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REVIEW ARTICLE

Is obesity rather than the dietary supplement used for weight reduction the cause of liver injury?

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Abstract

Acute liver injury has been attributed to dietary supplements (DS) used for weight loss, but their causal role was much questioned, and obesity as an alternative cause of the liver injury remained unclear. A comprehensive search of the Medline database was conducted with terms that included "DS," "liver injury," "obesity," "obesity-related liver diseases," and "nonalcoholic steatohepatitis." For each term, we focused on the first 50 publications. We undertook a manual search to identify additional reports. Underlying liver diseases and other health issues are common in patients taking DS for weight reduction. These include obesity or morbid obesity, as well as complex metabolic disorders complicated by excess morbidity and mortality due to associated liver diseases. Among these are nonalcoholic fatty liver disease with potential progression to nonalcoholic steatohepatitis and cirrhosis, often classified as cryptogenic with a rare risk of hepatocellular carcinoma. With the exception of hepatocellular carcinoma, these obesity-related liver diseases were observed to varying degrees in patients, and some even required a liver transplant. This raises the question whether the liver injury that occurred in these patients is due to DS consumed for weight loss or to the underlying obesity-related liver diseases. This analysis showed that, in many instances, the causal role of obesity has been neglected. Obesity-associated liver diseases should be considered as differential diagnosis of liver injury in obese patients using DS.

Introduction

Liver injury by drugs, herbs, and dietary supplements (HDS) was comprehensively reviewed in 2016[1] and 2017,[2] with extensive information provided in a HDS case series published in 2017.[3] These topics were also discussed in a special issue on "Drug, Herb, and Dietary Supplement Hepatotoxicity" in 2016.[4–8] Liver injuries related to herbs[5,7] and dietary supplements (DS)[7,8] represent a major clinical and regulatory challenge. Some issues including product variability, low product quality, and lack of clear identification of the product used are specific to these products and others such as incomplete case data sets, poor or lack of causality assessment, confounding variables such as comedications or pre-existing liver diseases are common to all related cases. Consequently, more rigorous approaches are needed to evaluate these causes of liver injury,[1,2,9] in addition to transparent, complete, and systematic case data documentation.[9]

Poor evaluation of the early cases of drug-induced liver injury (DILI) cases required thorough causality reassessment, which questioned the initial diagnosis of liver injury.[6] This is in line with the cases of herb-induced liver injury (HILI) or liver injury by DS, for which alternative causes were found later,[10–12] not unexpected in an environment of frequent acute and chronic

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liver diseases in the population, a problem not sufficiently discussed up to now. Indeed, it is estimated that the worldwide prevalence of chronic liver diseases is around 1.3 billion individuals, most commonly nonalcoholic fatty liver disease (NAFLD) (>600 million) and less frequently chronic hepatitis B virus (HBV) (>350 million) as evidenced by hepatitis B surface antigen (HBsAg) positivity, or chronic hepatitis C virus (HCV) (200 million) as evidenced by anti-HCV positivity, or alcoholic liver disease (ALD) (>150 million).[13] In the USA, the prevalence of chronic liver diseases from various etiologies accounts for 14.8% of the adult population in the period 2005–2008.[14] Considering the US population of 323.2 million in 2016, around 47.8 million individuals would be affected by a chronic liver disease. This compares with a much lower incidence of DILI, which is commonly estimated to be around 14/100 000 inhabitants and, applied to the USA, this corresponds to around 45 000 DILI cases, that is, a prevalence rate of 1000 times less than in cases of chronic liver disease; it also compares with an extremely low incidence of liver-injury cases by herbs[15,16] and DS.[17] This is important in clinical practice, since patients using herbs or DS and experiencing a liver injury or abnormal liver tests are more likely affected by a chronic liver disease than by an acute liver injury by herbs or DS.

In this review, we analyze and discuss the role of preexisting liver diseases in patients with obesity, who experienced liver injury initially attributed to the consumption of DS intended to reduce body weight. It is shown that, in some cases, the liver injury is less likely due to DS than to obesity, complicated by an associated liver disease.

Literature search strategy

Search and identification terms. Relevant original reports and reviews were identified using a computerized search of the Medline database. The following terms were considered: DS liver injury, DS, obesity, obesity-related liver diseases, and nonalcoholic steatohepatitis (NASH). For each term, we focused on the first 50 publications. We reviewed and selected reports relevant to the aim of our study.

Data analysis, evaluation approach, and publication selection. Publications were analyzed for their clinical and scientific value and data quality. Those of good quality and in English language were considered for evaluation. We undertook a manual search to identify additional reports, including key publications cited in the first 50 in each targeted search.

Obesity

Obesity is widespread and increasing in many developed countries. It is most often defined by the body mass index (BMI).[18,19] Calculated as weight in kilograms divided by the square of height in meters, BMI is a good diagnostic marker to differentiate obesity from overweight.[18] Obesity is defined as a BMI ≥ 30 kg/m^2, whereas overweight is considered at a BMI between 25 and 30 kg/m^2. Caused by excessive fat accumulation, obesity is a complex and complicated metabolic disease, triggered at the molecular level by oxidative stress with generation of toxic free radicals and reactive oxygen species (ROS), which appears to play a critical role also in its associated diseases.[19,20] However, rarely discussed and poorly assessed in humans is the role of autophagy in obesity and NAFLD. Prevailing comorbidities substantiate that obese individuals were not healthy and often need a specific therapy consisting of several drugs, associated with an increased risk of DILI.[21–23]

As a severe disease, obesity shortens life expectancy,[24] not a problem among centenarians of Okinawa in Japan who have been lean throughout their extraordinary long lives, with an average BMI that ranged from 18 to 22 kg/m^2, while lean is less than 23.[25] The clinical outcome of obesity with its reduced life expectancy is defined by its comorbid conditions and closely associated risk factors.[19,20,24,26,27] These include poor health status, early death, metabolic syndrome, type 2 diabetes mellitus, insulin resistance, dyslipidemia, hypercholesterolemia, atherosclerosis, hypertension, cardiovascular disease, asthma, sleep apnea, arthritis, special cancers, and liver disease.

NAFLD and NASH

Later stages are NASH, with the risk of progressing to liver cirrhosis including the so-called "cryptogenic" cirrhosis, which is still debatable, and eventually hepatocellular carcinoma (HCC).[28,29] A liver transplantation may be the therapy of choice.[30] Defining various stages of obesity-related liver diseases requires a liver histology, considered the gold standard, obtained by invasive liver biopsy.[28,29] However, in epidemiological studies, ultrasound is commonly used as a noninvasive method to assess the prevalence of NAFLD.[26]

Obesity-related end-stage liver diseases and orthotopic liver transplantation. In parallel to the data of problematic obesity and NASH, the high occurrence of associated end-stage liver diseases leading to orthotopic liver transplantation (OLT) is an even more critical issue.[30,31] In a recent US study from 2003 to 2014, an overall 63 061 adult patients underwent OLT, including 20 782 HCV (32.96%), 9470 ALD (15.02%), and 8262 NASH (13.11%).[30] NASH surpassed ALD and became the second leading indication for OLT beginning in 2008, accounting for 17.38% of OLT in 2014. From 2003 to 2014, the number of OLT secondary to NASH increased by 162%, whereas OLT secondary to HCV increased by 33% and ALD increased by 55%. Due to a resurgence in ALD, the growth in NASH and ALD was comparable from 2008 to 2014 (NASH, +50.15% *vs* ALD, +41.87%). Here, the issue is that the reason for OLT is acute liver failure, cirrhosis, or HCC, which are not really a differential diagnosis of DILI.

Epidemiology data in comparison

Obesity and NASH. According to the World Health Organization (WHO), worldwide obesity has nearly tripled since 1975.[32] In 2016, more than 1.9 billion adults (18 years and older) were overweight and, among these, over 650 million were obese, corresponding to 13% of the world's adult population (11% of men and 15% of women). Global prevalence of NASH among obese patients is difficult to estimate because it would require liver biopsies from a large study population, not feasible

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in part because of ethical issues and the procedural risks. Some information may be gleaned from a prospective study of 134 patients with suspected fatty liver on ultrasound imaging, who underwent liver biopsy.[33] In 5 of these, the liver was normal, in 89 patients there was steatosis but no NASH, while NASH was found histologically in 40 patients (29.9%) including 9 patients with advanced fibrosis.[33] In the NASH cohort, the BMI was 34.4 ± 5.41 kg/m^2 (mean ± SD), implying a close association of obesity with NASH.

For the USA, the high prevalence of NAFLD and NASH has been confirmed with an increased tendency in a recent article.[34] Estimates were based on the historical and projected changes in adults with prevalence of obesity and type 2 diabetes mellitus, derived from published literature where available. Accordingly, prevalent NAFLD cases are forecasted to increase 21%, from 83.1 million (2015) to 100.9 million (2030), while prevalent NASH cases will increase 63% from 16.52 million to 27.00 million. Similar increases are expected for decompensated cirrhosis and HCC. Liver deaths will increase 178% to an estimated 78 300 deaths in 2030. All these estimates will need to be considered when analyzing liver injury in obese patients, before attributing liver damage to DS, drugs, or herbs.

An internet search for the search term "NASH prevalence based on liver histology" provided around 440 000 hits, substantiating much interest on this topic and providing a good basis for further studies. An in-depth analysis of these reports is outside the focus of the present review article, since data derived from the published cohorts require stratification of the degree of obesity in all individuals and evaluation of variable case inclusion and liver histology criteria with differentiation of NASH from NAFLD.

Liver injury by HDS. Compared to the high prevalence of obesity, NAFLD, and NASH in the general population, robust data on the prevalence of liver-injury cases specifically due to HDS are still missing.[1–3,7,8] In particular, there is a lack of prospective studies focusing on cases with causality gradings by Roussel Uclaf Causality Assessment Method (RUCAM).[5] However, some incidence data for such cases have been published.[15–17] For instance, a recent report from Germany presented, for the first time, liver-injury data derived from a prospective, large-scale hospital-based study of 21 470 patients, who had no liver disease prior to treatment with herbal traditional Chinese medicines (TCM),[15] in which product falsification and adulteration were excluded. Products were also screened for microbial contaminations, aflatoxins, pesticides, and four heavy metals (lead, cadmium, mercury, and arsenic). This study was carried out from 1994 to 2015 on 21 470 patients under herbal TCM treatment. 26 patients (0.12%) experienced alanine aminotransferase (ALT) values ≥5 × upper limit of normal (ULN). RUCAM-based causality for TCM herbs was probable in 8/26 patients, possible in 16/26, and excluded in 2/26 cases. The 24 possible or probable liver-injury cases correspond to an incidence rate of 1.1%. The low number of newly detected liver-injury cases is at variance to the long list of liver-injury cases related to herbal TCM treatment, mainly published in Asian countries. It is unclear whether the high quality standard applied to the herbal TCM products used in the German hospital may have contributed to the low case numbers.[15] A low incidence of 0.6% for HILI cases was also reported in a prospective study of 1001 patients with RUCAM-based causality gradings of possible and higher from Korea.[16] In the US State of Delaware, a small, preliminary, and prospective study involving gastroenterologists only, 6 cases per 100 000 adults were reported, corresponding to 1.2 cases of HDS-induced liver injury per 100 000 adults.[17] However, no distinction was made between HDS, the offended product was not clearly identified, and case narratives were not available, how alternative causes were excluded, and a product specific causality grading such as by RUCAM[7] was not provided.[17] These shortcomings and lack of transparency do not allow for re-evaluations by peers. Nevertheless, these few reports seem to indicate a low hepatotoxic risk of HDS.

Suspected liver injury by DS for obesity

DS cannot escape issues of product variability, product definition, and poorly documented criteria of efficacy and safety, which are characteristic features of DS as a group.[4,5,7,8] Indeed, as a product for human use, DS need a clear definition of ingredients, risks, and benefits. These products also do not supplement specifically any diet of an individual who regularly consumes a well-balanced diet.[8] Clearly, whenever dietary deficiencies are clinically detected, specific substitution therapies under the guidance of a health care provider must be initiated. DS are often enriched by one or several products such as vitamins, minerals, herbs or other botanical, amino acids, organ tissues, or a concentrate of these ingredients, and their use is rarely associated with adverse effects including liver injury.[7,8] However, up to now, diagnostic problems have been insufficiently recognized and poorly analyzed in patients with obesity, who experience suspected liver injury when DS were used for weight reduction. Patients with obesity are confronted with comorbidities[21–23] and cannot be considered as healthy as occasionally assumed.[35,36] The potential causes of liver disease in such patients are multiple: obesity-related NAFLD, NASH, cirrhosis, or acute liver failure (ALF); obesity-associated multimorbidity and requirement of treatment with several drugs; other pre-existing liver diseases unrelated to obesity. Another problem is the concomitant use of multiple drugs by obese patients, who are multimorbid,[21–23] adding to DILI another specific cause of liver injury. For some drugs, underlying liver diseases such as NAFLD may represent another risk factor of DILI by some drugs,[37,38] referring also to pharmacological toxicity of certain drug classes due to genetic polymorphism in xenobiotic metabolizing enzymes and referencing important publications on the human leucocyte antigen (HLA) genotype as a strong risk factor for the development of DILI with a range of drugs, likely involving a drug-peptide complex to T cells, although HLA alleles are only associated with some forms of DILI; and with non-HLA genetic risk factors, which appear to play a contributory role, especially those related to drug metabolism, detoxification, and disposition.[37] Involved genes may cause polymorphism of bioactivation pathways via the cytochrome P450 (CYP) systems (phase I), detoxification reactions (phase II), and excretion and transport (phase III). For some drugs, even a dual role of HLA and drug metabolism genes is under consideration.[37]

Of note, in case reports of suspected liver injury due to DS used for weight reduction, data on BMI were not or poorly presented: weight or BMI prior to DS use and after cessation was

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often not provided; sometimes BMI at DS cessation was found to be increased, substantiating the diagnosis of obesity or even morbid obesity; or conversely, BMI was normal or subnormal at DS cessation, suggesting an effect on weight reduction by DS used for several months or years.

It is outside the focus of this review to consider aspects of potential liver injury in all 50 000 HDS marketed in the USA between 1995 and 2015.[8] Instead, this analysis is limited to the cases of liver injury attributed to DS that attracted the interest of consumers, clinicians, regulators, and manufacturers in the last few years. For this purpose, green tea extracts (GTE), Herbalife, Hydroxycut, and OxyELITE Pro (OEP) were selected as examples of products, all used for weight reduction.[10–12,21–23,35,36,39–51] Except for a few reports,[22,23] all publications failed to mention obesity-associated liver comorbidities as potential causes for the liver injury.

Green tea extracts

GTE are used for weight reduction but studies and reviews on liver injury rarely considered BMI values and obesity-related hepatic comorbidities as potential contributory factors.[36,39–41] Hepatotoxicity of GTE was proposed in reports based on causality assessment by RUCAM that provided causality levels of highly probable,[40] probable,[39,40] or possible,[39] in addition to positive re-exposure tests[40] using defined diagnostic criteria.[5] Conversely, a causal relationship between GTE and liver injury was not found in studies with volunteers[42] and questioned in a systematic review of 34 randomized controlled trials where liver injury was reported in 4 trials.[43] These adverse reactions involved seven patients in the GTE group and one patient in the control group. The odds ratio was 2.1. The few events reported in both groups were elevations of liver enzymes. Most were mild, and no serious liver-related adverse event was reported. Although the authors concluded that liver injury after intake of GTE is rare,[43] BMI at treatment initiation with GTE and obesity-related liver diseases were not taken into account.

A possible causality in all cases was assumed by the United States Pharmacopeia (USP) using the Naranjo scale.[39] However, this scale was judged as a problematic method since virtually all cases can reach a possible causality grading just because the herbal extract has been taken.[44] In addition, the Naranjo scale was not constructed for liver-injury cases.[5] These issues prompted case re-evaluations with the updated RUCAM,[5] which has likely been done in the meantime by the USP members at a recent meeting, the 2015–2020 USP GTE hepatotoxicity expert panel meeting 04, held from 31 August–2 September 2017 in Rockville, MD, USA. In the interest of consumers and the scientific community,[36,39–44] expectations are high that the GTE product mislabeling in the USA is being better addressed and the final report will fulfill the requirements of a robust causality assessment using, for instance, the updated RUCAM as a quantitative approach of individual key elements. USP experts should also take into consideration in causality assessment the alternative causes represented by the obesity-associated liver diseases.

Herbalife

Liver injury associated with the use of Herbalife[45–49] has been a matter of debate due to questionable retrospective case analyses, incomplete case data, and use of liver unspecific causality assessment methods such as the WHO method based on global introspection, and alternative causes.[10–12] In only one case, a positive re-exposure test was confirmed by established test criteria.[11] Confirming the poor case data and the results of previous studies,[10,11] an agreement has now been reached that little evidence exists of a major risk of liver injury with Herbalife.[10–12] RUCAM-based causality for Herbalife was excluded or unlikely in virtually all cases; among the alternative causes were hepatitis B, primary biliary cholangitis, liver steatosis, hepatitis E, giant cell hepatitis, acute alcoholic hepatitis, and liver injury due to comedications.[12] Liver diseases associated with obesity were not discussed.[10–12,45–49]

Hydroxycut

Hydroxycut was another DS taken with the intention to reduce body weight. It contained initially hydroxycitric acid in addition to several substances and herbs. However, safety issues including liver injury emerged.[8] Hydroxycut products with variable ingredients were on and off the market following FDA interventions. The original formulation contained the herbal TCM Ma Huang with ephedra as an ingredient, a substance that was banned by the FDA in 2004 because of its association with cardiovascular, neuro-psychiatric, and gastrointestinal adverse effects. Accordingly, the manufacturer removed ephedra from the formulation, but cases of liver injury continued to occur.[8] This indicated that other substances or herbs were responsible for the liver injury. Additional ingredients of Hydroxycut formulas included calcium, chromium, potassium, hydroxagen plus, *Garcinia cambogia* extract, *Gymnena sylvestre* extract, soy phospholipids, *Rhodiola rosea* extract, *Withania somnifera* extract root, hydroxy tea, GTE (*Camellia sinensis*), white tea extract, oolong tea extract, and caffeine anhydrous.[8] Which of these components is the cause of the liver injury remains uncertain, but suspicion has fallen on *Camellia sinensis.* In view of the numerous liver-injury reports of Hydroxycut, the Food and Drug Administration (FDA) warned the public of the severe risk of liver injury attributable to the herbal product, and the manufacturer withdrew it from use. However, Hydroxycut returned to the market with a different formulation, entitled Hydroxycut, SX-7 Clean Sensory, but a new case of liver injury has been reported.[8] Analysis of the case reports[8,50,51] revealed that little attention was paid to obesity, BMI values, and associated liver diseases.

OxyELITE Pro

Used for obesity, OEP was another DS suspected to induce liver injury in eight patients at the Honolulu Queens Medical Center (QMC).[35] However, causality for OEP was not confirmed based on causality assessment by RUCAM and critical case re-evaluation,[21–23] which received encouraging comments from US scientists.[1,2] In short, serious flaws became evident in the eight QMC cases, such as lack of case data transparency, hidden case data, incomplete data transfer from clinical files to the publication, overt pre-existing diseases, issues of incorrect scoring of causality gradings in all cases, and alternative causes in a few cases that were assessable.[21–23] In virtually all QMC patients, obesity with a BMI ≥ 30 kg/m^2 was reported.[21–23,35] However, liver diseases associated with obesity were not mentioned in the

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original report[35] or discussed in a subsequent review article[36] but only in reports of case reassessment.[22,23] This raises the question whether obesity-associated liver diseases might have played a role in some cases for which alternative causes were not found so far. For only four of the eight patients, liver histology data were available but hardly interpretable[21–23] and not suitable for the usual histological scoring system for NAFLD.[28,29] As expected, evaluation of liver histology was problematic for patients with end-stage liver diseases such as cirrhosis, where remaining intact liver tissue is scarce and does not allow for an etiological evaluation.[29] Nevertheless, in a few partially assessable cases, ballooning of liver cells, fat containing liver cells, microgranuloma, or perisinusoidal and periportal fibrosis were described.[21–23,35] Although not pathognomonic, these features are compatible with and certainly suggestive of NASH,[28,29] whereas causality of liver injury for the DS had to be denied[21,22] using the updated RUCAM.[5] One of the patients had a previous liver histology with fatty liver. In another, fatty liver was diagnosed based on Computed Tomography (CT) assessment at hospital admission.[21–23] Taken together, there is evidence that NASH was associated with obesity or morbid obesity in a few patients, representing a potential alternative cause of the liver injury.

Conclusions

Patients with obesity or morbid obesity suffer from a potentially severe disease with an increased risk of early mortality and morbidity. Obesity may be associated with NAFLD, NASH, and cirrhosis (mostly classified as cryptogenic cirrhosis), creating potential candidates for liver transplantation. Obese individuals, mostly unaware of their serious comorbidities and liver disease, often turn to DS for help with weight reduction. Whenever liver injury is observed in this context, patients and physicians are often quick to blame the DS used for weight loss, rather than the underlying liver disease associated with obesity. However, causality of liver injury for many suspected DS products has been disputed and has not been verified in many cases. Examples are GTE, Herbalife, Hydroxycut, and OEP. In addition, the issue of obesity-related liver comorbidities as a cause was poorly handled in these cases, a major clinical and regulatory shortcoming. The general low incidence of liver injury by herbal and DS should be weighed in relation to the high prevalence of acute and especially chronic liver diseases in the general population. Much more attention should be paid to obesity-associated liver diseases in the causality assessment of DS used for weight reduction, using also the updated version of RUCAM to dismiss or establish the diagnosis of liver injury due to DS.

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