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REVIEW

Pathogenesis of hepatic steatosis: The link between hypercortisolism and non-alcoholic fatty liver disease

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Abstract

Based on the available literature, non alcoholic fatty liver disease or generally speaking, hepatic steatosis, is more frequent among people with diabetes and obesity, and is almost universally present amongst morbidly obese diabetic patients. Non alcoholic fatty liver disease is being increasingly recognized as a common liver condition in the developed world, with non alcoholic steatohepatitis projected to be the leading cause of liver transplantation. Previous data report that only 20% of patients with Cushing's syndrome have hepatic steatosis. Aiming at clarifying the reasons whereby patients suffering from Cushing's syndrome - a condition characterized by profound metabolic changes - present low prevalence of hepatic steatosis, the Authors reviewed the current concepts on the link between hypercortisolism and obesity/metabolic syndrome. They hypothesize that this low prevalence of fat accumulation in the liver of patients with Cushing's syndrome could result from the inhibition of the so-called low-grade chronic-inflammation, mainly mediated by Interleukin 6, due to an excess of cortisol, a hormone characterized by an anti-inflammatory effect. The Cushing's syndrome, speculatively considered as an *in vivo* model of the hepatic steatosis, could also help clarify the mechanisms of non alcoholic fatty liver disease.

Key words: Nonalcoholic fatty liver disease; Cushing's syndrome; Hypercotisolism

Core tip: This overview of the literature is related to hepatic steatosis, its prevalence, clinical consequences and, in particular, the pathogenesis of this disorder. The authors focus on the link between hypercortisolism and obesity/metabolic syndrome. The main question of the work relates to the low prevalence of hepatic steatosis (only 20%) described in 50 newly diagnosed patients with Cushing's syndrome based on appropriate computed tomography scans available for retrospective analysis. The authors try to explain this finding by the anti-inflammatory effect of high circulating levels of glucocorticoids.

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INTRODUCTION

In Cushing's syndrome, high circulating glucocorticoid (GC) levels cause visceral obesity, insulin resistance, diabetes mellitus, dyslipidemia, hypertension, hepatic steatosis and an increased risk of coronary artery disease (CAD)[1,2]. GCs excess stimulates gluconeogenesis in the

liver and inhibits insulin sensitivity both in the liver and in skeletal muscles, which represent the most important sites responsible for glucose metabolism. In particular, glucocorticoid excess stimulates the expression of several key enzymes involved in the process of gluconeogenesis, with a consequent increase in glucose production, and an impairment of insulin sensitivity either directly by interfering with the insulin receptor signaling pathway or indirectly, through the stimulation of lipolysis and proteolysis and the consequent increase in fatty acids and amino acids, which contribute to the development of insulin resistance (IR). Moreover, the peculiar distribution of adipose tissue throughout the body, with the predominance of visceral adipose tissue, significantly contributes to the worsening of IR and to the development of a metabolic syndrome, which has a role in the onset and maintenance of impaired glucose tolerance[3].

METABOLIC SYNDROME AND 11β-HYDROXYSTEROID DEHYDROGENASE TYPE 1

The much more prevalent "metabolic syndrome" a medical condition with a clustering of risk factors for cardiovascular disease and type 2 diabetes, such as IR, type 2 diabetes, dyslipidemia and hypertension, typically in association with visceral obesity and hepatic steatosis shares metabolic alterations and physical findings with Cushing's syndrome[1]. However, any pathogenic role for GCs in the metabolic syndrome or idiopathic obesity is still unclear[4]. Recent studies in humans and rodents suggest a role for tissue rather than plasma GCs excess in the development of idiopathic obesity and the metabolic syndrome, *via* intracellular steroid reactivation of inert circulating 11-dehydrocorticosterone (cortisone in humans) into active corticosterone (cortisol) by 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1. Surprisingly, this enzyme is highly expressed not only in adipose tissue and brain but in the liver as well[5].

The 2- to 3-fold-increased 11β-HSD1 activity in adipose tissue in obese Zucker rats[6] and in some[7,8] but not all[9] studies on obese humans may be causal to visceral obesity and its metabolic consequences. Supporting this hypothesis, visceral obesity, hyperlipidemia, IR, glucose intolerance/diabetes[10] and hypertension[11] are driven in transgenic mice by overexpression (2- to 3-fold) of 11β-HSD1 selectively in adipose tissue.

Notably, as with the human metabolic syndrome, circulating plasma corticosterone levels in aP2-HSD1 TG mice are unaltered[10]. Conversely, 11β-HSD1 null mice exhibit a protective glycemic, lipid, and lipoprotein profile[12,13] and show increased expression of hepatic mRNAs encoding regulators of fatty acid beta-oxidation[13]. While intra-adipose but not systemic corticosterone concentrations are elevated in aP2-HSD1 TG mice, corticosterone delivery to the liver is also increased about three-fold *via* spillover of adipose steroid production into the portal vein. The highest expression of 11β-HSD1 occurs in the liver[14], and hepatic 11β-HSD1 mRNA levels are regulated by diet, gender and hormones[1,14-16]. Heterogeneity of hepatic 11β-HSD1 activity may be relevant to the development of specific fatty liver, insulin-resistant, and hypertensive syndromes without obesity in humans; it is also likely to play a role in myotonic dystrophy, where marked insulin resistance and dyslipidemia have been shown to occur with elevated hepatic 11β-reduction of cortisone to cortisol, which is positively correlated to the severity of disease[17].

Dysregulation of the specific action of GCs and not of the alterations of GC levels has been proposed as a central feature of the metabolic syndrome[18]. In fact, states of GC excess recapitulate almost all features of the metabolic syndrome, but Cushing's disease is rare and circulating cortisol levels are normal in the vast majority of patients with obesity and type 2 diabetes. This finding has raised the possibility that the features of the metabolic syndrome could be due to an increase in locally available glucocorticoids through 11β-HSD1[19-21]. Subsequently, a range of studies explored the role of 11β-HSD1 in the pathogenesis of the components of the metabolic syndrome including obesity, IR, hyperglycemia, hyperlipidemia and nonalcoholic fatty liver disease (NAFLD), or generally speaking, hepatic steatosis.

Hepatic steatosis and visceral fat

Indeed, only 20% of patients with Cushing's syndrome have hepatic steatosis[22]. NAFLD ranges from fatty liver to non alcoholic steatohepatitis (NASH) and cirrhosis, and is being increasingly recognized as the most common liver disease in the developed world. NASH - which most Authors consider as completely different from the more benign form, *i.e.,* fatty liver - is projected to be the leading cause of liver transplantation. NAFLD has a great prevalence among people with diabetes and obesity and is almost universally present amongst morbidly obese diabetic patients[23-25].

Being a progressive form of liver injury, NASH carries a risk of developing hepatocarcinoma. There is strong evidence that IR and increased free fatty acids are the major cause ("first hit") of NASH[26,27]. Inflammation plays an important additional role ("second hit") with increased production of reactive oxygen species and proinflammatory cytokines. In addition, studies from different groups support the strict link between visceral adipose tissue and NASH[28,29].

In recent years, research has shown that amplification of GCs action by the intracellular enzyme 11β-HSD1 plays a key role in the development of central obesity[30,31] providing a basis for the phenotypic similarity between Cushing's syndrome and obesity in the metabolic syndrome; 11β-HSD1 increases intracellular glucocorticoid levels by converting inert cortisone to active cortisol.

In vivo reductase activity of 11β-HSD1 predominates and is driven by NADPH generated by the microsomal enzyme hexose-6-phosphate-dehydrogenase (H6PDH).

Epidemiological data indicate that hepatic steatosis is associated with IR, dyslipidemia and obesity, especially central obesity[32]. In clinical practice, the co-existence of these conditions defines the so-called metabolic syndrome[33]. Of note, NAFLD is considered by many authors as the hepatic manifestation of the metabolic syndrome[34-36].

Interestingly, the severity of hepatic steatosis is positively correlated with visceral adipose tissue accumulation in both obese and non-obese subjects, suggesting that hepatic fat infiltration may be influenced by visceral fat adipokines or, possibly, specific enzymes, regardless of body mass index[37].

As previously emphasized, some authors have pointed out the phenotypic similarities between central obesity, metabolic syndrome and patients with endogenous or exogenous glucocorticoid excess. These have led them to propose that cortisol contributes, at least in part, to the pathogenesis of those abnormalities, despite the fact that patients with obesity and metabolic syndrome have consistently normal cortisol levels in plasma and urine[38-40]. Accordingly, the concentrations of GCs found in the omental vein, draining into the portal vein, were not different from those detected in peripheral veins[41].

A plausible explanation for this phenomenon could be to consider the metabolic syndrome a result of increased local GC activity in certain organs, suggesting that central obesity might be, as proposed by Bujalska decades ago, a "Cushing's disease of the omentum"[42]. In connection with this concept, recent studies have shown that intracellular GC action not only depends upon the hypothalamo-pituitary-adrenal axis but also on local regulation at the pre-receptor level by the activity of two isoforms of the 11β-hydroxysteroid dehydrogenase enzyme type 1 and 2 (11β-HSD1 and 11β-HSD2)[43,44].

11β-hydroxysteroid dehydrogenase type 1 and visceral adipose tissue

Enzyme type 1, 11β-HSD1, is a microsomal enzyme, expressed mainly in the liver and adipose tissue, acting as a NADP (H)-dependent reductase converting inactive cortisone to active cortisol, which locally activates GCs receptors[45]. According to this view, progressive expansion of visceral fat would result in an increased production of cortisol by the action of 11β-HSD1, causing splanchnic and portal hypercortisolism, which could contribute to the pathogenesis of such metabolic disorders, including NAFLD[46-48]. Recently, it has been demonstrated that 11β-HSD1 expression levels in the liver and in visceral adipose tissue in morbidly obese patients, correlate with dyslipidemia and IR, suggesting that this enzyme might have a pathogenic role in obesity and the related metabolic disorders[49]. The role of 11β-HSD1 in NAFLD has been largely studied in humans, with conflicting results[46,47]. In any case, in two studies assessing sequential changes of enzyme expression in obese mice developing hepatic steatosis, the Authors found an overexpression of 11β-HSD1 in visceral adipose tissue and hepatic tissue with the occurrence of portal hypercortisolism[50,51]. However, further research is needed to precisely define the role of 11β-HSD1 in the origin and development of NAFLD.

In addition, the effects of treatment with specific 11β-HSD1 inhibitors[52] in NAFLD deserve more thorough exploration, as these agents have the potential to improve insulin sensitivity[53] and may ultimately add to the available treatment options. Indeed, the rationale behind this type of intervention is challenged by the observation that in NASH, the more severe form of NAFLD, the increased 11β-HSD1 activity and consequent cortisol regeneration is supposed to limit hepatic inflammation[54]. This point will be further dealt with later on.

In general, primary pre-adipocyte cultures isolated from human adipose tissue represent heterogeneous cell populations, some of which can be part of the immune system[55]. GCs affects the genes associated with immune responses, such as interleukin-6 (IL-6), TNFAIP6[56] and CD163. The simultaneous GC-induced downregulation of the TNFAIP6 and IL-6 in human preadipocytes might reflect the interaction between these two genes in adipose tissue inflammation. Glutathione peroxidase 3 precursor (GPX3), the plasma GPX3, catalyses the reduction of hydrogen peroxide, organic hydroperoxide and lipid peroxides, thus protecting cells against oxidative damage. GPX3 was reported to be present in human adipose tissue[57], and GPX3 was identified as being one of the most highly expressed genes in the pre-adipocyte compartment of human adipose tissue as well as a novel GC-target gene.

Recently, adipose tissue has been defined as a major site of production of serum amyloid A (SSA)[58], a well-known risk factor for CAD[59]. It has been shown that *ASSA* is a GC-target gene in omental preadipocytes. Together, these findings contribute to the role of omental tissue as a potential link between an inflammatory response and CAD.

11β-HSD1 EXPRESSION AND ACTIVITY IN THE LIVER

Conflicting observations have been made regarding this issue. Most studies suggest that 11β-HSD1 expression and activity in the liver is down-regulated in obesity[54, 60].

This down-regulation, however, appears to be defective in insulin resistant individuals[61]. The failure to down-regulate hepatic 11β-HSD1 could further contribute to IR and, on the basis of the fact that GCs stimulate lipid production, also exacerbate dyslipidemia.

These relationships are complicated by the expression of additional glucocorticoid metabolizing enzymes in the liver, most importantly the A-ring reductases (5α- and 5β- reductase)[15,54]. The expression of these enzymes also appears to be associated with IR and, in a similar manner, to 11β-HSD1, showing a pattern of down-regulation with increased adiposity and insulin resistance. A possible mediator of the hepatic changes seen in the metabolic syndrome could be the increased production of cortisol

from visceral fat in obesity. This increased cortisol would subsequently drain to the liver through portal circulation. However, recent studies examining cortisol and cortisone levels in peripheral, portal, and hepatic vein blood samples indicated that cortisol production from visceral adipose tissue, and thus the amount of exposure of the liver, does not significantly change with increasing obesity[62-64], confirming previous data[41].

ROLE OF INTERLEUKIN-6

IL-6 is expressed in and released from both the subcutaneous and omental adipose tissues[65] with a two- to three-fold higher *in vitro* release of IL-6 from omental compared to subcutaneous adipocytes *in vitro*. The *in vivo* release of IL-6 from fat contributes as much as 35% to the basal circulating levels and may at least in part explain the positive correlation between serum levels of IL-6 and obesity. In rodents, obesity is associated with macrophage accumulation in adipose tissue, and these macrophages release inflammatory mediators and molecules promoting inflammation. Inflammatory mechanisms play a key role in the pathogenesis of type 2 diabetes. This low-grade chronic inflammation has been proposed to be mediated by the IL-6 family of cytokines, tumor necrosis factor-alpha, interleukin-1 beta, IL-18, and certain other chemokines. In addition to its immunoregulatory actions IL-6 has been proposed to affect glucose homeostasis and metabolism directly and indirectly by its action on skeletal muscle cells, adipocytes, hepatocytes, pancreatic beta-cells and neuroendocrine cells[66]. It has been suggested that IL-6 might play a role in the pathogenesis of Cushing's disease[67]. Although an increased production of IL-6 has been reported in patients with either active or remitted Cushing's syndrome, elevated GCs levels in these patients may prevent excessive action of IL-6 due to the persistent accumulation of central fat[68]. In fact, it has been hypothesized that IL-6 deficiency exacerbates hepatic insulin resistance and inflammation, a process that appears to be related to defects in mitochondrial metabolism[69]. On the other hand, higher levels of circulating IL-6 were found in patients with the more severe form of NAFLD[70].

IR is strictly linked to anti-apoptotic serum Bcl-2 values[71], which were higher in simple fatty liver than in NASH patients, suggesting a protective role of the anti-apoptotic process in liver and perhaps in other areas[72]. Apoptotic cell death is caspase-dependent and is associated with mitochondrial membrane depolarization and cytochrome c release[73]. Adhering to the hypothesis that the exposure of hepatocytes to free fatty acids, resulting in increased reactive oxygen species production and mitochondrial damage, is balanced by the presence of anti-oxidant substances, circulating levels of gamma-glutamyl transferase, cytochrome c, triglycerides and unconjugated bilirubin were explored in patients suffering from non-alcoholic fatty liver disease with different severity[73]. The resulting findings likely reflect a balance between oxidative stress and anti-oxidant response rather than a lack of reliability of cytochrome c as a reliable biomarker of mitochondrial damage[73].

The inflammatory mediators that are biosynthesized in the liver and increased in NAFLD patients include C-reactive protein (CRP)[74], IL-6[70], fibrinogen and plasminogen activator inhibitor-1 (PAI-1)[75]. Consequently, fat in the liver represents a site beyond adipose tissue that independently contributes to the inflammatory process. In support of a certain sequence of cellular and molecular events that mediates hepatic IR in NAFLD, recent data lend credence to the fact that hepatic steatosis activates IκB kinase (IKK)-β and nuclear factor (NF)-κB[76]. Among the inducible transcription factors that control inflammatory gene expression, NF-κB plays a central and an evolutionarily conserved role in coordinating the expression of various soluble pro-inflammatory mediators (cytokines and chemokines) and leukocyte adhesion molecules. In non stimulated cells, NF-κB is sequestered in cytosol by the inhibitor of NF-κB (IκB), which masks the nuclear localization signal present along the NF-κB protein sequence.

Treatment of cells with pro-inflammatory cytokines such as TNF-α and IL-1, or with bacterial products such as lipopolysaccharide, leads to the activation of a specific-IKK complex that phosphorylates IκB and thereby tags it for ubiquitination and degradation by the proteasome[77]. The degradation of IκB thus allows NF-κB to translocate into the nucleus where it can act as a transcription factor that upregulates IL-6 production and secretion. IL-6 works locally through paracrine and/or endocrine mechanisms to activate IL-6 signaling in the liver. IL-6 is known to induce IR in hepatocytes[78]. Hepatic production of IL-6 also provides a further pathogenic link to extrahepatic organs such as muscle. *NF-κB* target genes are not upregulated in transgenic mouse muscle, unlike IL-6 target genes and the suppressor of cytokine signaling and signal transducer and activator of transcription proteins. These genes are reversed during IL-6 neutralization, which is consistent with the pathogenic involvement of IL-6. Activation of NF-κB leads to a severe syndrome of muscle wasting, without IR[79].

Fat mass in overweight/obese subjects has a primary role in determining low-grade chronic inflammation and, in turn, IR and ectopic lipid storage within the liver[80]. Obesity, aging, and fat mass all influence the growth hormone/insulin-like growth factor (IGF)- I axis, and chronic inflammation might reduce IGF- I signaling. Altered IGF- I axis is frequently observed in patients with hepatic steatosis[80]. In our study population, lower IGF- I status is associated with higher fat mass, spleen longitudinal diameter, CRP and more severe hepatic steatosis[80].

11β-HSD1 IN INFLAMMATION

At least some of the immunomodulatory effects of GCs in the inflammatory response are dependent on 11β-HSD1 activity. For example, 11β-HSD1 -deficient mice suffering from experimental arthritis exhibit a de-

layed resolution of the inflammatory response, probably due, in part, to attenuated macrophage phagocytosis of leukocyte apoptotic bodies[81,82]. As GCs regulate both the suppression of the early phase and the promotion of the late phase of the inflammatory response, it is conceivable that in generally deregulated - *i.e.,* both decreased and increased - GC levels could contribute to chronic inflammatory disease. Even if not characteristically for all chronic inflammatory conditions, some of them have been associated with increased 11β-HSD1 expression, in particular inflammatory diseases of the digestive tract, such as inflammatory bowel disease and colitis[82-85], as well as atherosclerosis[44,86]. These observations are in line with several reports evidencing the induction of 11β-HSD1 expression by pro-inflammatory cytokines TNF-α and IL-1β in various cell types and lines including fibroblasts, adipocytes, osteoblasts and smooth muscle cells[5-7,87-91].

PARADOX OF IL-6 IN HUMANS AND ANIMALS

If global deletion of IL-6 not only develops obesity, but also hepatosteatosis and liver inflammation in animal model[69], what is that determines the low prevalence of hepatic steatosis in patients suffering from Cushing's disease[22]?

Ahmed *et al*[54] defined hepatic GCs metabolism in progressive NAFLD, which can be summarized into two distinct phases of altered regulation of hepatic cortisol metabolism: (1) increased hepatic cortisol clearance in steatosis; and (2) increased hepatic cortisol regeneration in NASH. Failure to regulate in this way may worsen the phenotype of liver disease driving hepatic steatosis or unchecked progressive hepatic inflammation[54].

Considering the broadly accepted presence of inflammatory elements in the etiology of obesity, 11β-HSD1 probably plays an important causative role in the development of the metabolic syndrome, positioning itself at the interface of inflammation, hepatic steatosis and Cushing's syndrome.

From another perspective, under conditions that avoided changes in food intake, the efficacy of 11β-HSD1 inhibition to up-regulate hepatic fat oxidation gene expression - which reduces the glucocorticoid effects in liver and fat - functionally translates into enhanced hepatic lipid oxidation in vivo[92].

ANSWERED QUESTIONS AND CONCLUDING REMARKS

Considering the 50% five-year survival rate of patients with endogenous Cushing's syndrome (without any treatment)[93] and the fact that all patients enrolled into the study by Rockall *et al*[22] were all newly diagnosed patients, should we discuss the question of time exposure as a possible explanation for the relatively low prevalence of hepatic steatosis in patients with endogenous Cushing's syndrome? Should the relative hypercortisolemia (the increase in free cortisol or circadian disturbance) in patients with metabolic syndrome not be completely disregarded? At least two diagnostic studies aiming to evaluate patients with Cushing's syndrome among patients with obesity have found that late-night salivary cortisol (free cortisol) is increased in patients with obesity. Baid *et al*[94] reported that late night salivary cortisol was frequently above the laboratory-provided reference range in obese and overweight subjects (n = 369). In another paper late-night salivary cortisol was statistically significantly increased in patients with obesity and some features of Cushing' s syndrome, in whom endogenous Cushing's syndrome was excluded, *vs* healthy, normal BMI control subjects[95]. Since IL-6 also plays an anti-inflammatory activity, it seems reasonable to assume that favorable aspects exist, such as inactivating proinflammatory mediators that induce the production of cortisol during exercise, and thus influence insulin sensitivity, with enhanced insulin action at muscle level, immediately at early recovery[96]. Could this anti-inflammatory effect of high circulating GCs affect hepatic steatosis in Cushing's disease?

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