to severe sepsis. Experimental evidence shows that the liver is an important target organ in the development of multiple organ dysfunction during sepsis (Koo, DJ et al., 1999; Koo, DJ et al., 2000). Due to its major role in metabolism and host-defense mechanisms, the liver is pivotal in participating in the systemic response to severe infection, because it contains the largest mass of resident macrophage Kupffer cells (KC) in the body, making up approximately 15% of the liver cells (Szabo, G et al., 2002). KC are highly relevant in the inflammatory response to bacterial infection and non-bacterial inflammation by 1) playing a major role in both clearance and detoxification, e.g. removal of LPS from the circulation (especially the portal vein) and 2) producing inflammatory mediators (Van Amersfoort, ES et al., 2003).

## **8. Sepsis and hypoglycemia**

### **8.1 The use of intensive insulin therapy (IIT) to maintain normal blood glucose levels in septic patients**

At 2001 van den Berghe and colleagues published the clinical implications of tight euglycemic control (van den Berghe, G et al., 2001). This observation significantly and rapidly changed intensive care unit (ICU) practice. It has been suggested that insulin administered to maintain glucose at levels below 110 mg/dl decreased mortality, the incidence of infections, sepsis, and sepsis-associated multiorgan failure in surgical patients, reduced kidney injury, and accelerated weaning from mechanical ventilation and discharge from the ICU in medical patients. However, current evidences suggest that the tight euglycemic control which is implemented in intensive care units around the world could be detrimental. Increasing evidence suggest that tight euglycemic control is which is associated with development of hypoglycemia has detrimental outcomes (Brunkhorst, FM et al., 2008; Jeschke, MG et al., 2010). Therefore, In practice regulating blood glucose levels is recommended to target glucose level below 8.3 mmol/L. This is indicated for the management of severe sepsis by the Surviving Sepsis guidelines (Orford, NR, 2006)

The main problem with IIT is the risk of development of hypoglycemia. The recent trials reporting reduced morbidity and mortality in critically ill patients treated with IIT require careful examination, including the subsequent post-hoc analyses. An understanding of the molecular and metabolic mechanisms by which IIT may be beneficial and the evidence that it benefits patients with severe sepsis, and a review of the risks of hypoglycaemia are also necessary when deciding whether to implement IIT in severe sepsis. Patients with severe sepsis are likely to benefit from IIT based on metabolic effects and their prolonged stays in the intensive care unit. All together, The current evidence suggests IIT should be implemented, aiming for the lowest glycaemic range that can be safely achieved while avoiding hypoglycaemia.

### **8.2 Development of hypoglycemia in septic patients without IIT**

The severity of sepsis is shown to correlate with the risk of sustaining hyperglycemia as well as critical hypoglycemia (Kransley, JS, 2008). Hypoglycemia during hospitalization occurs in

patients with and without diabetes. In elderly hospitalized patients a predicted increase in-hospital 3- and 6-month cumulative mortality has been documented (Kagansky, N et al., 2003). In addition, sepsis is 10 times more common in these patients than in non-hypoglycemic patients. Previously, it has been shown that features of hepatitis and steatosis are the primary histological findings in the liver of patients dying from sepsis (Koskinas, J et al., 2008). The hypoglycemic effect due to fatty liver is also a known phenomenon in alcoholic patients and is related to the fatty liver sudden death syndrome (Denmark, LN, 1993; Randall, B, 1980; Yuzuriha, T et al., 1997). Altogether, the accumulated data suggest that although fatty liver and inflammation can generate a phenotype of insulin resistance, it can also lead to severe hypoglycemic life-threatening situations in patients with steatosis and acute inflammation due to an increase in hepatic insulin sensitivity (Thompson, BT, 2008; van der Crabben, SN et al., 2009). The mechanism(s) for hypoglycemia with sepsis is not well defined. Depleted glycogen stores, impaired gluconeogenesis and increased peripheral glucose utilization may all be contributing factors. Incubation of bacteria in fresh blood at room temperature does not increase the normal rate of breakdown of glucose suggesting that the hypoglycemia occurs in vivo by increased glucose utilization or by a decrease in glucose production. Hypoglycemia is an important sign of overwhelming sepsis (Miller, SI et al., 1980). Fischer et al" have reported that hypoglycemic episodes in nondiabetics were associated with infection and septic shock. The majority of cases of hypoglycemia reported in their study were related to liver disease, infections, shock, pregnancy, neoplasia, or burns. Hypoglycemia was not the apparent cause of death in any patient, but the overall hospital mortality was 27 percent and was related to the degree of hypoglycemia and the number of risk factors for hypoglycemia (Fischer, KF et al., 1986).

In 1991 Charles et al have studied the mechanism by which infection can lead to hypoglycemia. A hypermetabolic septic state was produced in rats by subcutaneous injections of live *Escherichia coli*. Sepsis increased whole body glucose disposal by 53% under basal euglycemic conditions and this increase resulted from an enhanced rate of glucose removal by liver, spleen, lung, ileum, and skin. In sepsis, the rate of non-insulin-mediated glucose uptake (NIMGU) was 46% higher than in nonseptic animals. Severe hypoglycemia (2 mmol/L) produced a relative insulin deficiency and decreased whole body glucose disposal in both septic and nonseptic animals by 53% to 56%. Compared with euglycemic insulinopenic animals. The decrease in blood glucose decreased glucose uptake by all tissues examined, except brain and heart. However, sepsis still increased glucose uptake by liver, spleen, lung, ileum, and skin (25% to 50%), compared with hypoglycemic nonseptic rats. Therefore, the conclusion of the study was that sepsis increases NIMGU under basal conditions due to an increased glucose uptake by macrophage-rich tissues, and that this enhanced rate is maintained during hypoglycemia (Lang, CH & C Dobrescu, 1991).

It is therefore suggested that during sepsis there is increased glucose utilization by macrophages-rich tissues, which may lead to hypoglycemia. However, there is also a strong connection between the liver capacity to generate glucose and the development of hypoglycemia. A case report which connect hypoglycemia with sepsis and liver disease was reported at 1994 in Japan. A 78-year-old woman that was admitted to a hospital because of disturbance of consciousness. On admission, the body temperature was 35.5 degrees C and systolic blood pressure was 50 mmHg. Ascites and semicomatose consciousness were detected. Laboratory evaluation demonstrated the following values: leukocyte count 38800/microliters, blood sugar 3 mg/l and arterial blood pH 6.9. Therapy with



catecholamine and antibiotics was started, but she expired 10 hours after admission. *Bacteroides ovatus* was detected from her blood. Autopsy findings disclosed the connection to advance liver disease and indicated abscess and perforation of the uterus, and liver cirrhosis (Suzuki, A et al., 1994). It is known that Sepsis suppresses fatty acid oxidation, It has been reported that fatty acid oxidation is significantly suppressed under conditions of sepsis and endotoxemia. During the acute-phase response, fatty acid oxidation decrease is associated with hypertriglyceridemia. LPS was demonstrated to suppress FFAs oxidation, and consequently contributes to elevated plasma levels of FFAs and TGs. LPS suppresses FFAs oxidation through decreasing the expression levels of key FFA oxidative genes including CPT-1 and MCAD in both liver and kidney tissues. LPS has been shown to selectively suppress the levels of PPARalpha and PGC-1alpha in tissues (Maitra, U et al., 2009). The decrease was rapid and occurred at very low doses of LPS. Similar decreases in levels of these genes occurred during zymosan- and turpentine-induced inflammation, indicating that suppression of the PGC-1alpha, and medium chain acyl coA dehydrogenase pathway is a general response during infection and inflammation (Kim, MS et al., 2005). We have demonstrated in a model of liver steatosis and endotoxemia that the expression of gluconeogenic enzymes and gluconeogenesis are strongly suppressed. This was accompanied with lowered blood glucose levels. The treated mice had a phenotype of insulin sensitivity with decreased blood insulin levels (Tirosh, O et al., 2010). Therefore, the effect of free fatty acids and triglycerids on expression of key gluconeogenic enzymes was studied. The effect of exposing hepatocytes to free fatty acids was to suppress the inducible expression of gluconeogenic enzymes Figure 5 and Figure 6.

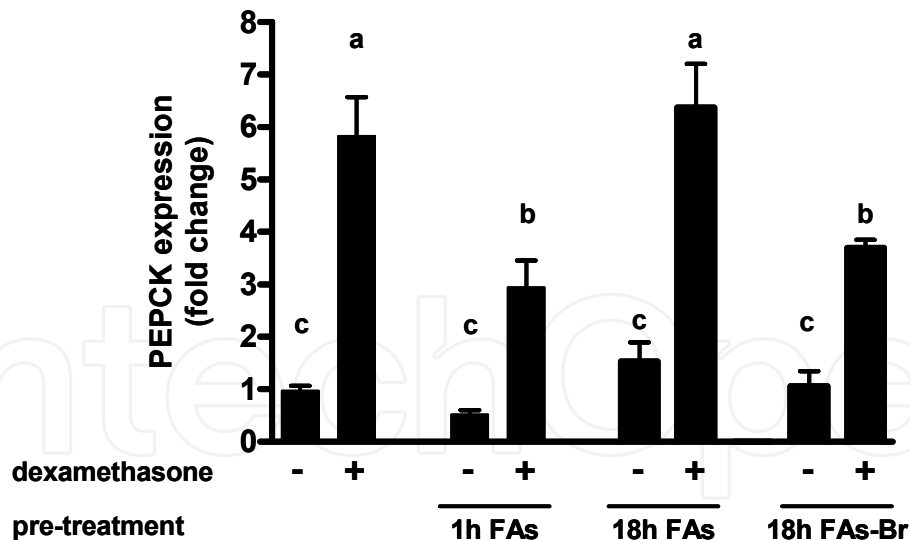


Fig. 5. **Inhibition of gluconeogenic response by free FAs in FaO cells.** FaO cells were cultured and pre-treated with FAs mixture (2:1 oleate/palmitate with 1% BSA) or with FAs-Br mixture (2:1 oleate/2-Bromopalmitate with 1% BSA) to final concentration of 1mM FAs. After that, dexamethasone (1 $\mu$ M) was added to cells media for 6 hours. mRNA expression levels of PEPCK was measured by quantitative real-time RT-PCR. Means with different letters differ at  $P < 0.05$ .



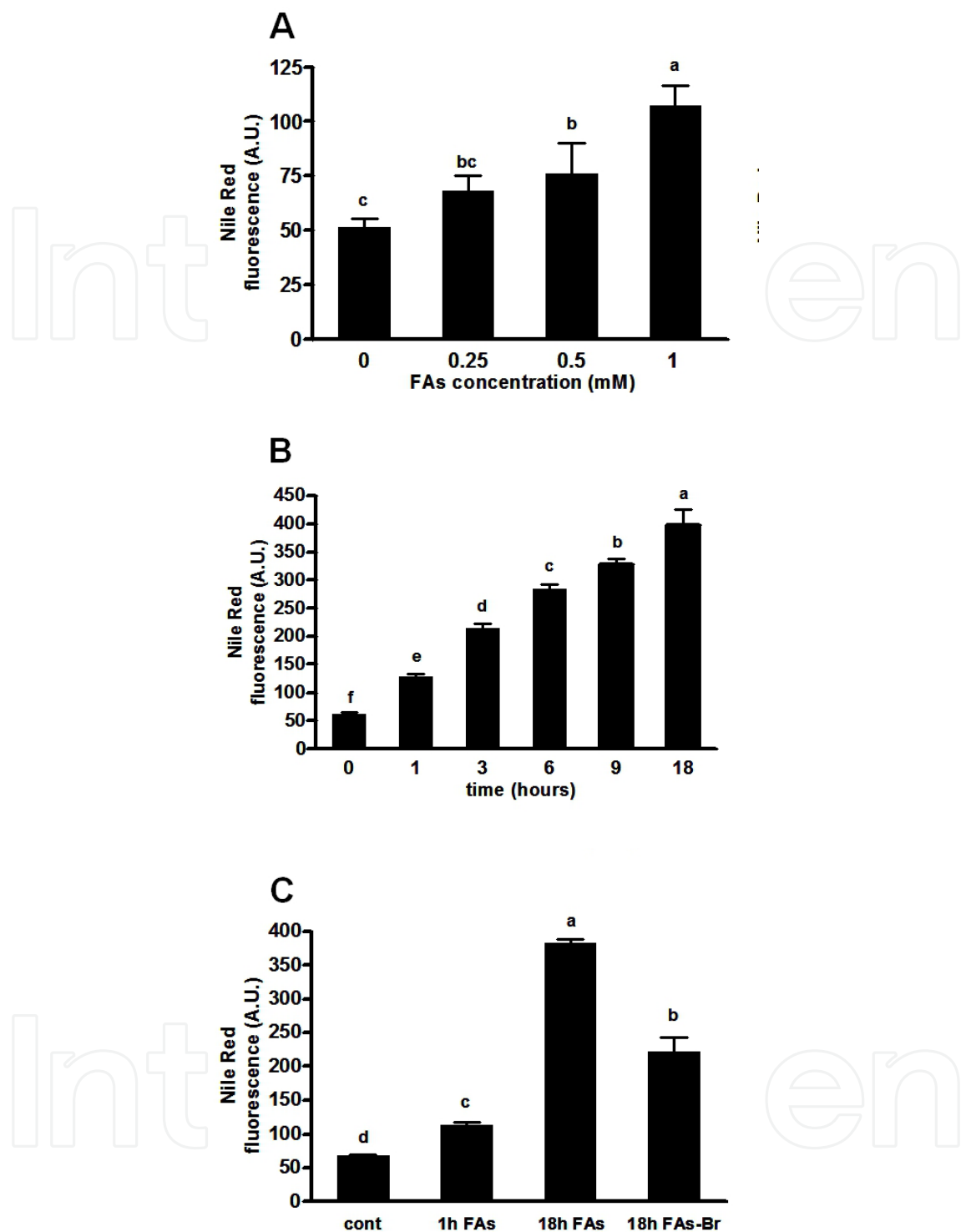


Fig. 6. **Fat accumulation in FaO cultures.** FaO cells were cultured and exposed to FAs mixture (2:1 oleate/palmitate with 1% BSA) at different concentrations for 18 hours (A) or to final concentration of 1mM FAs for different times (B). Alternatively, FaO cells were cultured and exposed to FAs mixture (2:1 oleate/palmitate with 1% BSA) or to FAs-Br mixture (2:1 oleate/2-Bromopalmitate with 1% BSA) to final concentration of 1mM FAs (C). After that, cells were stained with Nile-Red and fluorescence was examined by FACS analysis. Means with different letters differ at  $P < 0.05$ .

The mechanism for the development of hypoglycemia during sepsis and the lipid connection can be therefore explained by the following figure 7:

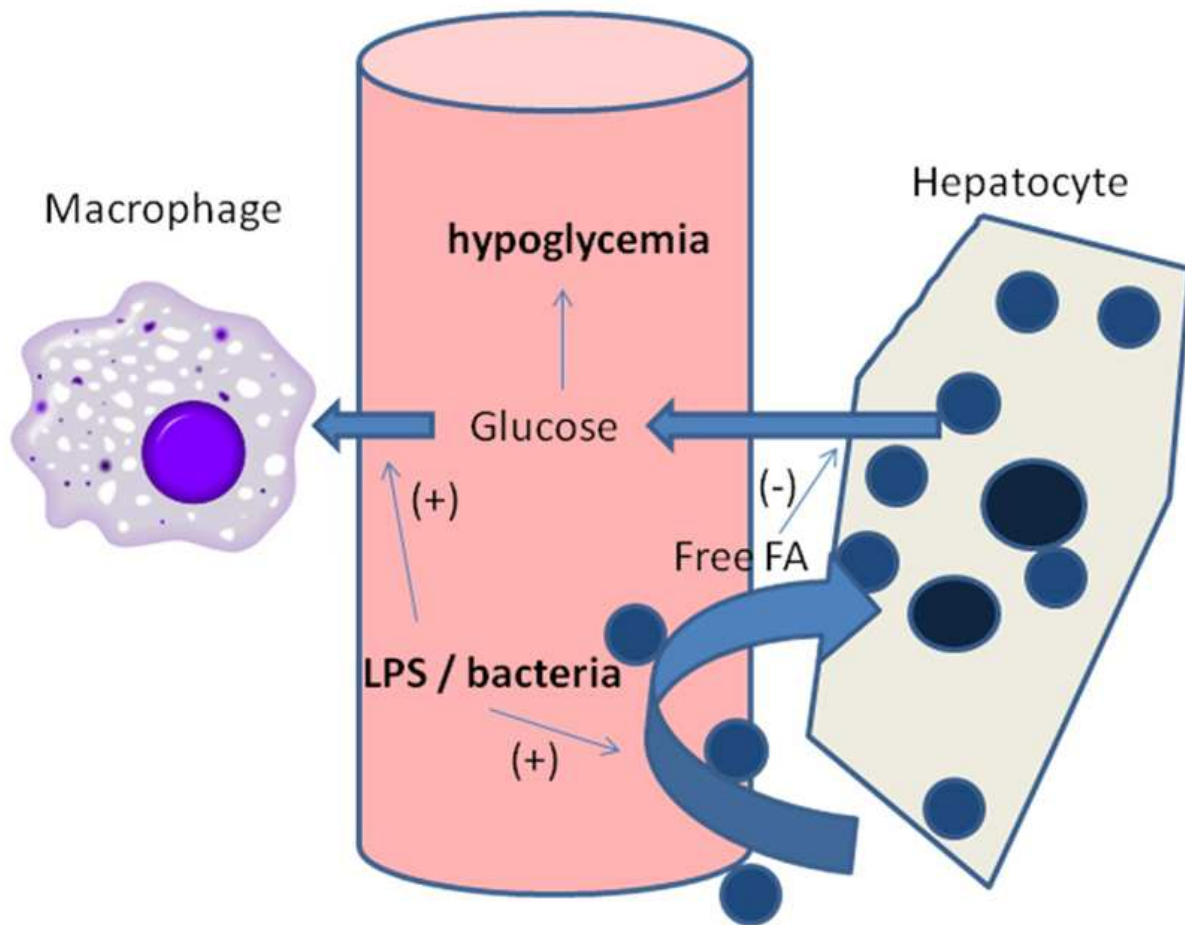


Fig. 7. LPS and bacteria facilitate 1) non-insulin-mediated glucose uptake 2) release of triglycerides and suppression of beta-oxidation in hepatocytes therefore elevating the FFA levels. This results in suppression of liver glucose output capacity. The results is hypoglycemia.

## 9. Nitric oxide as a potential antihypoglycemic agent

### 9.1 Nitric oxide involvement in liver damage and sepsis

One of the main effects of the inflammatory response in the liver is an increase in the levels of inducible nitric oxide synthase (iNOS). Therefore, it has been postulated that nitric oxide (NO) would contribute to hepatotoxicity through inhibition of ATP synthesis, increased reactive oxygen species (ROS), and the inability to adapt to hypoxic stress (Mantena, SK et al., 2008). Other studies imply that decreased production of NO from endothelial nitric oxide synthase (eNOS) contributes to liver pathology via dysregulation of blood flow and oxygen delivery (Liu, J & MP Waalkes, 2005). Furthermore, in iNOS knockout mice, hepatocytes undergo necrosis and apoptosis after PH, indicating that the production of NO is essential to protect hepatocytes from death after liver resection (Rai, RM et al., 1998). We have demonstrated that a decreased in eNOS expression precedes formation of liver damage

following intensive blood infusion of triglycerides (TGs) in rats (Tirosh, O et al., 2009). Thus, it appears that NO can be both toxic or protective, depending on the acute physiological environment in the liver.

In the case of sepsis, there are also contradictory reports concerning the role of NO. Although it has been suggested that NO is a mediator of organ dysfunction, different opinions suggest a protective role of NO in sepsis. Indeed, numerous reports of benefits associated with NO donor administration in clinical and preclinical studies of sepsis have been published (Lamontagne, F et al., 2008). Obesity increases sensitivity to endotoxin liver injury. It is known that fatty liver sensitivity to acute inflammation injury is much higher compared to normal livers (Yang, SQ et al., 1997). Our published studies in a mouse model of fatty liver and endotoxemia demonstrated a significant protective role for iNOS expression. iNOS(-/-) mice were found to be more sensitive to liver damage thereby supporting the hypothesis that iNOS has a protective effect. Additionally, iNOS(-/-) mice with fatty liver suffered from severe fatal hypoglycemia after endotoxic treatment (Tirosh, O et al., 2010).

## **9.2 Hyperglycemia or hypoglycemia: A paradox of inflammation, and the involvement of nitric oxide**

Along with a rising prevalence of non-alcoholic fatty liver disease (NAFLD), there is a marked increase in individuals suffering from metabolic impairments. One widespread imbalance is the insulin resistance syndrome or metabolic syndrome which refers to a constellation of symptoms, including glucose intolerance, obesity, dyslipidemia, and hypertension. This syndrome is known to promote the development of type 2 diabetes, cardiovascular disease, cancer, and other disorders. The liver plays a major role in the regulation of glucose, lipid and energy metabolism, which are tightly regulated by insulin (Leclercq, IA et al., 2007; Raddatz, D & G Ramadori, 2007). In addition, insulin resistance is now recognized as a pathological factor in the development of NAFLD (Leclercq, IA et al., 2007; Raddatz, D & G Ramadori, 2007). It has been suggested that prolonged elevation of the levels of sterol regulatory element binding proteins (SREBPs) is responsible for inhibition of insulin signaling in fatty liver (Shimano, H, 2007) and that the intracellular accumulation of lipids—namely, diacylglycerol—triggers activation of novel protein kinases C (PKC $\epsilon$ ) with subsequent impairments in insulin signaling (Samuel, VT et al.). Hepatic insulin resistance can be defined as the failure of insulin to adequately suppress hepatic glucose production (Weickert, MO & AF Pfeiffer, 2006).

Several studies indicate the involvement of inflammatory activation in the development of hepatic and peripheral insulin resistance (Cai, D et al., 2005). On the other hand, acute inflammation induced by lipopolysaccharides (LPS) facilitates a hypoglycemic effect and impairment of hepatic Glucose-6-phosphatase (G6Pase) expression (Lo, YC et al., 2004; Maitra, SR et al., 1999; Oguri, S et al., 2002). Indeed, as mentioned above in critically ill patients, sepsis-induced hypoglycemia is a well known event (van der Crabben, SN et al., 2009). We showed by temporal kinetics that the rapid induction of iNOS played a role in counteracting hypoglycemic effect of LPS and lipids rather than exacerbating it (Tirosh, O et al.). NO had a direct stimulatory effect promoting liver glucose production, making iNOS expression necessary for survival. Experiments performed with the NO donor DETA-NONOate in cultured hepatocytes showed a positive effect of NO on expression of gluconeogenic enzymes. Our data indicate that NO generated by the iNOS protein can support the expression of PGC 1 $\alpha$  and liver gluconeogenic genes during acute

inflammation. We believe that this effect is mediated by NO's capacity to promote the removal of free fatty acids (FFAs). Indeed, NO was found to act as a signaling molecule that can activate the transcription factor co-activator PGC 1alpha facilitating mitochondrial biogenesis (Nisoli, E & MO Carruba, 2006; Nisoli, E et al., 2007).

Our results that nitric oxide produced during the acute inflammatory process in fatty liver promotes PGC1 expression and liver glucose production supports the hypothesis that it acts as an antihypoglycemic factor. The lipotoxicity during acute inflammation in the fatty liver is manifested by increased oxidative stress and lipid peroxidation and therefore NO also function as an antioxidant (Kanner, J et al., 1991; Kanner, J et al., 1992; Volk, J et al., 2009) protecting the liver. Therefore, NO derived from inducible nitric oxide synthase (iNOS) may paradoxically function as an antioxidant protecting fatty liver during acute inflammation. This phenomenon is probably quite the reverse of the reactive nitrogen species and ROS effect in long term chronic inflammation which leads to liver cirrhosis (Wei, CL et al., 2005).

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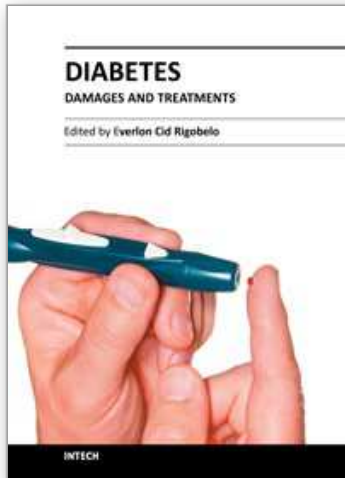
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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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