Hepatic PTEN deficiency improves muscle insulin sensitivity and decreases adiposity in mice

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Abstract

PTEN is a dual lipid/protein phosphatase downregulated in steatotic liver with obesity or HCV infection. Liver-specific PTEN knockout (LPTENKO) mice develop steatosis, inflammation/fibrosis and hepatocellular carcinoma with aging, but surprisingly also enhanced glucose tolerance. This study aims at understanding the mechanisms by which hepatic PTEN deficiency improves glucose tolerance, while promoting fatty liver diseases.

Reference


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Hepatic PTEN deficiency improves muscle insulin sensitivity and decreases adiposity in mice

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Background & Aims: PTEN is a dual lipid/protein phosphatase, downregulated in steatotic livers with obesity or HCV infection. Liver-specific PTEN knockout (LPTEN KO) mice develop steatosis, inflammation/fibrosis and hepatocellular carcinoma with aging, but surprisingly also enhanced glucose tolerance. This study aimed at understanding the mechanisms by which hepatic PTEN deficiency improves glucose tolerance, while promoting fatty liver diseases.

Methods: Control and LPTEN KO mice underwent glucose/pyruvate tolerance tests and euglycemic-hyperinsulinemic clamps. Body fat distribution was assessed by EchoMRI, CT-scan and dissection analyses. Primary/cultured hepatocytes and insulin-sensitive tissues were analysed ex vivo.

Results: PTEN deficiency in hepatocytes led to steatosis through increased fatty acid (FA) uptake and de novo lipogenesis. Although LPTEN KO mice exhibited hepatic steatosis, they displayed increased skeletal muscle insulin sensitivity and glucose uptake, as assessed by euglycemic-hyperinsulinemic clamps. Surprisingly, white adipose tissue (WAT) depots were also drastically reduced. Analyses of key enzymes involved in lipid metabolism further indicated that FA synthesis/esterification was decreased in WAT. In addition, Ucp1 expression and multilocular lipid droplet structures were observed in this tissue, indicating the presence of beige adipocytes. Consistent with a liver to muscle/adipocyte crosstalk, the expression of liver-derived circulating factors, known to impact on muscle insulin sensitivity and WAT homeostasis (e.g., FGF21), was modulated in LPTEN KO mice.

Conclusions: Although steatosis develops in LPTEN KO mice, PTEN deficiency in hepatocytes promotes a crosstalk between liver and muscle, as well as adipose tissue, resulting in enhanced insulin sensitivity, improved glucose tolerance and decreased adiposity.

Keywords: Steatosis; Beige adipocyte; Glucose tolerance; Gluconeogenesis; Organ crosstalk; FGF21.

Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver metabolic disorders, starting with an excessive accumulation of neutral lipids in cytoplasmic droplets of hepatocytes (steatosis), which can then progress towards inflammation, fibrosis and cirrhosis. Obesity and viral infections are common causes of these chronic liver diseases, which are often accompanied by insulin resistance (IR). Indeed, lipotoxicity, resulting from excessive overloading of hepatocytes with lipids, was reported to affect insulin-stimulated signalling pathways that control glucose and lipid metabolism [1]. Hepatic IR is likely to represent a precursor event, leading to systemic and long-standing IR [2]. Uncontrolled hepatic glucose output may indeed induce hyperglycaemia and compensatory hyperinsulinemia, favouring IR development in other organs. In turn, insulin-resistant muscle and adipose tissue exacerbate hepatic metabolic disorders, thus nourishing a vicious circle of peripheral IR. Lipotoxicity, inflammation and systemic IR contribute with time to the alteration of pancreatic β-cell function and survival, resulting in their inability to secrete enough insulin to counteract peripheral tissues IR, therefore leading to the development of type 2 diabetes [2,3]. In turn, diabetes favours steatosis evolution towards steatohepatitis, fibrosis/cirrhosis and hepatocellular carcinoma, again creating a vicious circle [4].

Insulin signalling is highly regulated at different levels by multiple mechanisms. Among them, the phosphatase and tensin homolog (PTEN) is a dual specificity protein and phosphoinositi- 

dide phosphatase that dephosphorylates PtdIns(3,4,5)P3, the product of PI3K [5]. By metabolizing PtdIns(3,4,5)P3, PTEN interrupts insulin signalling downstream of PI3K. This PTEN antagonistic effect on PI3K signalling [6] and its nuclear function

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on chromosomal stability [7] position PTEN as an important tumour suppressor, which is often deleted/mutated or downregulated in human cancers [6]. Alterations of PTEN expression/activity are also expected to deeply affect lipid and glucose homeostasis. Indeed, PTEN heterozygosity and PTEN tissue-specific deletions in muscle or adipose tissue all lead to improved glucose tolerance in healthy or obese/diabetic mice [8–10]. However, adding to the complexity of PTEN function, transgenic mice, overexpressing PTEN, display increased energy expenditure and insulin sensitivity [11,12]. Regarding the liver, we previously reported that PTEN is downregulated in steatotic livers of obese patients, as well as in rat models of genetic or diet-induced obesity [13]. Likewise, PTEN is downregulated in the liver of patients infected with hepatitis C virus (HCV) [14]. Interestingly, both obesity and HCV infection are associated with the development of steatosis and IR. However, liverspecific PTEN knockout mice (LPTEN KO) exhibit an ambiguous phenotype. Indeed, LPTEN KO mice develop sequentially hepatic steatosis, inflammation/fibrosis and hepatocellular carcinoma with aging, indicating that PTEN plays a crucial role in the development of these pathologies [15,16]. Yet, LPTEN KO mice also exhibit an improved glucose tolerance, which is unexpected with NAFLD [15,16]. This study aimed at understanding the mechanisms through which liver-specific PTEN deficiency improves glucose tolerance, while promoting NAFLD.

Materials and methods

Reagents, antibodies, and cell cultures

All reagents, antibodies, commercial kits, cell isolation and cell culture are described in the Supplementary Materials and methods section.

Animals

Ptenflaxflox (CTL) and AlbCre-Ptenflaxflox (LPTEN KO) mice generated as previously described [15], were housed at 23 °C; light cycle: 07.00 am–07.00 pm and had free access to water and standard diet. All experiments were conducted in accordance with the Swiss guidelines for animal experimentation and were ethically approved by the Geneva Health head office. 4-month old mice were sacrificed using isoflurane anaesthesia followed by rapid decapitation and blood/tissues collected and stored at −80 °C.

Metabolic phenotyping, EchoMRI, and CT-scan

Energy expenditure and the respiratory exchange ratio were determined by indirect calorimetry: locomotor activity was recorded by an infrared frame, and food and fluid intake were measured by highly sensitive feeding and drinking sensors. These parameters were measured in mice housed individually in Labmaster metabolic cages (TSE, Bad Homburg, Germany) after 5 days of adaptation prior to recording. Fuel (carbohydrate plus protein vs. fat) oxidation was calculated as described by Bruss et al. [17]. An EchoMRI-700 quantitative nuclear magnetic resonance analyzer (Echo Medical Systems, Houston, TX) was used to measure total fat and lean mass. Distribution, volume and weight of fat depots were analysed by a multidetector CT-scan (Discovery 750 HD, GE Healthcare, Milwaukee, USA) and dissection after sacrifice. For cold exposure, mice were housed in a 6 °C cold room up to 24 h and body temperature was measured at the indicated time points.

Glucose, pyruvate tolerance tests (GTT, PTT) and insulin injections

After overnight starvation, mice were administered intraperitoneally with glucose (1.5 g·kg⁻¹) or pyruvate (2 g·kg⁻¹) and glycæma was measured from tail blood during 2 h. To investigate insulin signalling in organs, mice were injected intraperitoneally with 150 mU·l⁻¹ of insulin (or PBS) 40 min before sacrifice, as previously validated [18].

Euglycemic-hyperinsulinemic clamps

4 h fasted mice were anesthetized with intraperitoneal pentobarbital (80 mg·kg⁻¹). As previously described [19], euglycemic-hyperinsulinemic clamps were performed, using insulin infusion at a dose suppressing hepatic glucose production (18 mU·kg⁻¹·min⁻¹), and the glucose infusion rate was measured. At steady state, a bolus of 2-deoxy-D-(1-³H)glucose (30 mCi) was injected to determine the in vivo glucose utilization index of insulin-sensitive tissues. 2-deoxy-D-(1-³H)glucose-6-phosphate in peripheral tissues was measured using a liquid scintillation analyzer (Tri-Carb 2900TR, Perkinelmer, MA, USA).

Histological analyses

Tissues were fixed in 4% paraformaldehyde and 6 μm thin sections were stained with haematoxylin/eosin for morphological investigations. Quantifications were performed using the Metamorph software.

Plasma and tissue analyses

Plasma triglycerides (TGs) were determined by an automated Abbott Architect analyzer (Abbott Architect, Paris, France). Plasma glucose, insulin, non-esterified fatty acids (NEFA), lactate, ketone bodies and FGF21 levels, as well as liver content of TGs, glycerone and ketone bodies were measured with commercial kits.

Real-time PCR

RNA was extracted using Trizol according to the manufacturer’s instructions. 1 μg of RNA was reverse transcribed using a VILO kit. Quantitative RT-PCRs were performed using a SYBR green detector on a StepOne PCR system (Life Technologies, Carlsbad, USA). Primer sequences are listed in Supplementary Table 1.

Western blot analyses

Homogenized cells/tissues were lysed in ice-cold RIPA buffer. Proteins were resolved by 5–20% gradient SDS-PAGE and blotted onto nitrocellulose membranes. Proteins were detected with specific primary antibodies and HRP-conjugated secondary antibodies using chemoluminescence. Quantifications were performed using the ChemiDoc™ XRS from Biorad (Cressier, Switzerland) and the Quantity One™ Software.

Statistical analysis

Results expressed as means ± SEM of at least 3 independent experiments or at least 4 different animals per group. Results were analysed by Student’s t test or two-way ANOVA followed by a Sidak’s multiple comparisons test when more than 2 groups or multiple time points were analysed. Values were considered significant when *p < 0.05, **p < 0.01 or ***p < 0.001.

Results

Hepatic steatosis in LPTEN KO mice is associated with increased glycolysis but decreased gluconeogenesis and glucose output

As previously reported, LPTEN KO mice have an increased liver weight related to triglyceride (TG) accumulation in hepatocytes (Supplementary Fig. 1 and [16]). We found two mechanisms contributing to excessive TG accumulation in the liver of LPTEN KO mice. First, mRNA expression levels of FA transporters, in particular Cd36, Fas and Fabp1, were significantly upregulated, suggesting increased FA uptake from the bloodstream by PTEN-deficient hepatocytes (Supplementary Fig. 2). Secondly, critical effectors promoting de novo lipogenesis were strongly overexpressed in the liver of LPTEN KO mice. In particular, the mRNA expression of Fas, Act1, Acc2, Scd1, Ppara and Srebpl was upregulated. In addition, protein expression of key enzymes involved in
FA biosynthesis, i.e. FA synthase (FAS) and acetyl-CoA carboxylase (ACC), was also strongly increased in PTEN-depleted hepatic tissue. On the contrary, the general expression pattern of rate-limiting key enzymes controlling hepatic FA oxidation, lipolysis and export, as well as cholesterol metabolism, mainly remained unchanged with the exception of a few enzymes weakly up- or downregulated (Supplementary Fig. 2).

Hepatic steatosis is usually tightly associated with IR [20]. However, glucose tolerance tests (GTT) indicated that LPTEN KO mice paradoxically exhibited an improved glucose tolerance (Fig. 1C). Although impaired hepatic gluconeogenesis and glucose output likely contribute to the improved glucose tolerance of LPTEN KO mice, insulin sensitivity and glucose uptake by peripheral organs, i.e. skeletal muscle and adipose tissues, are also important potential mechanisms to be considered. To address this issue, we first examined the phosphorylation/activation of AKT, a major insulin signalling effector, in peripheral organs of LPTEN KO vs. CTL mice injected with insulin. As shown in Fig. 2A, LPTEN KO mice, stimulated with insulin, displayed lower activation of the insulin receptor (INSR) in the liver, but higher basal and insulin-stimulated AKT phosphorylation, due to a lack of the PTEN antagonistic effect on PI3K signalling. Surprisingly, although PTEN expression was not altered in non-hepatic and metabolically active tissues of LPTEN KO mice (Supplementary Fig. 1E and F) and despite the presence of higher TG levels in muscle (Supplementary Fig. 5), phosphorylation of the INSR and its downstream effector, AKT, was significantly increased in muscles of LPTEN KO mice, indicating muscle insulin hypersensitivity (Fig. 2B). Contrasting with skeletal muscle, AKT phosphorylation in white adipose tissue

These results indicate that FA synthesis is fostered by an increase in glucose utilization, whereas inhibition of gluconeogenesis and glucose output contributes to the improved glucose tolerance in LPTEN KO mice.

LPTEN KO mice display enhanced systemic insulin sensitivity and insulin-stimulated glucose uptake in skeletal muscle

Fig. 1. Increased hepatic glycolysis and decreased gluconeogenesis in LPTEN KO mice. Relative mRNA expression of genes involved in hepatic glycolysis (A) and gluconeogenesis (B). (C) Pyruvate tolerance test after overnight fasting. (D) Ketone bodies and glycogen levels in liver tissue. (E) Ketone bodies and lactate levels in plasma. Values are mean ± SEM of at least 4 animals per group.
(WAT) of LPTEN KO mice was reduced, although INSR phosphorylation was unaffected (Fig. 2C).

To further evaluate the influence of skeletal muscle on the glucose tolerance of LPTEN KO mice, we performed euglycemic-hyperinsulinemic clamps under conditions of complete suppression of hepatic glucose production. We observed that the glucose infusion rate (GIR) measured at the end of the clamps was highly increased in LPTEN KO mice, confirming
enhanced peripheral insulin sensitivity (Fig. 2D). Consistent with this observation, insulin-induced glucose uptake was increased in almost all skeletal muscle types examined, while it remained unaffected in WAT (Fig. 2E).

These results indicate that hepatic PTEN-deficiency induces muscle insulin hypersensitivity, which importantly contributes to the improved glucose tolerance observed in LPTEN KO mice.

Hepatic PTEN deletion decreases lipid storage in fat depots

Analysis of the overall phenotypic characteristics of LPTEN KO mice showed that their body weight and food intake were unaltered compared to CTL mice (Fig. 3A and B). The same was also the case for locomotor activity, energy expenditure and the respiratory exchange ratio (RER) measured by indirect calorimetry, as well as thermal regulation upon cold exposure (Supplementary Fig. 3). Furthermore, when body composition was assessed by EchoMRI analysis, the total lean and fat mass remained similar in both groups (Fig. 3C). However, LPTEN KO mice exhibited marked hepatic steatosis, as previously reported (Supplementary Fig. 1 and [16]). In view of these results, the normal overall fat content of LPTEN KO mice suggested a decrease in adipose tissue depots. We therefore used quantitative CT-scan imaging to measure fat depot volumes. Data obtained indicated that the volumes of interscapular, subcutaneous and intraperitoneal WAT depots were drastically reduced in LPTEN KO mice (Fig. 3D). This was further confirmed by accurate dissection and weighing of all visible fat depots (e.g. interscapular) were unchanged in LPTEN KO as compared to CTL mice.

We then analysed the mRNA expression of major effectors involved in lipid metabolism of mesenteric WAT (a representative WAT in the context of metabolic diseases) and did not detect
any important and significant change in the expression of key enzymes regulating FA uptake or lipolysis (Supplementary Fig. 4A and C), consistent with the absence of significant changes in plasma TG and non-esterified fatty acid (NEFA) levels (Supplementary Fig. 5A). Although the RER (ratio of VCO₂/VO₂) tended to decrease and fat oxidation to increase (Supplementary Fig. 3C and D) during the diurnal period, the expression of critical rate-limiting enzymes, controlling fatty acid β-oxidation, was not significantly altered (Supplementary Fig. 4C). However, Western blot analyses of FAS and ACC, two major enzymes required for FA biosynthesis, revealed a decrease in the expression of these proteins in WAT of LPTEN KO mice with no change in their respective mRNAs (Supplementary Fig. 4B). Reduction in FA esterification was also suggested by a decreased mRNA expression of Gpat1 (Supplementary Fig. 4A).

Together, these data indicate that Pten-deficiency in the liver decreases adiposity through crosstalk mechanisms between the liver and WAT, preventing FA synthesis and esterification in WAT.

Recent evidence indicates that browning of WAT (appearance of brown-like adipocytes called “beige cells” in WAT) may also importantly contribute to a decreased adiposity and improved metabolic status in mice [21]. Beige cells with high FA oxidation capacity in WAT are differentiated from classical white adipocytes by mainly two specific characteristics: (i) the expression of the uncoupling protein Ucp1 and (ii) multilocular lipid droplet structures, instead of a single large lipid droplet [21]. As shown in Fig. 4A, Ucp1 expression was increased in specific WAT depots of LPTEN KO mice, such as the mesenteric depot, indicating the presence of multilocular lipid droplets in LPTEN KO (Fig. 4B).

The effect of hepatic Pten-deficiency on muscle insulin sensitivity and fat storage in adipocytes highly suggests the presence of a crosstalk between the liver and peripheral organs. Liver-derived circulating factors, such as hepatokines and cytokines, play critical roles in these processes. We therefore assessed the expression of various factors secreted by the liver, and as shown in Fig. 4C, the expression of several hepatokines and cytokines, previously reported to modulate muscle insulin sensitivity and/or WAT homeostasis, was significantly affected in the liver of LPTEN KO mice. Of particular interest, was the fibroblast growth factor 21 (FGF21), which has a positive effect on muscle insulin sensitivity and browning of adipose tissue [22–25]. Expression of Fgf21 was also strongly upregulated in isolated primary hepatocytes of LPTEN KO mice and plasma FGF21 levels mirrored the liver mRNA expression, altogether supporting a major hepatic action of several dysregulated liver-derived factors, including a hepatokine is of particular interest since it is known to enhance browning of specific WAT depots of LPTEN KO mice. However, we do not favour this hypothesis since no significant difference in circulating NEFA levels was observed in LPTEN KO mice as compared to CTL mice and because the expression of key enzymes controlling adipocyte lipolysis was not significantly changed. Instead, inhibition of lipogenesis and FA esterification in WAT could partly explain the fat mass loss in LPTEN KO mice. Another mechanism may lie in the browning of white adipocytes (presence of beige cells), as detected by a significant upregulation of Ucp1 and the presence of multilocular lipid droplets in the mesenteric WAT depot. Interestingly, the presence of beige adipocytes in WAT has been linked with improved glucose tolerance [28], which is precisely observed in LPTEN KO vs. CTL mice. This might be related to decreased lipogenesis, mentioned above, and/or to an increase in peripheral insulin sensitivity. With regard to the latter parameter, one of the key findings, arising from our analyses of insulin signalling in skeletal muscle and euglycemic-hyperinsulinemic clamps, was a marked enhancement of insulin sensitivity and resulting glucose uptake in skeletal muscles from LPTEN KO. This effect on muscles, together with the decreased adiposity, highly suggests the existence of a crosstalk between liver and muscle/adipose tissue. Supporting this hypothesis, we found an altered pattern of cytokines/hepatokines expression and/or secretion (e.g., IL-8, FGF21 and fetuin A) that were previously reported to mediate the crosstalk between liver and peripheral tissues and to have an action on muscle insulin sensitivity and adiposity [29]. Among them, FGF21 was overexpressed in the liver of LPTEN KO mice, resulting in elevated plasma FGF21 levels. This insulin-sensitizing hepatokine is of particular interest since it is known to enhance glucose uptake in muscle [22,23] and to increase energy expenditure in WAT [30]. Interestingly, FGF21 was also reported to stimulate UCP1 expression and browning of WAT [24,25], in accordance with our data. How Pten controls FGF21 expression triggering improved muscle insulin sensitivity and decreased adiposity.

Discussion

Alterations of inter-organ communications can lead to drastic phenotypical changes in the metabolic status of organisms. Herein, we demonstrate that impaired Pten signalling in the liver leads to the development of NAFLD, while positively impacting on muscle and adipose tissue homeostasis, thereby improving systemic insulin sensitivity, glucose tolerance, and decreasing adiposity.

As previously reported, LPTEN KO mice develop a marked hepatic steatosis [16]. Based on our results, steatosis development arises not only from an increased de novo lipogenesis and decreased VLDL export as shown by Qiu et al. [26], but also from an increased FA uptake, as suggested by the significant upregulation of several FA transporters. This is linked with substantial changes in hepatic glucose metabolism, including enhanced glycolysis (whose products are essentially used for de novo lipogenesis), as well as decreased gluconeogenesis.

Given the increased liver glycolysis and inhibition of gluconeogenesis, hepatic-dependent sources of energy during starvation are likely restricted. Although kidneys and the gut may take over to maintain normoglycemia [27], other sources of energy might be provided by an increase in adipose tissue lipolysis, releasing FAs in the circulation. Such mechanisms might be responsible for the drastic reduction in adipose tissue depots of LPTEN KO mice. However, we do not favour this hypothesis since no significant difference in circulating NEFA levels was observed in LPTEN KO mice as compared to CTL mice and because the expression of key enzymes controlling adipocyte lipolysis was not significantly changed. Instead, inhibition of lipogenesis and FA esterification in WAT could partly explain the fat mass loss in LPTEN KO mice. Another mechanism may lie in the browning of white adipocytes (presence of beige cells), as detected by a significant upregulation of Ucp1 and the presence of multilocular lipid droplets in the mesenteric WAT depot. Interestingly, the presence of beige adipocytes in WAT has been linked with improved glucose tolerance [28], which is precisely observed in LPTEN KO vs. CTL mice. This might be related to decreased lipogenesis, mentioned above, and/or to an increase in peripheral insulin sensitivity. With regard to the latter parameter, one of the key findings, arising from our analyses of insulin signalling in skeletal muscle and euglycemic-hyperinsulinemic clamps, was a marked enhancement of insulin sensitivity and resulting glucose uptake in skeletal muscles from LPTEN KO. This effect on muscles, together with the decreased adiposity, highly suggests the existence of a crosstalk between liver and muscle/adipose tissue. Supporting this hypothesis, we found an altered pattern of cytokines/hepatokines expression and/or secretion (e.g., IL-8, FGF21 and fetuin A) that were previously reported to mediate the crosstalk between liver and peripheral tissues and to have an action on muscle insulin sensitivity and adiposity [29]. Among them, FGF21 was overexpressed in the liver of LPTEN KO mice, resulting in elevated plasma FGF21 levels. This insulin-sensitizing hepatokine is of particular interest since it is known to enhance glucose uptake in muscle [22,23] and to increase energy expenditure in WAT [30]. Interestingly, FGF21 was also reported to stimulate UCP1 expression and browning of WAT [24,25], in accordance with our data. How Pten controls FGF21 expression
in hepatocytes remains currently unclear. AKT activation was previously reported to stimulate FGF21 expression in muscle [31], raising the possibility that FGF21 overexpression in the liver of LPTEN KO mice is a direct consequence of PTEN-dependent AKT over-activation. However, our data with primary hepatocytes, in which PTEN expression is either up- or downregulated, argue against this hypothesis, and suggest that other hepatic metabolic stress and/or injuries are the main trigger of FGF21 overexpression, as previously described in various conditions and tissues [32]. Future studies should also evaluate whether the beneficial effects of hepatic PTEN deletion on muscles and WAT are related to the mere overproduction of FGF21 by the liver, or to a concerted action of several hepatic circulating factors, modulated by PTEN-deficient signalling in hepatocytes.

In addition to our study, PTEN overexpression in transgenic mice was recently shown to induce increased energy expenditure, hyperactive brown adipose tissues and reduced body fat accumulation [11,12]. It is therefore clear that chronic alterations of PTEN signalling in peripheral organs are correlated with adipose tissue plasticity. However, it is likely that alterations of
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PTEN signalling in specific organs exert distinct effects on adipose tissue biology, through either direct or indirect mechanisms that are currently not fully understood. A deep understanding of the role of PTEN in metabolically active tissues and of PTEN-dependent molecular mechanisms, mediating crosstalks between peripheral organs, would not only improve our general understanding of inter-organ communications, but would also allow envisaging new therapeutic options to treat IR and obesity.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors’ contributions

M. Peyrou, L. Bourgoin: study concept and design; acquisition, analysis, and interpretation of data; drafting of the manuscript. A.-L. Poher, J. Altirriba, C. Maeder, A. Caillon, M. Fournier, X. Monnet: acquisition, analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding. M. Foti: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; study supervision.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.09.012.

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