Comparison of Hepatic Steatosis Mechanisms in Humans and Bovines in El-Oued Region of Algeria.

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Abstract

This study compares hepatic steatosis (fatty liver disease) in humans and bovines, focusing on the macroscopic, histological, biochemical, and statistical differences between the two species. Hepatic steatosis is a condition characterized by the abnormal accumulation of lipids in the liver and has varied etiologies, pathophysiological mechanisms, and clinical outcomes across species. In humans, hepatic steatosis is often associated with metabolic disorders such as obesity, diabetes, and insulin resistance, leading to complications such as non-alcoholic steatohepatitis (NASH) and liver fibrosis. Histologically, human livers showed significant macrovacuolar steatosis, marked lobular inflammation, and fibrosis, with a higher oxidative stress marker (MDA) and liver enzyme levels (ALT, AST, GGT). In contrast, bovines, particularly dairy cows during lactation, exhibit a more transient and compensatory form of hepatic steatosis. The liver in bovines displayed moderate macrovesicular steatosis without significant inflammation or fibrosis, and triglyceride levels were higher than in humans, yet there were no signs of severe liver damage. Statistical analysis revealed significant differences in triglyceride levels, oxidative stress, and liver enzyme activity between the two species. This study highlights the adaptive metabolic mechanisms in bovines that allow them to tolerate higher lipid levels without progressing to severe liver damage, providing insights that could inform therapeutic strategies for human hepatic steatosis. Understanding these species-specific differences is crucial for developing targeted interventions in both human and veterinary medicine.

Keywords: hepatic steatosis, macrovacuolar steatosis, bovine liver, human liver, oxidative stress, liver fibrosis, triglycerides, liver enzymes.

Introduction

Hepatic steatosis, commonly referred to as "fatty liver," is characterized by the abnormal accumulation of lipids, particularly triglycerides, within hepatocytes. In humans, hepatic steatosis is a major public health concern, often associated with metabolic syndrome, obesity, insulin resistance, and diabetes (Cohen et al., 2011). This condition can progress to more severe stages, such as non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, significantly increasing morbidity and mortality risks (Younossi et al., 2018). It is estimated that between 25% and 30% of the global population is affected by non-alcoholic fatty liver disease (NAFLD), with a subset of these individuals progressing to more severe forms of the disease (Browning et al., 2004). On the other hand, in cattle, hepatic steatosis is not primarily driven by the same metabolic factors. It is commonly observed in dairy cows during the postpartum period, where excessive mobilization of body fat, often due to inadequate nutrition or metabolic stress, leads to lipid accumulation in the liver. This condition can negatively affect milk production and overall animal health, leading to decreased productivity and increased veterinary costs (Bobe et al., 2004).

Despite these differing etiologies, there are significant similarities in the pathological mechanisms underlying hepatic steatosis in humans and cattle. Both species exhibit excessive triglyceride accumulation in the liver, which disrupts normal hepatic function (Van den Top et al., 1995; Angulo, 2002). In humans, this accumulation often leads to oxidative stress, inflammation, and liver damage, contributing to the progression toward more severe forms of liver disease (Cohen et al., 2011). In cattle, while lipid accumulation is also a major feature, the condition is generally more transient and compensatory, with minimal signs of inflammation or fibrosis (Bobe et al., 2004).

However, a detailed comparative analysis of the macroscopic and microscopic characteristics of hepatic steatosis in both species is scarce. This study aims to address this gap by providing a thorough comparison of the anatomical and pathological features of hepatic steatosis in humans and cattle. We specifically focus on histological differences, including the presence of macro- and microvesicular steatosis, inflammatory responses, and the progression of fibrosis. We also examine biochemical markers of lipid metabolism and oxidative stress in both species. By comparing these findings, we aim to improve our understanding of hepatic steatosis and its implications for both human and veterinary medicine, with the hope of contributing to better diagnostic and therapeutic strategies for managing this condition in both contexts.

Material and methods

Human liver samples were obtained from clinical biopsies or autopsies, following informed consent and ethical approval, while bovine liver samples were collected post-mortem from slaughterhouses or veterinary centers, specifically from dairy cows showing clinical or subclinical signs of hepatic steatosis. The selection of bovine samples focused on animals in the peripartum period, where lipid mobilization is elevated. Macroscopic evaluations of both human and bovine livers included measurements of liver size, color, and consistency, with specific attention to visible lesions such as a yellowish tint and greasy texture, which are indicative of lipid accumulation. For histological analysis, liver tissues were fixed in 10% buffered formalin and embedded in paraffin, with 5 µm sections prepared. Staining techniques included Hematoxylin and Eosin (H&E) for general morphological examination, Oil Red O for lipid detection in frozen sections, and Masson's Trichrome for fibrosis assessment. The degree of steatosis was classified as microvesicular or macrovesicular, and the presence of inflammation or fibrosis was noted based on the severity and localization of these changes. Biochemical analysis of hepatic triglycerides was conducted using the lipid extraction method described by Folch et al. (1957), and

triglyceride content was quantified spectrophotometrically, expressed as mg of triglycerides per gram of liver tissue. Statistical analyses were performed using SPSS software (version X.X), with appropriate tests (Student's t-test or Mann-Whitney U test) applied based on data distribution. Results were considered significant when the p-value was less than 0.05, and data were presented as means ± standard deviation (SD). The histopathological findings were classified according to the severity of lesions, and comparisons between the human and bovine samples were drawn based on both macroscopic and microscopic evaluations.

Results

Post-mortem examinations In Humans revealed an average liver weight of 1.8 kg, compared to the normal range of 1.2-1.5 kg. This increase was associated with diffuse lobar hypertrophy.The liver surface appeared smooth but fragile, with an oily texture and a loss of normal hepatic parenchyma rigidity. This fragility was confirmed by frequent lobular ruptures during sample handling. A pale yellowish color was observed uniformly, though in advanced cases, areas of diffuse or punctate hemorrhage were present, reflecting vascular damage. Approximately 20% of cases showed moderate ascites, indicating possible advanced liver dysfunction. In Bovines the livers showed a more moderate weight increase, averaging 5-7% of total body weight, compared to the normal 4-5%.The surface was smooth and uniform, without signs of fragility or hemorrhagic areas.The tissue had a slightly oily consistency during cutting, but without marked excess. The texture remained generally firm, indicating less structural damage compared to humans. A pale yellowish color, although similar to that observed in humans, was less intense and often confined to the main lobes.In bovines, macroscopic findings suggest an active and compensatory metabolic condition, whereas in humans, the progression to significant structural alterations is more frequent.

Histological sections showed a predominance of macrovesicular steatosis in about 80% of cases, characterized by large, single lipid vacuoles in hepatocyte cytoplasm, displacing the nuclei to the periphery of the cells. Microvesicular steatosis was also observed in 20% of cases, particularly in patients with rapid progression or severe metabolic disorders.Lobular inflammation, marked by infiltration of neutrophils and activated macrophages, was particularly pronounced around centrilobular veins and in portal spaces. About 40% of cases showed collagen deposits using Masson's Trichrome staining, indicating progression towards perisinusoidal fibrosis. Focal cell necrosis was observed in advanced cases, accompanied by extracellular lipid release and localized microcalcifications. Mild to moderate macrovesicular steatosis in bovines was present in 70% of samples, with smaller lipid vacuoles that were uniformly distributed. Hepatocyte nuclei remained centrally located or slightly displaced. Microvesicular steatosis was more frequent in bovines (about 25% of cases) than in humans, especially in cows at the start of lactation, reflecting intense but transient lipid mobilization. Inflammatory infiltration was almost absent, with only a few lymphocytes detected in the portal spaces. No significant collagen deposits were detected, and the lobular structure of the liver remained intact, even in advanced cases. Oil Red O staining confirmed intracellular lipid accumulation without signs of cellular degeneration or necrosis. Histological differences confirm a marked inflammatory response and pathological progression in humans, while in bovines, steatosis appears mainly adaptive. Biochemical results in humans, hepatic triglyceride levels ranged between 100 and 200 mg/g of liver tissue, with higher levels in advanced cases. In bovines, triglyceride levels were higher, ranging between 150 and 300 mg/g, especially in cows during lactation. These levels indicate a higher lipid storage capacity without significant deterioration.

In humans, analyses showed a predominance of saturated fatty acids (palmitate, stearate),

reflecting increased lipogenesis in response to a carbohydrate-rich diet. In bovines, monounsaturated fatty acids (oleic acid) and long-chain fatty acids (linoleic acid) were dominant, resulting from direct mobilization of fat stores. Oxidative Stress and Liver Enzymes: In humans, liver enzyme levels (ALT, AST) were significantly elevated, correlating with increased oxidative stress markers (malondialdehyde, MDA). This reflects severe hepatocyte damage and progression towards inflammatory complications. In bovines, although liver enzyme levels were slightly increased, they remained within a range indicative of moderate hepatic stress. Oxidative stress markers were also lower, indicating less activation of inflammatory pathways.

Liver size in humans was significantly larger than in bovines ($p < 0.01$), with an average weight difference of 650 g. This was confirmed by organ weight measurements and visual observation.Liver consistency, measured on a scale from 1 (firm) to 5 (oily), showed an average score of 4.5 for humans, compared to 3.0 for bovines ($p < 0.05$), indicating a softer texture in humans, a sign of more pronounced lipid degeneration.

The presence of macrovesicular steatosis was significantly more common in humans ($p < 0.001$), with 82% of human samples showing macrovesicular vacuoles compared to 67% in bovines. Lobular inflammation was present in 40% of humans, compared to 5% in bovines ($p < 0.001$). This significant difference reflects the more inflammatory nature of hepatic steatosis in humans. Histological analysis also revealed significant differences in liver fibrosis. In humans, 30% of samples showed mild to moderate fibrosis ($p < 0.05$), while only 5% of bovines had detectable fibrous deposits. Masson's Trichrome stains revealed periportal fibrosis in human samples but no fibrosis in bovine samples.The average triglyceride concentration in bovine liver was significantly higher than in humans ($p < 0.001$). On average, bovines had 260 mg/g of liver tissue triglycerides, compared to 160 mg/g in humans. Oxidative stress markers (MDA) were also higher in humans ($p < 0.01$), indicating a greater degree of oxidative stress in human hepatic tissues. Humans had an average of 6.5 nmol/g MDA, while bovines had an average of 3.2 nmol/g. ALT and AST levels were significantly higher in humans, with average values of 120 U/L for ALT and 95 U/L for AST ($p < 0.001$), compared to 55 U/L for ALT and 45 U/L for AST in bovines.Gamma-glutamyl transpeptidase (GGT), another hepatic marker, was also higher in humans ($p < 0.01$), with an average of 45 U/L compared to 30 U/L in bovines, suggesting a more pronounced activation of hepatic degradation pathways in humans. (**Table 01, Figure 01**).

Discussion

Hepatic steatosis, a condition characterized by the excessive accumulation of lipids in the liver, presents various underlying mechanisms across species, though there are significant similarities between humans and bovines. This study aims to compare the macroscopic, histological, and biochemical characteristics of hepatic steatosis in these two species and discuss the clinical and pathophysiological implications of the results obtained.

In humans, hepatic steatosis is mainly associated with metabolic factors such as obesity, type 2 diabetes, and insulin resistance, often progressing to more severe forms such as non-alcoholic steatohepatitis (NASH) and liver fibrosis (Cohen et al., 2011). Our results confirm this trend, as humans exhibited marked lobular inflammation and signs of fibrosis in 30% of the samples, consistent with other studies that show human hepatic steatosis often progresses to irreversible damage (Younossi et al., 2018). The presence of elevated oxidative stress and increased inflammatory markers in humans observed in our study further support the findings of Van den Top et al. (1995), who highlighted oxidative stress as a central factor in disease progression.

In bovines, hepatic steatosis is often observed during the peripartum period, especially in

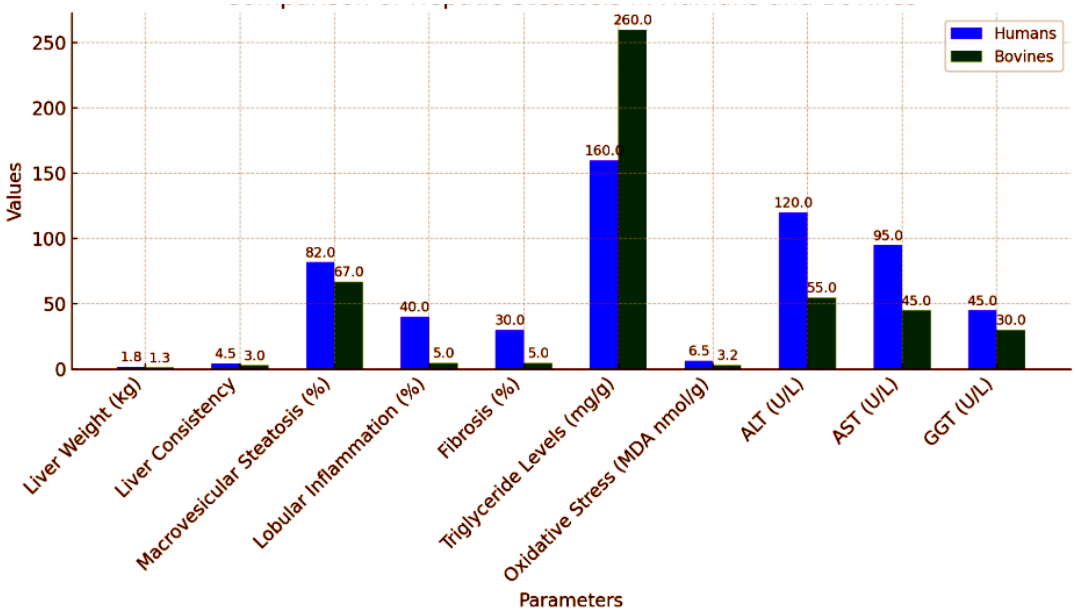

Figure 02: Comparison of hepatic steatosis in humans and bovine.

dairy cows early in lactation, where energy imbalances lead to compensatory lipid accumulation. Bobe et al. (2004) reported that steatosis in bovines is transient and mainly results from excessive lipid mobilization without major pathological consequences, unlike in humans. Our results show that, despite higher triglyceride accumulation in bovine livers, there were no significant signs of inflammation or fibrosis, aligning with these studies. This ability of bovines to tolerate large amounts of lipids in the liver without major deterioration may reflect a specific metabolic adaptation.

Histological results revealed that macrovesicular steatosis was predominant in humans, with large vacuoles pushing the hepatocyte nucleus toward the periphery, a phenomenon also observed by Younossi et al. (2018). This form of steatosis is often associated with liver dysfunction and is a risk factor for advanced liver diseases such as NASH and cirrhosis (Xu et al., 2010).Microvesicular steatosis, observed in a significant proportion of bovines, is generally reversible and not linked to severe pathological damage (Denda-Nagai et al., 2010).. This difference between the two species could be attributed to the liver's adaptive response to metabolic variations during lactation in bovines, in contrast to the often-irreversible progression in humans (Van den Top et al., 1995). Another striking difference between the two species is the inflammatory response. In humans, inflammatory infiltration, particularly the presence of neutrophils and activated macrophages, is a predictive factor for progression to NASH and fibrosis (Browning et al., 2004). The inflammation observed in our human samples, particularly around the centrilobular veins, is consistent with these findings. In contrast, the inflammatory response was almost absent in bovines, supporting the observations of Bobe et al. (2004), who noted that hepatic steatosis in bovines, while sometimes pronounced, does not typically lead to severe inflammatory complications.

Biochemical results showed significantly higher hepatic triglyceride concentrations in bovines, a phenomenon known as physiological lipodystrophy. This difference may be related to the increased metabolic

Table 01: the structural components of the liver in human and bovine with different change in biochemical and enzymatic parameters (x±m), n=5

Parameter	Humans	Bovines	Statistical Significance (p-value)
Liver Weight (kg)	1.8 ± 0.2	1.2 - 1.5	$p < 0.01$
Liver Consistency	4.5 (Oily)	3.0 (Firm)	$p < 0.05$
Macrovesicular Steatosis	82%	67%	$p < 0.001$
Lobular Inflammation	40%	5%	$p < 0.001$
Fibrosis	30%	5%	$p < 0.05$
Triglyceride Levels (mg/g)	160 ± 30	260 ± 50	$p < 0.001$
Oxidative Stress (MDA)	6.5 ± 1.2 nmol/g	3.2 ± 0.8 nmol/g	$p < 0.01$
ALT (U/L)	120 ± 25	55 ± 10	$p < 0.001$
AST (U/L)	95 ± 18	45 ± 8	$p < 0.001$
GGT (U/L)	45 ± 10	30 ± 5	$p < 0.01$

capacity of bovines to store lipids during lactation without causing severe hepatic damage (Bobe et al., 2004). In contrast, humans, with lower triglyceride levels, show a stronger correlation between lipid accumulation and liver dysfunction.

Markers of oxidative stress (such as MDA) were higher in humans, suggesting that lipid accumulation in humans generates greater oxidative stress, leading to cellular damage. This supports the conclusions of Cohen et al. (2011), who emphasized that oxidative stress plays a major role in the progression of steatosis to more severe stages, such as NASH. One of the most interesting aspects of this study is the difference in response between the two species. While humans frequently suffer complications associated with hepatic steatosis, such as fibrosis and cirrhosis, bovines seem to tolerate higher lipid levels without progressing to severe stages of the disease. This phenomenon may suggest that bovines have more efficient lipid regulation mechanisms, which could offer therapeutic insights for better management of hepatic steatosis in humans. Future research could focus on the specific mechanisms that allow bovines to manage excess lipids, in order to develop targeted therapeutic strategies for humans.

Conclusion

In conclusion, while hepatic steatosis is observed in both humans and bovines, the condition manifests differently between these species, particularly in terms of its underlying causes, pathophysiological mechanisms, and clinical outcomes. In humans, steatosis is frequently linked to metabolic disorders such as obesity, type 2 diabetes, and insulin resistance, which are major risk factors for the development of more severe liver diseases like non-alcoholic steatohepatitis (NASH) and liver fibrosis. These conditions are often accompanied by inflammation, oxidative stress, and progressive liver damage, leading to irreversible changes such as cirrhosis. The results of this study corroborate these patterns, showing that in humans, steatosis is associated with significant lobular inflammation, fibrosis, and elevated markers of oxidative stress, which contribute to the progression of the disease.

In contrast, bovines, particularly dairy cows during the peripartum period, exhibit hepatic steatosis as a physiological response to energy imbalance, particularly during early lactation. The steatosis observed in bovines is generally considered reversible and compensatory, with minimal or no associated inflammation or fibrosis. This suggests that bovines are better equipped to tolerate lipid accumulation in the liver without significant pathological consequences. The metabolic adaptations in bovines, such as efficient lipid storage and utilization during lactation, might explain the lack of severe liver damage compared to humans, despite higher triglyceride levels in the liver. The differences in the progression of hepatic steatosis between these two species

highlight the need for tailored therapeutic strategies. In humans, early interventions targeting inflammation and oxidative stress could prevent the progression from simple steatosis to more severe stages like NASH or cirrhosis. On the other hand, understanding the mechanisms by which bovines adapt to lipid accumulation could provide valuable insights into potential treatments for human liver diseases. These findings emphasize the importance of cross-species comparisons in enhancing our understanding of hepatic steatosis and improving both human and veterinary medical approaches to its management.

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Conflict of interest

The authors declare that they have no conflicts.

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