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Original Article

Impact of Stearic Acid on The Regenerative Outcome of Cell Therapy in Induced Liver Failure

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Summary

Introduction: Hepatocyte transplantation has been investigated as an alternative approach for acute liver injury; however, factors influencing engraftment and tissue response remain incompletely defined. This study evaluated whether dietary stearic acid modifies histological and ultrastructural outcomes following hepatocyte transplantation in a rat model of acetaminophen (APAP)-induced acute liver failure.

Methods: Nine-week-old Wistar rats were used; male rats served as hepatocyte donors and female rats as recipients. Acute liver injury was induced by intraperitoneal APAP (1 g/kg). A selected group received stearic acid–enriched food pellets (180 g/kg pellet) for 10 days. Twenty-four hours after APAP administration, 1×10^7 freshly isolated hepatocytes were injected into the lower pole of the spleen. Liver tissues were evaluated using H&E staining and transmission electron microscopy (TEM). PCR assessed donor cell presence in recipient livers for the sex-determining region Y (SRY) gene using liver DNA. For a subset of animals, the nuclei of donor cells were labeled before injection to support short-term localization, and the limitations of this approach were considered in the interpretation.

Findings: SRY amplification was detected in groups receiving hepatocyte transplantation, supporting the presence of donor-derived cells in recipient liver tissue. However, no clear difference in SRY detection was observed between the transplantation group and the transplantation plus stearic acid group. Histopathological and ultrastructural assessments indicated that APAP induced marked hepatic injury, while transplantation groups showed features consistent with partial structural improvement; stearic acid supplementation did not produce a distinct quantitative advantage over transplantation alone in the reported endpoints. DAPI-positive cell counts are reported as mean ± SEM for each group.

Conclusion: In this APAP-induced acute liver failure model, hepatocyte transplantation was associated with histological and ultrastructural changes consistent with partial recovery. Dietary stearic acid, as administered here, did not demonstrate a robust additional effect over transplantation alone based on the presented analyses. Further studies using validated long-term cell tracking and expanded quantitative endpoints are warranted.

Keywords: Hepatocyte transplantation, Stearic acid, Acetaminophen, Acute liver failure, Histology, TEM

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Introduction

The liver is an essential organ which has contributes to detoxification, homeostasis, glucose metabolism, protein synthesis, cholesterol metabolism, immune defense, and bile production.[1-3] The main cells, including 65-80% are hepatocytes in the liver.[4] Many damages by medications or toxins cause different diseases, such as hepatitis, cirrhosis, and hepatocellular carcinoma in the liver.[5] Liver-related diseases place a heavy burden on socioeconomics and generally affect 1.7% of the population. Severe liver failure is associated with a poor prognosis, and only liver transplantation can compensate for hepatic functions. However, liver transplantation is a costly, time-consuming, and complicated procedure because of limited donor availability and the need for sophisticated technology and experienced support teams at advanced centers.[6] These obstacles make cell therapy a promising alternative to liver transplantation. The main advantage of the method is the minimal invasiveness of the procedure.[7,8]

The efficacy of hepatocyte transplantation for damaged liver is not entirely satisfactory in terms of survival and function of the transplanted cells.[9] Tissue engineering approaches to transplant cells in extrahepatic locations have also been proposed.[10] The most important requirements are cell therapy and supplementary to successful transplantation. The supplementary diet of the host is an important step in preparing the host. There are very few studies focusing on the effect of nutritional and metabolic status on the success of liver cell therapy.

Stearic acid is a common nutritional long-chain fatty acid and is known as a potent anti-inflammatory lipid.[11] On the other hand, other saturated fatty acids like meristic acid and palmitic acid are positively associated with inflammation.[12] This acid is the third most abundant fatty acid in human hepatocytes and is involved in several liver functions, for example, cholesterol metabolism and

lipoprotein biogenesis.[13] Recent data indicate that, unlike oleic acid and linoleic acid, dietary stearic acid reduces adiposity and inhibits cancer growth.[14] These properties have been attributed to a selective anti-apoptotic effect of stearic acid on preadipocytes and cancer cells.[15] Dietary stearic acid increases serum oleic acid most probably through activation of hepatic enzymes.[16]

Chronic hepatic damage caused by drugs, chemicals, alcohol abuse, or viral infections is the predominant pathologic cause of cirrhosis.

Acetaminophen or paracetamol (N-acetyl-p-aminophenol, APAP) toxicity are is the most common cause of severe liver damage in united states, and best induced liver failure strategy for studying by increasing cytoplasmic organelles permeability such as mitochondria.[17]

Several studies of hepatic cell transplantation give credence to the hypothesis that the relevant functional unit of the liver could be used to correct and protect enzymatic and metabolic liver defects after injury whilst it regenerates.

There is no data available on the effect of stearic acid in liver cell therapy. Considering the profound effect of stearic acid on the histopathology of the liver, the present study aimed to investigate the effect of dietary stearic acid on the histophysiology of the liver after hepatocyte transplantation in a rat model of liver damage induced by acetaminophen.

Methods

Animals and treatments

Forty female and four male nine-week-old Wistar rats (average weight ~260 g) were obtained from the animal house of Tabriz University of Medical Sciences (Tabriz, Iran). Animals were maintained under standard conditions (12 h light/dark cycle, 24 ± 2 °C, 50 ± 10% humidity) with ad libitum access to water and standard chow. Male rats were used as hepatocyte donors and female rats as recipients. All procedures were approved by the local ethics committee (Ethical code: TBZMED. REC.1394.1173).

Female recipient rats were randomly assigned to four experimental groups (n = 10 per group): (1) Sham, (2) APAP, (3) APAP + hepatocyte transplantation (CT), and (4) APAP + hepatocyte transplantation + stearic acid (CT + SA). Acute liver injury was induced by a single intraperitoneal injection of acetaminophen (APAP; 1 g/kg). To potentiate APAP toxicity, phenobarbital was co-administered in drinking water until the end of the experiment (day 10). In the CT + SA group, animals received a stearic acid–enriched pellet diet (180 g stearic acid per kg pellet) from day 0 to day 10. Animals were euthanized on day 10. The dose and duration were chosen based on a similar research carried out to show the metabolic effect of oil ingestion in rat models.[19] Other studies have reported that major cell engraftment occurs as early as 3-5 days after transplantation.[18,20]

To determine the migration pattern of donor hepatocytes in the injected spleen, in a subgroup of per forth groups, randomly chosen animals, cells were stained with DAPI (4, 6-diamidino-2-phenylindole, Roche Mannheim, Germany) before injection.

To support short-term localization of infused hepatocytes, a subset of donor cells used for transplantation was subjected to nuclear labeling before injection. Because nuclear dyes may require membrane permeabilization and can affect cell viability, these observations were treated as supportive and interpreted cautiously; primary evidence of donor cell presence was based on SRY-PCR.

Hepatocyte isolation and transplantation

Hepatocytes were isolated from male Wistar rats by means of the collagenase perfusion method as described previously.[21] In brief, the rats were anesthetized by inhalation of diethyl ether. The liver was exposed by surgery and perfused with collagenase (Type V collagenase, Sigma, St. Louis, MO) through the portal vein and digested in situ in Hanks' buffer. Dissociated hepatocytes were separated by sedimentation. The isolated hepatocytes were suspended (1×10^6 cell/mL) in Krebs-Henseleit buffer containing 12.5 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid). Cell viability was assessed by estimation of plasma membrane disruption as determined by the trypan blue uptake test.[22]

After 24 h of APAP administration, 1×10^7 hepatocytes were injected through the lower pole of the spleen. To prevent vessel damage and bleeding, and cell leakage after cell transplantation, the lower zone of the spleen was ligated.[18] The female rats were randomly divided into four groups: sham (n = 10), APAP (n = 10), APAP + hepatocyte transplantation (n = 10), and APAP + hepatocyte transplantation + stearic acid (n = 10).

Assessment of cell engraftment

To detect infused male cells in the liver of female recipient rats, liver DNA was extracted with Trizol (Invitrogen, USA) on the tenth day after euthanization. Polymerase chain reaction (PCR) of the SRY gene was performed using the following primers: (for 5'AAGCGCCCCATGAATGCATT 3', rev 5'CAGCTGCTTGCTGATCTCTG3'). The amplified products were visualized in 1.5% agarose gels and stained with ethidium bromide.[18]

Histopathological analysis

For histopathological studies, all animals in the control and experimental groups were anesthetized with ketamine/xylazine (5/1) and perfused with cold PBS, then sacrificed, and 1-1.5 ml of blood was taken from the heart for biochemical analysis. In addition, livers were removed and fixed in 10% buffered formalin for 72 hours, and then the fixed tissues were embedded in paraffin. Liver specimens were sectioned serially with 50μm intervals and

5µm thickness and stained with H&E and studied with a light microscope. The 50µm interval was chosen based on the size of classic lobules in the liver. Portal space, central vein, hepatocyte plates, and sinusoids were confirmed according to morphological characteristics. For DAPI-stained analysis, liver samples were removed and fixed in 10% buffered formalin solution for 24 hours, were mounted in Prolong Gold anti-fade reagent with DAPI. To investigate, histopathological unstained sections were analyzed by fluorescent microscopy, and DAPI- positive cells were counted in 100 high-power fields.

Ultrastructural analysis

To analyze ultrastructure by electron microscope, the tissue pieces of livers were dissected out and fixed in 2% glutaraldehyde (ProSciTech, Thuringowa, Australia) in 0.1 M phosphate buffer and post-fixed in 1% O_SO_4 (TAAB, Berkshire, UK). The liver specimens were dehydrated through graded concentrations of ethanol and embedded in resin. One-micron semi-thin sections were stained in toluidine blue. Ultra-thin-sections were stained with uranyl acetate and lead citrate and visualized by LEO 906 transmission electron microscope (*TEM,* Oberkochen, Germany).

Statistical analysis

In this study, experiments were repeated three times with similar results, and the mean value and standard deviation were calculated (Mean ± SEM). Statistical analyses were performed by G-Pad software, P value ≤ 0.05 was considered to be significant.

Results

SRY-PCR was used to assess the presence of male donor-derived DNA in female recipient livers. SRY amplification was observed in samples from animals that received hepatocyte transplantation (CT and CT + SA groups), while it was not expected in non-transplanted female groups. Notably, SRY detection did not indicate a clear difference between the CT and CT + SA groups in this dataset (Figure 1). Therefore, SRY-PCR findings were interpreted as supportive of donor cell presence rather than as evidence of improved engraftment with stearic acid.

In the subset analyzed for nuclear labeling, DAPI-positive cells were quantified in 100 high-power fields and are presented as mean ± SEM. The mean number of DAPI-positive cells per animal was 59.2 ± 12.7 in the sham subgroup, 20.0 ± 0.8 in the APAP subgroup, 41.0 ± 18.3 in the CT subgroup, and 50.2 ± 21.09 in the CT + SA subgroup (Figure 2). Given the limitations of nuclear labeling for definitive long-term tracking, these data are presented as supportive observations.

Histopathological evaluation of livers from the control group revealed that in classic lobules the central vein (CV) with endothelial cell lining is clearly visible. Polyhedral hepatocytes with their nucleus and cytoplasm, and liver sinusoid with normal morphology are observable (Figure 3). The contact location of a hepatic sinusoidal pathway with lobular central vein is also easily recognized. Kupffer cells (arrow) near the sinusoidal space with triangle nucleus were observed.

Control livers showed preserved lobular architecture with normal-appearing hepatocytes and sinusoids (Figure 3). APAP administration induced marked hepatic injury characterized by hepatocyte necrosis and inflammatory cell infiltration, particularly around the central vein region (Figure 4). In transplantation-treated groups (CT and CT + SA), liver architecture demonstrated features consistent with partial structural improvement relative to the APAP group, including reduced overt necrotic appearance and more frequent euchromatic nuclei in hepatocytes (Figures 5–6). However, comparisons between the CT and CT + SA groups were primarily descriptive based on the available endpoints.

The effect of APAP on rats' liver toxicity is shown in Figure 4. Our result indicates the hepatocyte nucleus and cytoplasm become dense and wrinkled, and the portal space area has been reduced in comparison with the

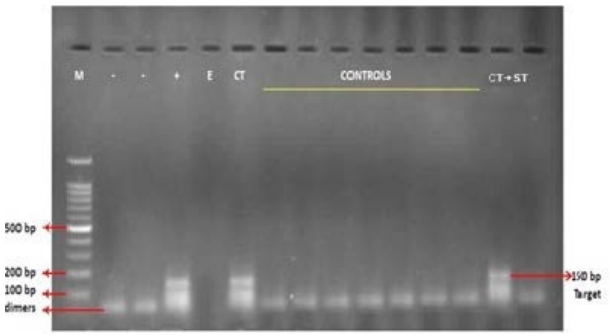

Figure 1. Gel electrophoresis image of DNA extracted from samples of liver tissue from rats. M: DNA marker, (-): negative control, (+): positive control, control: The group that did not receive hepatocyte, CT + ST cell therapy, and stearic acid, CT cell therapy

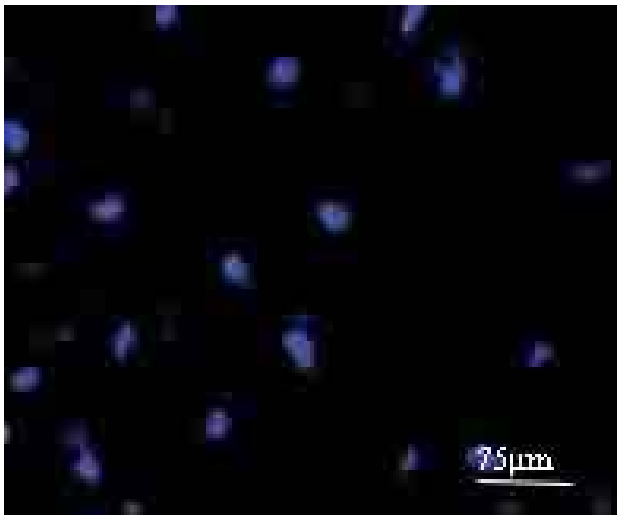

Figure 2. Photomicrograph of DAPI-positive cells in the liver of rats in the sham group

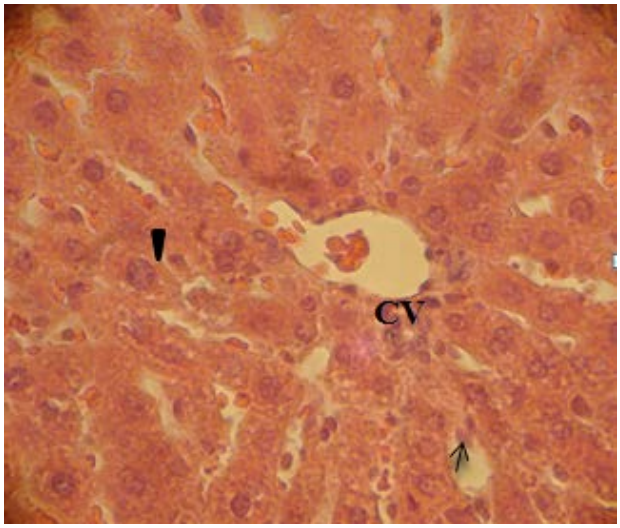

Figure 3. Micrograph of liver section from the control group showing normal histology of rat liver. Central vein (CV), Kupffer cells (arrow), hepatocyte (arrow head), H&E staining, (Bar 20µm) 440X

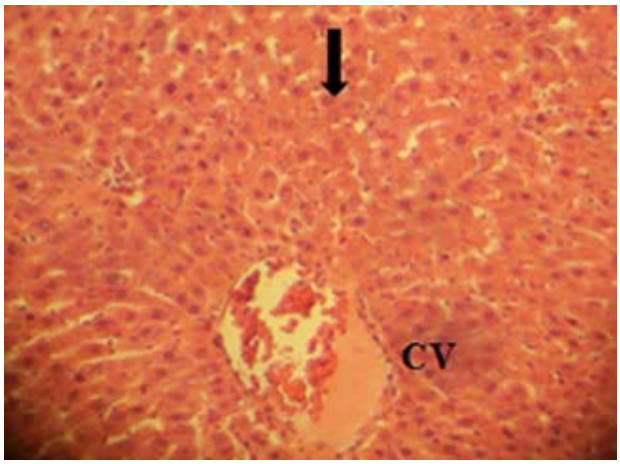

Figure 5. Micrograph of liver section from the acetaminophen-treated group that received cell transplantation. Central vein (CV), hepatocyte (arrow), H&E staining, (Bar 20µm) 440X

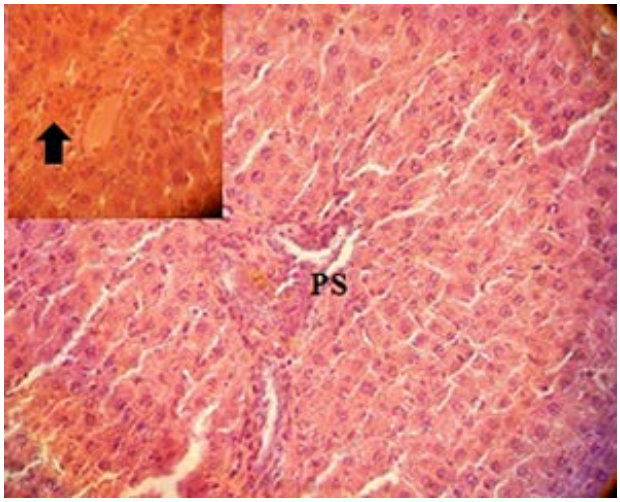

Figure 4. Micrograph of liver section from the group that received a toxic dose of acetaminophen. Note hepatocyte necrosis (arrow) in the portal space (PS), H&E staining, (Bar 20µm) 440X

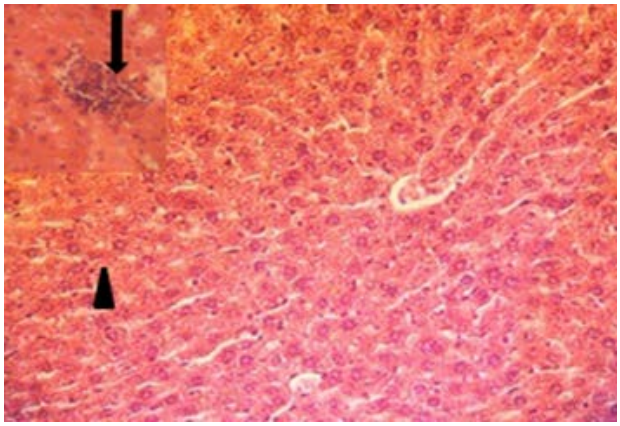

Figure 6. Micrograph of liver section from the group that received a toxic dose of acetaminophen, was treated with cell transplantation, and fed stearic acid. Lymphocyte (arrow), lipid droplets (arrow head), H&E staining,(Bar 20µm) 440X

control group. The sinusoids are dilated, and lipid droplets are dispersed in the cytoplasm of hepatocytes. Moreover, a large number of lymphocytes around blood vessels can be seen in the portal space migrant. Deleterious effects of acetaminophen were detectable on all the elements, such as compression of the hepatocytes and lining cells of sinusoids. The result indicates that when animals were treated with APAP, an extensive necrosis of liver parenchymal cells and inflammatory cells was noticeable. Remarkable coagulative hepatocyte necrosis observed within one of the three zones, especially around the central vein, can be seen in all images.

Histopathological evaluation of livers from rats that were treated with acetaminophen and received cell transplantation revealed classic lobular central vein and portal space (Figure 5). Hepatocytes with euchromatin nuclei from liver sheets are drawn toward the lobular central vein. Sinusoidal endothelial cells, lining normal hepatocytes, are observed. Within the port area hepatic artery, the portal vein, and the bile duct with normal histologic structure are visible. Cental vein endothelial cells can be seen. Further, minimal inflammation can be seen in the portal space. However, necrotic changes were not seen in hepatocytes in Comparison with the acetaminophen-treated group.

This study found that rats that received a toxic dose of acetaminophen and were treated with cell transplantation and stearic acid showed histological characteristics of liver cells that closely resemble those of the third group, which received acetaminophen and cell treatment (Figure 6). The third group consisted of euchromatin hepatocytes and cells with normal morphology. The euchromatin nuclei of liver cells indicate high biological activity. In this group, the cytoplasm of a limited number of hepatocytes is filled with fat droplets or lipids. A small number of lymphocytes were visible in the liver parenchyma. Kupffer cells were easily identified in this group. We found that the toxic effects of acetaminophen in the group that was fed stearic acid and received cell transplantation were

significantly reduced compared to the group treated with acetaminophen and receiving cell transplantation.

TEM findings in the APAP group included hepatocyte nuclear condensation, disrupted mitochondria, cytoplasmic vacuolization, and apoptotic/necrotic features (Figure 7B). In the CT group, ultrastructural abnormalities remained evident (Figure 7C). In the CT + SA group, several hepatocytes displayed euchromatic nuclei and relatively preserved organelles compared with the APAP group (Figure 7D). These observations suggest qualitative differences among groups; additional quantitative ultrastructural scoring would strengthen between-group comparisons.

Healthy liver specimens from the control group showed similar ultrastructural morphology with round and euchromatic nuclei of hepatocytes, normally oval or round mitochondria, several ribosomes, and ERs (Endoplasmic Reticulum). In addition, the cytoplasm contained some lipid droplets (Figure 7A). In the APAP group, ultrastructural alteration in the liver was apparent, that is, the nucleus of hepatocytes appears more condensed, irregular in shape, and heterochromatic than in the control group. In the hepatocyte, the organelles were more sparsely distributed throughout the cytoplasm. Some hepatocytes showed typical features of apoptosis, such as nuclear condensation, formation of crescent-like heterochromatin, changes in nuclear morphology, and the appearance of autophagic vacuoles and several apoptotic bodies. Vesiculation of cytoplasm, disrupted mitochondria, and dilated nuclear membrane were also observed in hepatocytes (Figure 7B). Ultrastructural evaluation of livers from rats that had been treated with acetaminophen and received cell transplantation showed a dilated nuclear envelope, several macrophages containing phagocytic vacuoles, and several necrotic features of hepatocytes with fibrotic intercellular space. In this group, histological and ultrastructural characteristics of hepatocytes are to a large extent similar to the APAP group (Figure 7C). Ultrastructural characteristics of liver from the group that received a toxic dose of acetaminophen, were treated with cell transplantation, and fed stearic acid showed euchromatic nucleus of hepatocyte, several cytoplasmic organelles, few lipid droplets, and abnormal nuclear envelope, almost similar to the control group (Figure 7D).

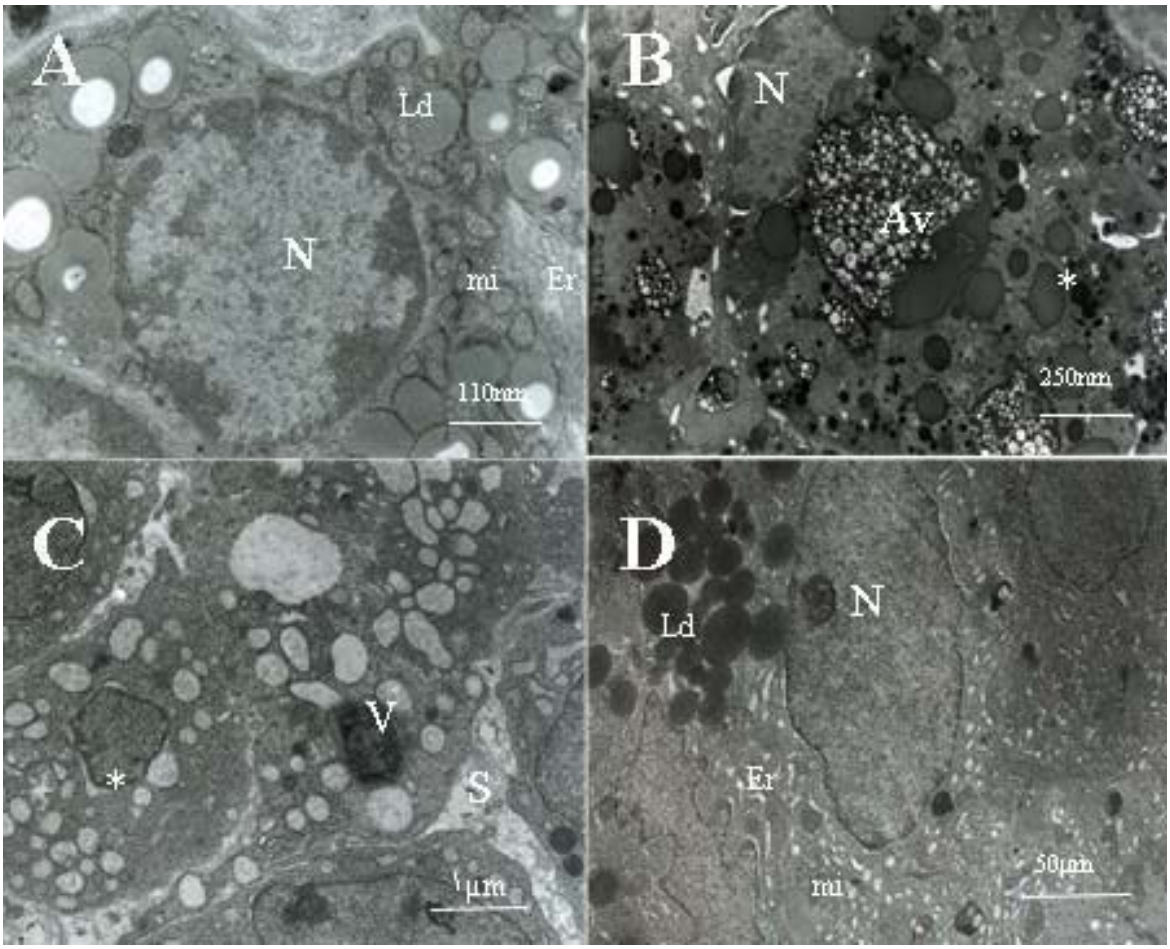

Figure 7. Electron micrographs from the liver of (A) Control group, (B) APAP group, (C) Treated group with APAP and cell transplantation, (D) Treated group with APAP and cell transplantation and stearic acid. (A) Hepatocyte with euchromatic nucleus (N) and normal Mitochondria (m) as well as endoplasmic reticulum (Er), Lipid droplet (L), nuclear envelope (*). (B) Condensed and heterochromatic nucleus with apoptotic features (N), autophagic vacuoles (Av), and apoptotic bodies (*). (C) Dilated nucleus envelop (*), phagocytic vacuoles (V), remarkable widening of intercellular space (S). (D) Euchromatic nucleus (N), Lipid droplet (L), and normal Mitochondria (m) as well as endoplasmic reticulum (Er)

Discussion

Cell transplantation can be an alternative and new method for the treatment of liver disease requiring liver transplantation.[6] Cell transplantation is a non-invasive technique, and donor cells can be used for a variety of purposes.[5,23] Histological evaluation is an important component in the safety assessment of newly discovered or experimental drugs or cell therapies, and often provides essential information on underlying pathogenic mechanisms. Our study evaluated the efficacy of hepatocyte transplantation on the recovery of the liver after liver damage from a toxic dose of acetaminophen and the role of a stearic acid diet in the hepatocyte transplantation. In this study, there are significant differences between the numbers of DAPI-positive hepatocytes in the control and APAP groups. In addition, no differences were found between APAP + cell transplantation and APAP + cell transplantation + stearic acid groups.

According to several studies, the spleen is the most widely used recipient site for hepatocyte injection because of its available location. Nassler's colleagues demonstrated that donor hepatocytes transplanted into the spleen could migrate to other organs, in particular to the host liver.[24] In our study, the engraftment of hepatocytes in the liver was revealed by PCR analysis for the SRY gene in female recipient organs and DAPI staining to show transplanted cells.

In recent studies, novel targets have been defined to improve engraftment of transplanted cells, and several drug-based strategies have been developed in experimental models to enhance cell engraftment in the liver.[25] The major development of this has concerned unseeing of drugs or diet to treat subjects before cell therapy.[26]

Our previous study showed the effectiveness of hepatocyte transplantation on liver function after APAP-induced liver damage and the role of stearic acid in the hepatocyte transplantation based on biochemical analyses. Correlation of histologic pattern with biochemical parameters was demonstrated in this study. However, histological analysis does a better job at predicting the presence of hepatocellular damage, as there is good correlation between histological patterns and biochemical analysis of AST, ALT, and ALP.[27] The presence of neutrophils and lymphocytes based on liver parenchyma with sinusoidal dilatation and the presence of lipid droplets in the cytoplasm of hepatocytes demonstrated a toxic effect from the drug on the liver structure. Our study revealed that transplanted hepatocytes alone have a weaker liver regeneration ability than hepatocytes transplanted with a stearic acid diet. Several studies have shown that liver regeneration after acute liver failure can be improved by allogeneic hepatocyte transplantation.[18,28] Therefore, hepatocyte transplantation alone had not decreased APAP-deficient induced liver injury, and the beneficial effect of stearic acid, accompanied by hepatocyte transplantation, leads to positive effects on liver repair.

We evaluated these two elements in our experiments. Using a rat model for hepatotoxicity with acetaminophen induced acute liver failure. We showed positive histopathologic effects of liver cell therapy, in particular in rats with a stearic acid diet, compared with control groups with euchromatic features of the nucleus, decreasing necrotic and pro-apoptotic morphology. Although the toxic effects of acetaminophen in liver histology were reported after acetaminophen-induced liver failure, histopathological assessment showed improvement of histopathological markers in the group with cell transplantation and that had been fed stearic acid, in contrast to other groups. Our results offer an important protective role of stearic acid in acute liver failure induced by acetaminophen. This protective effect can be attributed to stearic acid's anti-inflammatory properties.[29] Pan et al show the beneficial effect of a stearic acid diet in liver failure.[30] Stearic acid can reduce liver inflammation by suppressing inflammatory cell recruitment/accumulation and/or NF-κB activity.[30,31] Assessment of pro-inflammatory transcription factors, enzymes, and cytokines in experiments similar to ours suggests that the mechanism of the positive effects of stearic acid on hepatocyte transplantation should be further elucidated.

In the present research, numerous autophagic and phagocytic vacuoles are also observed in the liver of the APAP group. As autophagic vacuoles contain acid phosphatase activity, they are lysosomal in origin and, in part, responsible for the deterioration of hepatocytes. The phagocytic vacuoles and hepatocytes with pro-apoptotic morphology are observed in the parenchyma of livers. It has been proposed that apoptotic and necrotic cells induce invasion of macrophages and lymphocytes, possibly by releasing chemotactic factors.[32] In accordance with the aforementioned assumption, lymphocytes and macrophages were frequently seen in the APAP and APAP + cell therapy groups. It is known that these have the capacity to produce oxidative products such as nitric oxide and superoxide radicals.[33,34]

The ultrastructural findings from the present study indicate that pro-apoptotic features, together with necrotic damage of the liver, are in part responsible for the initiation of acute liver damage. Regarding the universal increase in liver damage with APAP.[35,36] Further morphological studies are needed to clarify the relationship between the induction of apoptosis or necrosis and APAP liver damage.

Moreover, in contrast to other saturated fatty acids such as palmitic acid, stearic acid has a significant cholesterol-lowering effect.[37] Promoting histopathological indices in stearic acid-fed rats can be related to the above effect. Homing of transplanted hepatocytes in the liver was positive. Although another study has shown the beneficial effect of stearic acid on liver function, this is the first study to examine the effect of stearic acid on the hepatocyte

therapy of an in vivo model. In this study, we assess several hepatic histopathological indices in relation to the SRY assay to assess cell transplantation. Future studies may be conducted with longer-term follow-up and may focus on possible mechanisms involved in the favorable effect of stearic acid. The results of the present study show that oral administration of stearic acid to rats, accompanied by hepatocyte therapy, decreased histopathological hepatic injury with APAP in an in vivo study of liver damage.

Conclusion

This study evaluated histological and ultrastructural outcomes after hepatocyte transplantation in a rat model of APAP-induced acute liver failure and explored whether dietary stearic acid modulates these outcomes. SRY-PCR supported the presence of donor-derived DNA in transplantation groups; however, a clear difference between transplantation alone and transplantation plus stearic acid was not demonstrated by SRY-PCR. Histological and TEM analyses indicated that transplantation groups exhibited features consistent with partial structural recovery relative to APAP alone, while the additional effect of dietary stearic acid in the reported endpoints was not robust. Future studies incorporating validated long-term cell tracking and expanded quantitative outcome measures are recommended.

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Authors' Contribution

Conceptualization: Leila Roshangar, Mehdi Sadigh herab, Ali Eghbal.
Data curation: Leila Roshangar, Mehdi Sadigh herab, Ali Eghbal.
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Investigation: Mehdi Sadigh herab, Shahla Meshgi.
Methodology: Leila Roshangar, Mehdi Sadigh herab,
Validation: Nostatollah Zarghami, Masood Darabi.
Project administration: Leila Roshangar.
Resources: Leila Roshangar.
Supervision: Leila Roshangar, Nostatollah Zarghami.
Visualization: Leila Roshangar, Mehdi Sadigh herab.
Writing-original draft: Leila Roshangar, Mehdi Sadigh herab.
Writing-review and editing: Leila Roshangar, Mehdi Sadigh herab.

Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

All procedures were approved by the local ethics committee of Tabriz University of Medical Sciences (Ethical code: TBZMED. REC.1394.1173).

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