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REVIEW

Drug-induced liver injury: Do we know everything?

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Abstract

Interest in drug-induced liver injury (DILI) has dramatically increased over the past decade, and it has become a hot topic for clinicians, academics, pharmaceutical companies and regulatory bodies. By investigating the current state of the art, the latest scientific findings, controversies, and guidelines, this review will attempt to answer the question: Do we know everything? Since the first descriptions of hepatotoxicity over 70 years ago, more than 1000 drugs have been identified to date, however, much of our knowledge of diagnostic and pathophysiologic principles remains unchanged. Clinically ranging from asymptomatic transaminitis and acute or chronic hepatitis, to acute liver failure, DILI remains a leading causes of emergent liver transplant. The consumption of unregulated herbal and dietary supplements has introduced new challenges in epidemiological assessment and clinician management. As such, numerous registries have been created, including the United States Drug-Induced Liver Injury Network, to further our understanding of all aspects of DILI. The launch of LiverTox and other online hepatotoxicity resources has increased our awareness of DILI. In 2013, the first guidelines for the diagnosis and management of DILI, were offered by the Practice Parameters Committee of the American College of Gastroenterology, and along with the identification of risk factors and predictors of injury, novel mechanisms of injury, refined causality assessment tools, and targeted treatment options have come to define the current state of the art, however, gaps in our knowledge still undoubtedly remain.

Key words: Acute liver failure; Drug-induced liver injury; Hepatoxicity; Acetaminophen toxicity; Cholestatic injury; Liver biopsy; Pharmacoepidemiology; Herbal-induced liver injury; Hy's law

Core tip: Drug-induced liver injury has gained a great amount of interest in the past decade, raising the question of whether we know everything. Various global registries have been established and the first guidelines for diagnosis and management have come to define the

state of the art. The identification of risk factors and predictors of injury, novel mechanisms of injury, refined causality assessment tools, and targeted treatment options have amplified our understanding of the impact of drug-induced liver injury, however gaps in our knowledge still remain.

Alempijevic T, Zec S, Milosavljevic T. Drug-induced liver injury: Do we know everything? *World J Hepatol* 2017; 9(10): 491-502 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i10/491.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i10.491

INTRODUCTION

Drug-induced liver injury (DILI) is a current hot topic for academics, clinicians, pharmaceutical companies and regulatory bodies, as seen by the increasing number of publications over the past fifteen years. Evidence to the fact is shown in the number of new monographs, revised chapters in textbooks, workshops and single-topic conferences specifically dedicated to DILI[1-5]. When DILI was the subject of a specific PubMed search, 44738 items were found in the past 5 and a half years (2010 through 2016), a number more than double the total number of items related to DILI published in the preceding decade (2000-2009).

This extensive body of new information leads us to a question that will be the focus of this review. By investigating the current state of the art of DILI, focusing on the latest scientific findings, controversies and guidelines, this review will take a clinician's point of view and attempt to find an answer to the question: Do we know everything?

DILI: A BRIEF HISTORY

Iproniazid, cinchophen, and sulfonamides were amongst the first prototypical hepatotoxins to be identified, paving the way for future histological and clinical descriptions that followed the second world war[6,7]. By the mid-1960s, hepatotoxic agents including halothane, isoniazid (INH), carbamazepine, phenytoin and alpha methyldopa were famously referred to by Popper *et al*[8] as "penalties for progress", and by the mid-1980s close to 1000 drugs were linked to hepatic injury[9]. Even though much of this early work[6,8] has remained the mainstay of diagnostic, and pathophysiologic principles even to this day, DILI remains a significant diagnostic challenge due to the fact that drugs can mirror acute and chronic hepatic diseases, and act through various mechanisms causing injury[10-15].

STATE OF THE ART OF DILI

Clinically, DILI ranges from asymptomatic transaminitis, acute or chronic hepatitis[16] to acute liver failure (ALF) or fulminant hepatic failure, defined as sudden and life-threatening liver dysfunction leading to coagulopathy and hepatic encephalopathy within 26 wk of the onset of illness[17]. Although severe DILI is rare clinically, drugs have become the overall leading overall cause of ALF in the United States and other western countries[7]. In the United States, approximately 1600 to 2000 people per year develop ALF, with 30% of these patients receiving aggressive therapy including liver transplant[18]. Acetaminophen (paracetamol) is the offending drug in 40%-50% of these cases, with a further 11%-12% of ALF cases being caused by herbal compounds and dietary supplements (HDS), equalling the frequency of ALF due to acute viral hepatitis and greater than that seen with all other individually identifiable causes[7,19,20]. Indeed, due to this significant morbidity and mortality, DILI remains an important reason for drug withdrawal from the market, with most recent examples including, bromfenac and troglitazone[21]. Due to the significant time and expense involved in bringing a novel drug to market, it should come as no surprise, that identification of potential toxicities early in the development process is paramount[22]. However, compounds cannot be guaranteed to be totally free of the potential to cause harm and liver injury in preclinical stages of development, and as such, tremendous steps have been undertaken in regulatory science, so as to identify DILI in clinical and post-approval settings[23-25]. The creation of the Evaluation of Drug-Induced Serious Hepatotoxicity plot[26], the "Rule-of-Two"[27,28], FDA Adverse Event Reporting System[29], the Sentinel projects[30], and Liver Toxicity Knowledge Base[31] has empowered clinicians to detect and predict DILI as early and successfully as possible. Working in parallel at the bedside, new hepatotoxins have been uncovered including dronedarone[32], ipilimumab[33,34], and tolvaptan[35,36] and our further understanding of known hepatotoxins including azithromycin[37], duloxetine[38], fluoroquinolones[39], statins[40], telithromycin[41], tyrosine kinase inhibitors[42] and others[43], has broadened.

Additionally, the identification of risk factors, predictors and biomarkers of injury[44-52], and novel mechanisms of injury[53-58], along with refined causality assessment tools[59-61], and targeted treatment options of hepatotoxicity[62-68], have come to define the current state of the art.

GUIDELINES AND REGISTRIES

Cumulatively, the aforementioned advances have led to the recent publication of the first guidelines for the diagnosis and management of DILI, offered by the Practice Parameters Committee of the American College of Gastroenterology[69]. The guidelines, as summarized in Table 1, provide key practical advice on all aspects and problems which may be faced in the work-up of a DILI case. This parallels the establishment of the United States DILI Network (US DILIN) in 2004[70,71], a prospective study with a database containing > 1200 patients with acute DILI caused by approximately 200

Table 1 Summary of drug-induced liver injury guidelines by the American College of Gastroenterology[7,69]

Elements necessary for the diagnostic evaluation of DILI
Known duration of exposure
Concomitant medications and diseases
Response to dechallenge (and rechallenge if performed)
Presence or absence of symptoms, rash, eosinophilia
Performing sufficient exclusionary tests (viral serology, imaging, *etc.*) to reflect the injury pattern and acuteness of liver function tests (*e.g.*, acute viral serology for A, B and C and autoimmune hepatitis when presenting with acute hepatocellular injury; routine testing for hepatitis E virus not recommended because of the problems with current commercial assays; Epstein-Barr virus, cytomegalovirus, and other viral serology if lymphadenopathy, atypical lymphocytosis present)
Sufficient time to determine clinical outcome - did the event resolve or become chronic?
Use of liver biopsy
Often not required if the acute injury resolves
Helpful in confirming clinical suspicion of DILI but rarely pathognomonic
Useful to differentiate between Drug-Induced autoimmune hepatitis and idiopathic autoimmune hepatitis
Useful to rule out underlying chronic viral hepatitis, non-alcoholic fatty liver disease, alcoholic liver disease, or other chronic liver disease
Used to exclude DILI where re-exposure or ongoing use of an agent is expected
Rechallenge: Generally best avoided, unless there is no alternative treatment
Use of Causality Assessment Methods
Roussel Uclaf Causality Assessment Method is best considered an adjunct to expert opinion (it should not be the sole diagnostic method)
Consensus opinion
Expert consultation
For patients with chronic viral hepatitis, DILI requires a high index of suspicion, knowledge of a stable clinical course before the new medication, and monitoring of viral loads to rule out flares of the underlying disease
Assigning causality to herbal compounds and dietary supplements can be especially difficult; require knowledge of all ingredients and their purity

DILI: Drug-induced liver injury.

agents other than acetaminophen, including HDS[72,73]. As of 2014, DILIN continued to publish analyses from the data in their registry, most notably defining clinical signatures of specific agents; chiefly, a new syndrome was identified to occur after a single intravenous dose of cefazolin, characterised by marked cholestasis and a self-limited moderate to severe clinical course, following a one to three week latency period[74]. Globally, numerous registries have been formed in the past decade, including those in Australia[75], Spain[76], Iceland[77,78], India[79], South Korea[80], and Serbia[81], amongst others[82-84]. In addition to DILIN and the other national databases, the United States National Institutes of Health and National Library of Medicine launched LiverTox[85] (https://livertox.nlm.nih.gov/) in April 2012. This comprehensive, up-to-date, interactive online resource, with over 650 agents currently listed, projects to expand its role into a virtual textbook on hepatotoxicity[7]. In the light of these collective efforts, gaps in our knowledge still undoubtedly remain[2,4,11].

EPIDEMIOLOGICAL ISSUES

One of the greatest challenges to furthering our understanding of the global epidemiology of DILI is the elusive nature of its clinical presentation. Illustration of the fact can be seen in several studies, which found that DILI is both under-recognized and under reported[83,86-89]. In one study[86], around 50% of the suspected DILI cases investigated were found to be common hepatic disorders when assessed by specialists and DILI experts. In another study from France[83], underreporting by clinicians untrained in the recognition of DILI was greater by a factor of 16, when compared to those specifically trained to identify cases.

The fact remains, that acute DILI is a relatively rare clinical entity, and as such, determining the exact incidence from individual drugs is arduous. The estimated incidence of non-acetaminophen-related DILI, reported from a population-based Icelandic study, was found to be 19.1 cases per 100000 inhabitants[78], similar to the 13.9 per 100000 found more than ten years prior, in France[83]. A higher incidence was found in Spain in 2005, with 34.2 per 1000000 inhabitants per year, and 16.6 per 1000000 inhabitants per year being serious life-threatening episodes[76]. In Great Britain, the estimated incidence per 100000 persons was 2.4 in 2004[86], however more recent data is unavailable. In the United States, a retrospective cohort study determined an incidence rate of drug-induced ALF of 1.61 events per 1000000 person-years[90]. By using population-based epidemiological data within the paediatric population, the incidence of acute liver injury was found to be comparable to that of the adult population, with higher incidence in Italy, when compared to the Netherlands (73 and 21 per 100000, respectively)[91]. Antibiotics were the most frequent offending drugs in this study and others, as comprehensively discussed by Björnsson[89], stating that amoxicillin-clavulanic acid and INH in particular, along with other antibiotics and antiepileptics are the most common agents linked to hepatotoxicity. If one takes into account data from the United States Acute Liver Failure Study Group, acetaminophen is the most common overall causative agent for ALF with 45.8%, followed by non-acetaminophen DILI with 11%[19], and INH the leading cause of DILI thereafter with 18.8%[20].

These findings come from large cohorts, however the vast majority of DILI research comes in the form of numerous case reports identifying novel hepatotoxic agents; the most recent example from 2016, being hepatotoxicity in HIV/HCV infected patients receiving ledipasvir/sofosbuvir with or without ribavirin[92,93].

Herbals pose yet another obstacle to our understanding of the epidemiology of DILI. Currently, the absence of regulatory guidelines for the production and sale of herbal compounds, means that the calculation of the true incidence of herbal-induced liver injury (HILI) becomes very difficult. Evidence is emerging from Asia, in particular China, where in a cohort of 21789 patients with DILI found that alternative medicines were one of the two most common etiologies reported[94]. It is estimated that 15% of DILI cases may be attributed to herbs and other traditional Chinese medicines[95]. In South Korea, DILI incidence was 12 per 100000 persons, with 70% due to herbal and folk remedies[80,96]. According to the DILIN registry, HDS were responsible for DILI in 16% of cases, second only to antimicrobials[72]. What is potentially worrying is that patients with chronic liver disease (CLD) have been increasingly using HDS[97], leading to an increase in safety alerts from the FDA and other regulatory bodies[43,73]. The most recent HDS to receive hepatotoxicity warning labels were the muscle building, fat burning product OxyELITE Pro[97] (USP Labs LLC, Dallas, Texas) and the weight loss supplement Herbalife[98]. Other causes of HILI include anabolic steroids, black cohosh, green tea, Hydroxycut (Iovate Health Sciences Inc, Oakville, Ontario, Canada), and kava[99], and therefore HDS should also be on one's mind in any case of suspected liver injury.

DEFINING, RECOGNISING AND PREDICTING DILI

At this stage, it may be helpful to remind one that DILI is initially defined as either intrinsic (predictable, dose-dependent) or idiosyncratic (unpredictable and non-dose dependent). By far the most common intrinsic cause of DILI is acetaminophen[19]. Twenty billion doses of non-prescription acetaminophen are sold annually in the United States, with $87 million dollars spent treating complications of overdose[100,101]. The intrinsic nature of acetaminophen hepatotoxicity stems from the production of N-acetyl-p-benzoquinone imine; excessive accumulation of this reactive metabolite leads to a depletion of intracellular glutathione, in turn leading to zone 3 centrilobular necrosis of the hepatocytes[102,103]. This predictable course of acetaminophen toxicity led to the introduction of N-acetylcysteine (NAC) as an antidote in 1977[104], remaining the drug of choice for overdose treatment today[100].

The mechanisms of idiosyncratic DILI on the other hand, have a far more complex nature and are the focus of the majority of current research. Broadly speaking they may be divided into two categories, hypersensitivity-type reactions (also known as immunologic), and metabolic types of injuries[10]. Hypersensitivity-type reactions, occurring due to reactive metabolites covalently binding proteins, forming drug-protein adducts, and thus triggering immune-mediated reactions or direct hepatic toxicity[12], account for 23%-37% of all idiosyncratic DILI cases[10]. In addition, lipophilicity combined with dose, also known as the "rule-of-two"[27,28], is known to enhance the risk of developing DILI, due to increased blood uptake into hepatocytes, forming greater amounts of reactive metabolites and subsequently interacting with hepatocanalicular transport and mitochondrial membranes[12]. As such, metabolic mechanisms include oxidative stress, mitochondrial liability and inhibition of hepatobiliary transporters[12]. In the case of INH induced DILI, hepatocellular injury may result from the creation of covalent drug-protein adducts, leading to hapten formation and an immune response, and/or through direct mitochondrial injury by INH or its metabolites, leading to mitochondrial oxidant stress and energy homeostasis impairment[54]. If such mitochondrial deficiencies are already present, even non-toxic concentrations of INH, may trigger marked hepatocellular injury, due to underlying impairment of complex I function[54]. Other examples of mitochondrial injury include: Impaired beta-oxidation, and mitochondrial respiration, membrane disruption and mtDNA damage, usually caused by tamoxifen, valproic acid, diclofenac and tacrine, respectively[12].

Indeed, hundreds of offending drugs have been identified thus far, with the list constantly growing. However, according to the DILIN registry[72], the top 10 drugs account for greater than one-third of all idiosyncratic DILI cases. The most common causative agents and drug classes, according to various registries, are summarized in Table 2. The lists are rather heterogenic, however, antibiotics amoxicillin-clavulanate and INH top most registries as individual agents. Unsurprisingly, antituberculous agents top the list of severe and often fatal DILI in India, where acetaminophen use is rare and tuberculosis is prevalent[79]. Of the drug classes, antibiotics are the most common agents amongst the registries investigated with the exceptions of Spain and Sweden, where "other" drugs are most common with 44% and 69%, respectively. Collectively, these data illustrate that DILI cases and the drugs responsible vary from country to country, based on the overall prevalence of certain diseases within each healthcare system.

Due to the large number of different causative agents, further division of idiosyncratic DILI is classically determined on three biochemical patterns of liver injury: Hepatocellular, cholestatic and mixed, and based on the ratio of alanine aminotransferase (ALT) to alkaline phosphatase (ALP) defined as an *R* value[105] (Table 3). The prognosis of each case is greatly dependant on which pattern of injury has occurred, and although bilirubin is not incorporated into the *R* value, it remains a central prognostic marker in calculating the Model for End-Stage Liver Disease score along with defining Hy's law[7].

Table 2 The most common individual drugs and classes responsible for idiosyncratic drug-induced liver injury according to various Global Registries

	Iceland[78], *n* = 96	India[79], *n* = 313	Spain[76], *n* = 446	Sweden[77], *n* = 784	United States DILIN[72], *n* = 899
Individual drugs (%)					
	Amoxicillin-clavulanate 22.9	INH + anti-TB 57.8	Amoxicillin-clavulanate 13.2	Flucloxacillin 16.5	Amoxicillin-clavulanate 10%
	Diclofenac 6.3	Phenytoin 6.7	INH + anti-TB 6.9	Erythromycin 5.4	INH 5.3%
	Nitrofurantoin 4.2	Dapsone 5.4	Ebrotidine 4.9	Disulfiram 3.4	Nitrofurantoin 4.7%
	Infliximab 4.2	Olanzapine 5.4	Ibuprofen 4	TMP-SMX 2.7	SMX-TMP 3.4%
	Azathioprine 4.2	Carbamazine 2.9	Flutamide 3.8	Diclofenac 2.6	Minocycline 3.1%
	Isotretinoin 3.1	Cotrimoxazole 2.2	Ticlopidine 2.9	Carbamazepine 2.2	Cefazolin 2.2%
	Atorvastatin 2.1	Atorvastatin 1.6	Diclofenac 2.7	Halothane 1.9	Azithromycin 2%
	Doxycycline 2.1	Leflunamide 1.3	Nimesulide 2	Naproxen 1.4	Ciprofloxacin 1.8%
		Ayurvedic 1.3	Carbamazepine 1.8	Ranitidine 1.3	Levofloxacin 1.4%
Drug classes (%)					
Antibiotics	37	65	32	27	45.4
HDS	16	1.3	2	NS	16.1
CNS	7	12	17	3	9.8
Hypolipidemic	3.1	1.6	5	1	3.7
Others	37	20	44	69	25.7

United States DILIN: United States Drug-Induced Liver Injury Network; INH: Isoniazid; SMX: Sulfamethoxazole; TMP: Trimethoprim; TB: Tuberculosis; HDS: Herbal and dietary supplements; CNS: Central nervous system; NS: Not specified.

Table 3 *R* values[105]

Calculation of *R* value
ALT/AST value divided by its ULN = fold elevation/fold elevation above ULN for alkaline phosphatise
Definitions
Hepatocellular injury = $R > 5$
Cholestatic injury = $R < 2$
Mixed injury = $R > 2 < 5$

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ULN: Upper limit of normal.

The cornerstone of any liver assessment rests on ALT and aspartate aminotransferase (AST) elevations indicating hepatocellular injury, however in the case of DILI, these indicators are neither sensitive nor specific and cannot predict the pattern of injury because they are elevated after injury has already occurred[22,105,106]. This brings into question the role of liver biopsy. The United States DILIN has recognized 18 distinct histological categories of damage: Acute hepatitis, chronic hepatitis, acute cholestatic, chronic cholestatic, cholestatic-hepatitic, granulomatous, macrovesicular steatotic, microvesicular steatotic, steatohepatitic, zonal necrosis, nonzonal necrosis, vascular injury, hepatocellular alteration, nodular regenerative hyperplasia, mixed or unclassified injury, minimal nonspecific changes, absolutely normal, and massive necrosis[107-109]. The most common of these are acute and chronic hepatitic, acute and chronic cholestatic, and mixed hepatitis-cholestatic[107], and are most often associated with fluoroquinolones, nitrofurantoin, methyldopa, and amoxicillin-clavulanate, respectively[10]. Although useful in narrowing the differential diagnosis to a specific drug or class, liver biopsy is not required for the clinical evaluation and diagnosis of idiosyncratic DILI, and is performed in less than half of suspected cases[76]. Testament to this reasoning is the fact that the histological patterns of DILI are neither pathognomonic nor do they perfectly correlate with the biochemical patterns[10,107]. Indeed, biochemical parameters underestimate the degree of cholestasis and bile duct injury[107], and although hepatocellular damage correlates better, the mixed biochemical pattern overestimates the degree of cholestasis compared to hepatocellular damage[107]. With this in mind, according to the first guidelines for DILI diagnosis and management[69], liver biopsy is integral in differentiating drug-induced autoimmune hepatitis (DI-AIH) from idiopathic autoimmune hepatitis (AIH) (Table 1). Histopathological evidence of portal neutrophils, and intracellular cholestasis, favours the diagnosis of DI-AIH over AIH[7,69], and therefore one may employ biopsy in such cases.

The clinician is therefore left with their experience and knowledge of mimickers of DILI, when distinguishing between drug and non-drug causes of hepatic injury. Employing *R* values and the absolute height of liver enzymes are helpful in ruling DILI in or out. In the latest DILIN series, the mean values of ALT were 825 IU/L overall, approximately 20 × the upper limit of normal (ULN), with mean peaks of 1510 IU/L[72]. For cholestatic DILI the mean peak of ALP was 682 IU/L (6 × ULN)[72]. For idiosyncratic drug-induced ALF the median peak values of ALT were around 500 IU/L[19], incomparable with the record elevations seen in acetaminophen injury[6]. Simply put, for values of ALT or AST > 7500 IU/L, the differential diagnosis is essentially shock liver, toxic mushroom or other chemical poisoning, and acetaminophen overdose, and not idiosyncratic DILI[6]. Similarly, the enzyme elevations of acute idiosyncratic DILI are different from those found in alcoholic liver disease[6,7]. With our growing clinical expertise, newly identified viral causes, including hepatitis E virus (HEV), have made clear recognition even more arduous[7]. Mimicry by HEV should therefore be on the clinician's mind when forming a differential diagnosis

Table 4 Classic Clinical Syndromes of drug-induced liver injury and the drugs most commonly associated[6,7,117]

Acute viral hepatitis-like: *e.g.*, INH: Absence of hypersensitivity symptoms; present with malaise, fatigue, anorexia, nausea, vomiting, right upper quadrant pain
Hypersensitivity syndrome: Fever, rash, and/or eosinophilia seen in 25%-30% of DILI cases, usually with short latency and prompt rechallenge response (*e.g.*, amoxicillin-clavulanate, phenytoin, carbamazepine, SMX-TMP, halothane)
Sulfone syndrome: *e.g.*, dapsone: Fever, exfoliative dermatitis, lymphadenopathy, atypical lymphocytosis, eosinophilia, hemolytic anemia, methemoglobinemia
Pseudomononucleosis syndrome: *e.g.*, phenytoin, dapsone, sulfonamides: Hypersensitivity syndrome with atypical lymphocytosis, lymphadenopathy, and splenomegaly
DILI associated with severe skin injury: Stevens-Johnson syndrome, toxic epidermal necrolysis, *e.g.*, beta-lactam antibiotics, allopurinol, carbamazepine
Autoimmune hepatitis associated with positive autoantibodies: *e.g.*, nitrofurantoin, minocycline, methyldopa
Immune-mediated colitis with autoimmune hepatitis: *e.g.*, ipilimumab
Acute cholecystitis-like: *e.g.*, erythromycin estolate
Reye syndrome-like: *e.g.*, valproic acid: Hepatocellular injury, acidosis, hyperammonemia, encephalopathy, abdominal pain, nausea, vomiting, paradoxical worsening of seizure activity, microvesicular steatosis on biopsy

INH: Isoniazid; SMX: Sulfamethoxazole; TMP: Trimethoprim; DILI: Drug-induced liver injury.

of DILI[7,60].

As early as 1978, Hyman Zimmerman stated that drugs causing acute hepatocellular injury with jaundice were associated with a case-fatality rate of 10% or higher[7,110], a statement that was termed "Hy's Law" by Robert Temple at the FDA[7,110]. The current, modified definition of Hy's Law[35,110,111] consists of ALT/AST > 3 × ULN in addition to total bilirubin > 2x ULN in the absence of cholestatic injury (ALP < 2 × ULN), with no other identifiable cause[69,111]. Of such importance is this law that it remains a key element in determining whether DILI is present or not, and may in fact be the sole reason for abandonment of a drug's development[112].

BIOMARKERS

In the light of such difficultly in distinguishing DILI from other causes of hepatic injury, researchers have begun investigating potential biomarkers in an attempt at earlier identification[113]. Many possible genetic associations between individual human leukocyte antigens and the potential for DILI have been explored[114-116], however no definitive biomarker has yet been found. Of promise, are microRNAs, cytokeratin-18, and high mobility group box protein 1[113].

DIAGNOSING, AND ESTABLISHING CAUSALITY

So, with no particularly sensitive or specific biomarker, and little use of liver biopsy, DILI essentially remains a diagnosis of exclusion[49,69,107]. Recognising the clinical picture of DILI is therefore paramount[6,117] (Table 4). With such diverse presentation and because many individual cases of DILI are presented as case reports or case series, it is essential for the clinician to establish solid causality when suspecting DILI. Nearly 25 years ago, an international meeting of hepatologists convened in an attempt to create an objective causality assessment tool for DILI[7,105]. Although not quite user-friendly, the Roussel Uclaf Causality Assessment Method (RUCAM) remains in widespread use today[60]. It is based on expert consensus, and thus scoring requires extensive knowledge, and along with its many omissions, RUCAM is under much scrutiny in clinical practice, with a re-evaluation and revision far overdue[60]. As such, it is not the only causality tool employed by the DILIN, which has created its own additional criteria based on expert opinion incorporated into RUCAM, as illustrated in Table 5[59,118]. Even with more accurate causality tools, the clinical problems in diagnosing DILI in the setting of underlying CLD[69,72], malignancy[119], or congestive heart failure[120] still rests heavily on physician's expertise which cannot easily be substituted by scoring systems[60,69]; a fact which is even more relevant in the face of HILI, because of the unknown and unregulated ingredients often incorporated into HDS[73], again indicating the need for future research in this field[121].

RISK FACTORS AND NATURAL PROGRESSION OF DILI

With the difficulty of establishing diagnosis and causality, an important point to remember is who is at the greatest risk for DILI. The exact pathogenesis of idiosyncratic DILI and HILI is poorly understood, and the risk factors arise from three diverse aspects: (1) clinical host-related; (2) environmental; and (3) drug-related. Non-modifiable risk factors include age and gender[122]; however one must remember discrepancies in DILI reporting when citing one particular age or gender at greatest risk, for example, males have been indicated as high risk patients for DILI associated with systemic antivirals, whereas liver injury and ALF has been reported with higher frequency in children[81,123]. In any case, females have been predominately identified in many registries[71,76-79]. As mentioned above, much research has focused on genome-wide studies[114-116,124], and this is an area where we should be focusing our future attention. Environmental factors are poorly understood, with no definitive studies linking diet, or alcohol and coffee consumption to increased DILI risk, again illustrating a need for answers. The "Rule-of-Two",

Table 5 Drug-induced liver injury network scoring criteria[59,118]

Causal relationship	Percentage of likelihood	Definition
Unlikely	< 25	Clear evidence that an etiology other than the drug is responsible
Possible	25-49	Evidence for the drug is present but equivocal
Probable	50-75	Preponderance of the evidence links the drug to the injury
Highly likely	75-95	Evidence for the drug causing injury is clear and convincing but not definite
Definite	< 95	Evidence of the drug being causal is beyond any reasonable doubt

defined as increased DILI risk with higher lipophilicity and drug dose or greater degrees of hepatic metabolism[27,28], is a known risk factor. It accurately predicted liver injury in 14 of 15 drugs withdrawn due to hepatotoxicity, with a warning affixed to the final drug, and successfully predicted hepatotoxicity in multidrug regimens[7]. In spite of this success, upon multivariate logistic regression analysis, high lipophilicity was not a significant factor[27], suggesting a redefinition may be necessary.

If a drug causes acute DILI, it is generally accepted that discontinuation will lead to a resolution of any injury within a few weeks[125], and this is definitely true for hepatocellular injury[76,126]. In the case of cholestatic injury, often caused by antimicrobials, this process of resolution may take months, and can even persist after drug discontinuation[126]; in fact mimicry of primary biliary cholangitis and the development of portal hypertension has occurred[127]. Chronically administered drugs such as methyldopa, minocycline and nitrofurantoin have been associated with an insidious and self-limited autoimmune hepatitis, which resolves after discontinuation of the offender[128]. As such, the United States DILIN follows patients for a minimum of 6 mo after any case of DILI[72]. However, as of August 2016, Medina-Caliz *et al*[129], on behalf of the Spanish DILI registry, defined a new cut-off for chronic DILI of 1 year, suggesting that ALP and total bilirubin measurements in the second month after acute injury may help predict chronicity. Furthermore statins were implicated as distinctly related to chronicity[129]. Therefore, it is prudent to consider acute DILI transforming into chronic DILI in certain patients.

PREVENTION AND TREATMENT OPTIONS

The saying goes, the best treatment is prevention, and in the case of DILI this sentiment holds true. Liver injury may be caused by most drugs, and labels often carry a warning to lower the dose in the setting of CLD[124], however, there is little evidence to support this reducing the risk for DILI[130]. As such, liver enzyme monitoring has been proposed as an option in all drugs with a high risk of hepatotoxicity[131]. An example is bosentan, however, even after stringent risk evaluation, adherence remained an issue[132], and therefore, testing for CYP2C9 prior to administration may prove effective[133]. Similarly, statins were recommended to be followed with regular enzyme monitoring based on animal toxicity[134], however again compliance was sub-optimal[135] and hence, ALT monitoring was dropped by the FDA[134]. Nevertheless, in CLD patients ALT monitoring of patients receiving statins in the first months is sensible, given the fact that potential benefits may outweigh risks[134]. The fact that INH remains a major cause of DILI and drug-induced ALF, illustrates that monitoring is not as effective as one would hope[79]. Whether ALT finger stick testing, such as in the case of glucose, could become a global standard practice and positively influence monitoring regimens, remains to be answered in the not too distant future[136,137].

A rather controversial issue is that of desensitization-rechallenge. Generally it is discouraged[69,131] for fear of an even more severe reaction or ALF, and death[138]. Nevertheless, for life-threatening diseases including active tuberculosis where no other therapy is adequate, rechallenge has been successfully carried out[139]. Studies investigating the effects of switching drugs within one class or between different classes with similar effects are sparse[7], yet drug substitutions have been reported with non-estolate salts of erythromycin[127], statins[140], and thiazolidinediones[141]. Albeit more likely to cause liver injury, cephalosporins are good substitutes for penicillin[142], though it should go without saying that if the benefits do not outweigh the risks, desensitization-rechallenge ought to be avoided.

Even though our ability to detect, diagnose and prevent acute idiosyncratic DILI has had many advances, treatment has largely remained unchanged, with removal of the offending drug as soon as possible being the only undisputable option[6,43,69,125]. This may at times place the patient at risk for not receiving efficacious and essential medications, and hence, alternatives and adjuvants to the removal of responsible agents have been investigated. Circumstantial success has been achieved in some patients with cholestatic DILI with the use of ursodesoxycholic acid and steroids[66], however a targeted treatment for hepatocellular idiosyncratic DILI remains to be found. In the case of intrinsic DILI, acetaminophen overdose is and has been prevented and managed with NAC for decades[100,104,143] with the identification of patients at high risk for anaphylactoid reactions to NAC being essential for optimal treatment[144]. For non acetaminophen drug-induced ALF, NAC has been shown to be of benefit in adults in the early stages of disease, however, once liver coma sets in, the use of NAC is futile[67]; and it is virtually useless in children with ALF[68]. Other treatments have shown some benefits for specific agents including: Folic acid in the case of methotrexate toxicity[145], carnitine supplementation in children for

valproic acid related liver injury[146], and increasing hepatic clearance with an enterohepatic washout regimen of cholestyramine for leflunamide associated injury[147]. Plasma exchange and bioartifical liver assist devices such as moleculer absorbant recirculating systems have proven to successfully bridge certain patients to liver transplant, which remains the best therapy for irreversible ALF[20,64,65,148]. The search for novel treatment options broadly ranges from the use of nanotechnology to deliver hepatoprotective agents directly to the liver[63], to the humble milk thistle[149]. So one can see that apart from some anecdotal treatment options and of course removal of the offender, we are mostly alone in the dark and in need of further advances.

CONCLUSION

Our knowledge of DILI has come a long way in the past 60 years. We have an extensive amount of knowledge about which drugs are responsible and how to detect them, our understanding of the various mechanisms involved is constantly expanding, and we are identifying which patients are most at risk, however our knowledge is far from complete. In keeping with our oath, Primum non nocere, the quintessential question should not be "do we know everything?", but rather, do we know enough to successfully prevent, accurately diagnose, and safely treat all of our patients.

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ORIGINAL ARTICLE

Case Control Study

Egg consumption and risk of non-alcoholic fatty liver disease

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Abstract

AIM

To evaluate the association between egg consumption and risk of non-alcoholic fatty liver disease (NAFLD) development.

METHODS

This case-control study was conducted on individuals who were referred to two hepatology clinics in Tehran, Iran in 2015. The study included 169 patients with NAFLD and 782 controls. Egg consumption was estimated using a validated food frequency questionnaire. The participants were categorized according to the frequency of their egg consumption during the previous year: Less than two eggs per week, two to three eggs per week, and four or more eggs per week.

RESULTS

In the crude model, participants who consumed 2 to 3 eggs per week, were 3.56 times more likely to have NAFLD in comparison to those who consumed less than 2 eggs per week (OR: 3.56; 95%CI: 2.35-5.31). Adjustment for known risk factors of NAFLD strengthened

this significant association so that individuals have consumed two to three eggs per week had 3.71 times higher risk of NAFLD than those who have eaten less than two eggs per week (OR: 3.71; 95%CI: 1.91, 7.75).

CONCLUSION

Our data indicate that higher egg consumption in common amount of usage is associated with higher risk of NAFLD.

Key words: Egg; Diet; Non-alcoholic fatty liver disease; Dietary cholesterol

Core tip: The data indicate that egg consumption in common amount of usage is associated with risk of non-alcoholic fatty liver disease. According to the case-control design of this study, it can not show the causality effect; thus, these findings should be confirmed in future prospective studies with separate parts of eggs to find the etiological relationships.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of liver disordersfrom simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and even hepatocellular carcinoma[1]. NAFLD is the most common cause of chronic liver diseases around the world[2] and may be considered as hepatic manifestation of metabolic syndrome[3]. The increasing prevalence of obesity, together with insulin resistance, hypertension, dyslipidemia, and eventually the metabolic syndrome dispose many people to the risk of NAFLD development in the futureyears[4].

Increasing evidence showed that dietary factors contribute to the pathophysiology and treatment of NAFLD[5-7]. Among the known dietary factors that involved in the development of NAFLD, dietary cholesterol has drown a great deal of attention. Current studies of animal models propose that excess dietary cholesterol is regarded as the key factorrelated to the riskof steatohepatitis and hepatic inflammation[8-10]. Addition of cholesterol to the diet of obese, diabetic mice increasedthe accumulation of hepatic free cholesterol, hepatocyte apoptosis, and liver fibrosis[11]. Moreover, an association between raised cholesterol intake and the risk or severity of NAFLD has been addressed by epidemiological studies[12-14].

Among single foods, eggs are regarded as a main source of dietary cholesterol, with one large egg containing almost 210 mg of cholesterol; on the other hand, eggs are rich in proteins, and other nutrients[15], which can improve human health. There is limited evidence on the relationship between egg consumption and NAFLD and its risk factorswith controversial results[16-18]. Therefore, the present study was designed to examine the association between egg consumption and risk of NAFLD development.

MATERIALS AND METHODS

Participants

The present case-control study was conducted on individuals who were undertaken a liver Ultrasound, and were referred to two Hepatology clinics in Tehran, Iran in 2015. The study included 169 patients with NAFLD and 782 controls. The cases were patients with NAFLD, which was diagnosed by a gastroenterologistaccording to the presence of hepatic steatosis in Ultrasound exam within previous month, and referred to our clinics to be examined by Fibroscan®, and the Fibroscan resultsshowed a Controlled Attenuation Parameter score of more than 263, and fibrosis score of more than 7. These patients were selected with the convenience-sampling procedure. Controls were randomly selected age- and sex-matched subjects from the sameclinic among patients with pancreatobiliay disorders who had been undertaken an Ultrasound showing no hepatic steatosis. The age ranges for matching were 20-40, 40-60 and > 60 years old. Data on each pair of cases and controls were collected at the same time. The participation rate in the study was 94% for cases and 98% for controls. Written informed consent was obtained from all the participants. The study protocol was approved by the local Ethics Review Committee.

Assessment of dietary intake

Dietary intake of patients was assessed using a valid and reliablesemi-quantitative food frequency questionnaire (FFQ), which included 168 items of foods with standard servingsizes, as commonly consumed by Iranians[19]. The consumptionfrequency of each food item was questioned ona daily, weekly or monthly basis and converted to dailyintakes. In the case of egg consumption, the participants were categorized according to the frequency of their egg consumptionduring the previous year: Less than two eggs per week, two to three eggs per week, and four or more eggs per week. Dietary nutrients intakes were calculated using NUTRITIONIST V (First Databank, Hearst Corp,San Bruno, CA, United States). The patients who had completed less than 90% of dietary questionnaires and subjects who reported extremely low or high energy intakes (< 500 or > 5000 kcal/d) were excluded from the study[20].

Assessment of other variables

Physical activity was evaluated using the metabolic

Table 1 Baseline characteristics, biochemical parameters and dietary intakes of study participants based on the patients with non-alcoholic fatty liver disease and control group

	Cases (n = 169)	Controls (n = 782)	P value[a]
Age (yr), mean ± SD	42.65 ± 12.21	43.71 ± 14.52	0.373
Male n (%)	81 (47.9)	314 (40.2)	0.063
BMI (kg/m^2), mean ± SD	33.19 ± 8.71	27.74 ± 4.495	< 0.001
Physical activity (MET), mean ± SD	31.89 ± 3.15	34.33 ± 2.85	< 0.001
Current smokers, n (%)	151 (89.9)	145 (18.5)	< 0.001
Drank alcohol in past year, n (%)	22 (13.1)	68 (8.7)	0.077
Diabetes type 2, n (%)	26 (15.6)	53 (6.8)	< 0.001
FBS (mg/dL), mean ± SD	109.29 ± 39.39	90.09 ± 29.24	< 0.001
Total cholesterol (mg/dL), mean ± SD	184.79 ± 54.94	177.72 ± 38.74	0.221
LDL (mg/dL), mean ± SD	121.17 ± 43.04	104.26 ± 31.65	< 0.001
HDL (mg/dL), mean ± SD	41.26 ± 16.72	47.72 ± 10.51	0.001
Triglycerides (mg/dL), mean ± SD	180.40 ± 123.81	131.97 ± 81.59	< 0.001
Total energy (kcal), mean ± SEM	2627.67 ± 61.39	2746.69 ± 27.23	0.068
Carbohydrate (% of total energy), mean ± SEM	58.12 ± 0.95	59.82 ± 0.44	0.001
Protein (% of total energy), mean ± SEM	15.84 ± 0.18	14.07 ± 0.08	< 0.001
Fat (% of total energy), mean ± SEM	29.23 ± 0.30	33.78 ± 0.20	< 0.001
Dietary cholesterol (mg/d), mean ± SEM	315.31 ± 11.50	263.41 ± 5.35	< 0.001
Saturated fat (g/d), mean ± SEM	30.62 ± 5.72	62.67 ± 2.67	< 0.001
Monounsaturated fat (g/d) (mg/d), mean ± SEM	29.85 ± 0.48	32.00 ± 0.23	< 0.001
Polyunsaturated fat (g/d) (mg/d), mean ± SEM	18.51 ± 5.74	59.58 ± 2.67	< 0.001
Dietary fiber (g/d), mean ± SEM	19.21 ± 0.50	14.68 ± 0.23	< 0.001
Red/processed meats (g/d), mean ± SEM	70.95 ± 2.66	36.00 ± 1.24	< 0.001

[a]Independent t-test for quantitative variables and χ^2 test for qualitative variables. Dietary intakes (except total energy) were adjusted for age and total energy intake. BMI: Body mass index; MET: Metabolic equivalent task; FBS: Fasting blood sugar; LDL: Low-density lipoprotein cholesterol; HDL: High density lipoprotein cholesterol.

equivalent task (MET) questionnaire[21,22]. Other covariate information including age, gender, smoking habits, alcohol consumption,medical history, and current use of medications were assessed using questionnaires. Weight and height of all participants were measured.

Statistical analysis

Baseline characteristics and dietary intakes were compared between cases and controls using t-test for continuous variables and χ^2 for categorical variables. Egg consumptionwas dividedinto three ascending categories on an ordinal scale. Mean or prevalence of baseline characteristics wascomputed for each category. Baseline characteristicswere also compared using ANOVA for continuous variables and χ^2 categorical variables. The relationship between NAFLDand egg consumptionwas assessed using multipleregression analysis. Estimates were presented inthree models; the first model was adjusted for age (continuous),and total energy intake (kcal/d). In thesecond model, we further controlled for body mass index (BMI), history of diabetes and smoking (non-smoker, current smoker). Finally, we further adjusted for physical activity (MET) and gender. All models were conducted by treating thefirstcategory of egg consumption (< 2/wk) as a reference. All the statistical analyses were done using SPSS for Windows (version 19; SPSS Inc., Chicago, IL).

RESULTS

Baseline characteristics, biochemical parametersand dietary intakes of the cases and controls are shown in Table 1. Mean age of the total study population was 43.54 ± 14.13 years and 41.5% (395) of participants were male. By design, cases and controls had the similar age and sex distribution. Patients with NAFLD had significantly more BMI, lower physically activity, lowerconsumption of alcohol, and were more likely to be smoker, and have diabetes in comparison to controls. Furthermore, the cases had elevatedfasting blood glucose (FBS), low-density lipoprotein cholesterol (LDL), Triglycerides, and reduced high density lipoprotein cholesterol (HDL) levels and increasedintake of protein, cholesterol, fiber and red/processed meats compared with the controls (Table 1).

Basic characteristics and dietary intakes of the studied participants by categories of egg consumption are presented in Table 2. Compared to egg consumption of lower than two per week, higher egg consumption was associated with a lower average age, male sex, current smoking, higher energy intake, lower percent of total energy from carbohydrate and fat. Additionally, the subjects with higher egg consumption tended toconsume more protein, cholesterol, monounsaturated fat and red/processed meats, but less saturated and polyunsaturated fatty acids (Table 2).

In secondary analysis, there wasa similar egg-NAFLD associationsin women (P-trend 0.001) and men (P-trend 0.048) (Table 3).

Multivariate adjusted odds ratios for NAFLD based on egg consumption categories are indicated in Figure 1. In the crude model, participants that consumed 2 to 3 eggs per week, were 3.56 times more likely to have NAFLD in

Table 2 Basic characteristics and dietary intakes of study participants by frequency of egg consumption *n* (%)

	Egg consumption categories			*P* value[a]
	< 2/wk (*n* = 589)	2-3/wk (*n* = 142)	⩾ 4 /wk (*n* = 220)	
Age (yr)	45.65 ± 12.26	39.73 ± 13.18	40.35 ± 13.30	< 0.001
Male gender	218 (37.0)	56 (39.4)	121 (55)	< 0.001
BMI (kg/m^2), mean ± SD	28.58 ± 5.44	29.60 ± 7.34	28.51 ± 5.87	0.150
Physical activity (MET), mean ± SD	33.99 ± 3.05	33.42 ± 3.21	33.94 ± 2.95	0.136
Current smokers	155 (26.3)	59 (41.8)	82 (37.3)	< 0.001
Total energy (kcal), mean ± SEM	2580.59 ± 30.68	2744.94 ± 57.45	3101.07 ± 51.20	< 0.001
Carbohydrate (% of total energy), mean ± SEM	60.44 ± 0.67	59.48 ± 0.63	58.14 ± 0.85	0.001
Protein (% of total energy), mean ± SEM	14.09 ± 0.10	14.71 ± 0.20	14.95 ± 0.17	0.001
Fat (% of total energy), mean ± SEM	33.06 ± 0.24	32.56 ± 0.49	32.97 ± 0.40	< 0.001
Dietary cholesterol (mg/d)	226.40 ± 5.75	291.95 ± 11.60	383.90 ± 9.53	< 0.001
Saturated fat (g/d)	56.70 ± 3.16	64.70 ± 6.38	52.57 ± 5.24	< 0.001
Monounsaturated fat (g/d) (mg/d), mean ± SEM	31.20 ± 0.26	31.32 ± 0.53	32.91 ± 0.44	< 0.001
Polyunsaturated fat (g/d) (mg/d), mean ± SEM	53.10 ± 3.20	57.26 ± 6.45	46.71 ± 5.30	< 0.001
Dietary fiber (g/d)	15.65 ± 0.28	16.25 ± 0.57	14.60 ± 0.47	< 0.001
Red/processed meats (g/d)	37.76 ± 1.53	47.79 ± 3.10	50.51 ± 2.54	< 0.001

[a]Dietary intakes (except total energy) were adjusted for age and total energy intake. BMI: Body mass index; MET: Metabolic equivalent task.

Table 3 Odds ratio for non-alcoholic fatty liver disease-according to egg consumption stratified by gender

	Multivariate adjusted model[a]	
Egg consumption	Female	Male
< 2/wk	1.00	1.00
2-3/wk	5.55 (2.30-13.37)	1.90 (0.50-7.16)
⩾ 4/wk	1.67 (0.68-4.10)	0.25 (0.06-1.01)
P for trend	0.001	0.048

[a]Adjusted for age, energy intake, body mass index, history of diabetes, smoking, and physical activity.

comparison to those who consumed less than 2 eggs per week (OR: 3.56; 95%CI: 2.35-5.31). After controlling for ageand total energy intake, consuming 2 to 3 eggs per week was positively associated with the risk of NAFLD (OR: 3.83; 95%CI: 2.49-5.89). These associations remained significant even after additionally controlling for BMI, history of diabetes and smoking (OR: 3.57; 95%CI: 1.89-6.75). Further adjustment for physical activity, and gender strengthened this significant association so that individuals who have consumed two to three eggs per week had 3.71 times higher risk of NAFLD than those who have eaten less than two eggs per week (OR: 3.71; 95%CI: 1.91-7.75). Egg consumption more than four per week was not significantly associated with the NAFLD risk.

DISCUSSION

The results of the present study showed that the egg consumption increases the risk of NAFLD in common range of its consumption (two tothree eggs per week). This relationship was also significant after adjustment forage, gender, BMI, history of diabetes, smoking, and physical activity.

The role of diet and dietary supplements on the pathogenesis of NAFLD have been shown previously[23-36]; however, to our knowledge, no study has yet evaluated the association of egg consumption and NAFLD risk. It is well established that eggscontain a wide variety of essential nutrients and bioactive compounds that can affecthuman health. Their high quality protein, fats and micronutrients and low price make theman important part of many people's diet[37]; despite the nutritional benefits of egg consumption,there are concerns abouttheir high content of cholesterol and saturatedfat and theirinfluences on metabolic disorders[38]. Thus, one possible explanation for theinverse association between egg consumption and risk of NAFLD development may be due to the highcholesterol content of egg. Previous studieshave shown that a higher consumption of cholesterolis associated with NAFLD and its exacerbation[12,13,39,40]. In addition, the presence of high amount of cholesterol in diet is necessary for development of NAFLD[41]. Baumgartner *et al*[39] have shown that daily egg consumption increases serum cholesterol and LDL-C concentrations inwomen; however, there was no effects on markers for inflammation, endothelial activity, and liver function. Interestingly, the consumption of egg white hydrolyzed with pepsin considerably improved hepatic steatosis[42]. Thus, it seems that the association between egg consumption and NAFLD is mainly due to high cholesterol content of it, and might not be seen when people consume only the white part of it. Therefore, more studies are recommended to evaluate the effects of consumption of different parts of egg on NAFLD risk[13].

An unexpected finding of the present study was that more than 4 eggs consumptionper week was not significantly associated with risk of NAFLD. This may be explained by the fact that nutritional factors are correlated with each other, and determining of the effect of particular nutrients or particular foods on a risk factor is difficult. The effects of egg cholesterol on serum cholesterol concentrations depends on the content of individuals' diet specially the fiber content of it[43,44]. It is possible that those who ate more than 4 eggs per week, consumed it in mixed dishes containing vegetables, which reduces the absorption of cholesterol. Thus, we

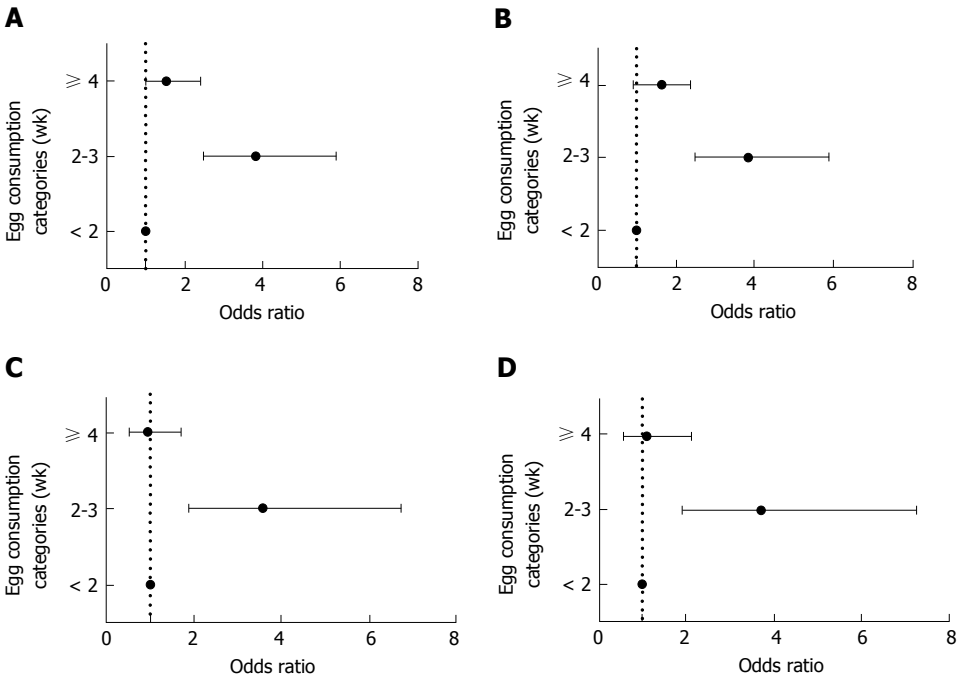

Figure 1 Multivariate-adjusted odds ratio for non-alcoholic fatty liver diseaseaccording to egg consumption. A: Crude model; B: Model 2, multivariate adjusted for age and energy intake; C: Model 3, further controlled for, body mass index, history of diabetes and smoking; D: Model 4, additionally adjusted for physical activity, and gender. Data are presented as the odds ratio (95%CI).

suggest that future studies assess the type of dishes with egg to find the possible interactions of different constituent of them.

It has been reported that dietary intake of patients with NAFLD was richer in saturated fat, cholesterol and was poorer in polyunsaturated fat[12]. Subramanian *et al*[40] have concluded that dietary cholesterol confers in progression of NAFLD to NASH. Furthermore, Zelber-Sagi *et al*[18] found that NAFLD patients have a higher intake of meat, which is another source of dietary cholesterol; however, some other studies only found a significant association between NAFLD and high dietary intake of carbohydrate and simple sugars[45,46], and some studies did find an association only between NAFLD and low intake of n-3 fatty acids and some antioxidants[16]. These dietary habits may accelerate the development of NAFLD by directly affecting steatosis of liver and oxidative injury[12].

This study was the first study that examined the relationship between egg consumption and risk of NAFLD in newly diagnosed patients who have not probably changed their diet due to the disease diagnosis; other strengths of this study includes its relatively large sample size, the high participation rate of participants, and socioeconomic differences of participants, which affects their dietary intakes.

Although we used a validated FFQ for measurement of dietary intakes, measurement error, and recall bias are unavoidable errors. Moreover, there might be some unknown risk factors that affect our results. Therefore, we recommend this analysis to be done in other populations.

In conclusion, our data indicate that egg consumption in common amount of usage is associated with riskof NAFLD. According to the case-control design of this study, it can not show the causality effect; thus, these findings should be confirmed in future prospective studies with separate parts of eggs to find the etiological associations.

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COMMENTS

Background

Among the known dietary factors that affect the pathogenesis of non-alcoholic fatty liver disease (NAFLD), dietary cholesterol has drown a great deal of attention. Current studies propose that excess dietary cholesterol is regarded as the key factor related to the risk of steatohepatitis and hepatic inflammation. Among individual foods, eggs are regarded as a main source of dietary cholesterol; on the other hand, eggs are rich in proteins, and other nutrients. Limited research has assessed therelationship between egg consumption and risk of (NAFLD) development.

Research frontiers

Understanding of the associationbetween egg consumption andrisk of NAFLD developmentcan contribute to clarifyhow intake of special food groups correlate with the disease and could lead to more particularguidelinesfor NAFLD prevention.

Innovations and breakthroughs

This study showed that egg consumption in common amount of usage is associated with risk of NAFLD. It seems that this association is mainly due to

high cholesterol content of it, and might not be seen when people consume only the white part of it.

Applications

According to the results of this study, the authors recommend low intake of eggs specially the yolk part of it for prevention of NAFLD; however, further studies are recommended to reach to a consus in this regard.

Peer-review

This is an interesting paper evaluating the association between egg consumption and NAFLD.

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ORIGINAL ARTICLE

Retrospective Study

Serum 25-hydroxyvitamin D deficiency and hepatic encephalopathy in chronic liver disease

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Institutional review board statement: The study has approved by the Ethics Review Committee (RPAH Zone).

Informed consent statement: Informed consent was not necessary due to the retrospective nature of this investigation.

Conflict-of-interest statement: There were no conflicts of interests for any of the investigators.

Data sharing statement: Technical appendix, statistical code and dataset are available from the corresponding author at helen.vidot@sswahs.nsw.gov.au. Informed consent was not sought as all data was collected as part of standard care and all data is anonymised and risk of identification is low. No additional data is available.

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Abstract

AIM

To investigate the relationship between 25-hydroxy-vitamin D (25-OHD) deficiency and hepatic encephalopathy (HE) in patients with chronic liver disease (CLD).

METHODS

A retrospective analysis of the results of 392 adult patients with chronic liver disease who were assessed for liver transplantation between 2006 and 2010 was undertaken. HE, severity of CLD, nutritional status and 25-OHD were analysed in patients assessed for liver transplantation between 2006 and 2010. Patients who presented with acute, fulminant or subacute disease, with a primary diagnosis of liver cancer, were assessed for re-transplantation or who did not have a 25-OHD

measurement were excluded from the analysis.

RESULTS

One hundred and sixty-five patients were included in this analysis. The mean age of all patients was 53 ± 8 years. Moderate to severe 25-OHD deficiency was identified in 49 patients of whom 36 had grade 2-3 HE compared with 13 patients who were not encephalopathic ($P \leqslant 0.0001$). Mild 25-OHD deficiency was not associated with HE. There was a significant correlation between the severity of 25-OHD deficiency and the severity of liver disease ($r = 0.39$, $P \leqslant 0.0001$) and disease severity and the presence of HE ($P \leqslant 0.0001$). Importantly, individuals with 25-OHD deficiency were more likely to have a diagnosis of overt HE (OHE) at a significantly lower model for end stage liver disease (MELD) score than individuals without OHE ($P \leqslant 0.0001$). This significant difference was observed with MELD scores from 10 to 38.

CONCLUSION

25-OHD deficiency was observed in the majority of patients with CLD and for the first time was found to be significantly worse in patients with OHE.

Key words: Vitamin D; Chronic liver disease; Hepatic encephalopathy; Model For End Stage Liver Disease; Dementia; Malnutrition; Cognitive function

Core tip: A strong association between vitamin D deficiency and deteriorating liver disease is identified in this investigation which supports previous reported findings. The novel finding in this investigation is the relationship between vitamin D deficiency and overt hepatic encephalopathy (OHE) in patients with chronic liver disease (CLD) which is independent of renal impairment and nutritional status. As repeated episodes of OHE may result in some residual neuropsychiatric alterations, maintenance of vitamin D levels within normal range in patients with CLD should be considered in clinical management. These results provide a strong rationale for future intervention studies in this group.

Vidot H, Potter A, Cheng R, Allman-Farinelli M, Shackel N. Serum 25-hydroxyvitamin D deficiency and hepatic encephalopathy in chronic liver disease. *World J Hepatol* 2017; 9(10): 510-518 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i10/510.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i10.510

INTRODUCTION

Hepatic encephalopathy (HE) describes a complex collection of neuropsychiatric symptoms ranging from sub-clinical neuropsychiatric changes to coma[1] and has been identified in up to 55% of patients with chronic liver disease[2]. Symptoms include impaired cognition and motor function and reduced energy levels[3] HE can be classified as covert or overt HE (OHE)[1]. Features of HE can be likened to symptoms seen in patients with dementia[4].

The aetiology of HE is complex and multifactorial, and includes abnormal ammonia metabolism, dysbiosis which promotes inflammation in the gut and liver[5], low levels of circulating branched chain amino acids[6], electrolyte abnormalities[7] and alterations in zinc and manganese levels[8]. Importantly, the features of HE can often be significantly reversed following treatment consistent with a largely functional not a structural cause of cognitive impairment[9].

The development of HE presents significant challenges to patients and their carers[10]. Until recently, lactulose was the major cornerstone in the management of HE and continues to be used as a first line management for the control of the symptoms of chronic HE and for the reversal of the symptoms of acute episodes of HE[11]. The introduction of Rifaximin has reduced the rate of OHE and the frequency of hospital admissions due to OHE and improved the quality of life for the patient and their carers[12].

Patients who experience repeated episodes of OHE can have persistent and cumulative deficits in working memory, response inhibition and learning[13]. There is growing evidence that some deficit in cognitive function remains in liver transplant recipients who were severely encephalopathic or who experienced multiple episodes of OHE prior to liver transplantation[9]. Therefore, the prevention of OHE is paramount to the preservation of mental integrity in patients with cirrhosis.

Vitamin D is a multifunctional steroid hormone with diverse actions that are only partially understood. It is increasingly apparent that vitamin D is not just involved in calcium homeostasis and bone metabolism but has multiple biological targets mediated by vitamin D receptors (VDR)[14] which are present in more than 30 tissues[15] including the brain, kidneys, intestine, parathyroid gland, pituitary, prostate, mammary glands, cardiac and skeletal muscle, non-parenchymal liver cells, endothelial cells and the immune system[16-20].

Vitamin D is obtained from dietary sources and ultraviolet light exposure. The first step in the activation of vitamin D is the hydroxylation of cholecalciferol to the active metabolite 25-hydroxyvitamin D (25-OHD) which occurs in the liver[21]. This is the major circulating metabolite of vitamin D, bound to the carrier protein vitamin D binding protein (DBP) with a half-life of 15-21 d[21,22]. The second activation process to 1,25 dihydroxy vitamin D occurs predominantly in the kidney[21] and to a lesser extent in a range of other tissues including bone, breast, brain, monocytes, parathyroid gland and placenta[21]. This active metabolite has a shorter half-life of 10-20 h[22]. Consequently, vitamin D status is commonly assessed by measuring circulating levels of 25-OHD[22].

Vitamin D has been identified as an immune modulator and anti-infective agent[23] and an association

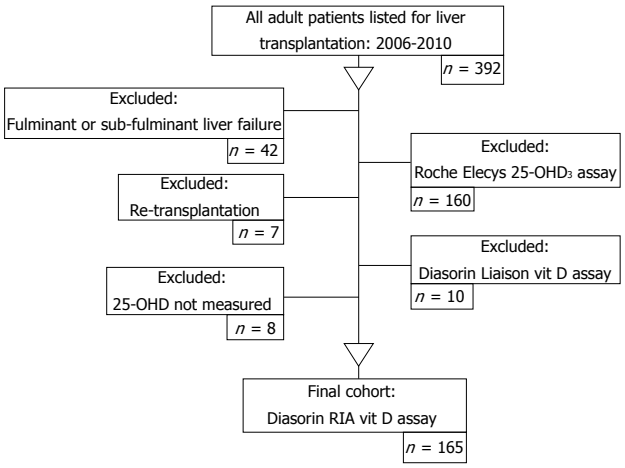

Figure 1 Study design. The selection and application of inclusion/exclusion criteria for inclusion in the final analysis. 25-OHD: 25-hydroxyvitamin D; RIA: Radioimmunoassay.

between vitamin D deficiency and the progression of liver disease has been identified in hepatitis C virus (HCV)[24], alcoholic liver disease (ALD)[25] and non-alcoholic fatty liver disease (NAFLD)[24].

There is growing evidence of clinical associations between vitamin D status and global and specific areas of cognitive function[26] and that vitamin D deficiency may be associated with both depression and schizophrenia[27]. Further, vitamin D deficiency is associated with low mood and impairment in some areas of cognitive functioning without any impairment in physical performance[28] and with an accelerated decline in cognitive function[29].

VDR protein is present in most neurons and the glia in the human brain[30]. The hypothalamus and the cortex of the human brain are key areas in cognition[31]. The presence of both VDR protein and vitamin D metabolites in these areas of the brain are an indication that the vitamin D system is involved in the normal functioning of the human brain[32].

As the first step in the hydroxylation of vitamin D occurs within the liver 25-OHD, levels decrease with progressive liver dysfunction. Vitamin D deficiency has been reported in up to 92% of patients with chronic liver disease and at least one third of these have severe 25-OHD deficiency[33]. 25-OHD deficiency is associated with increasing Child-Pugh classification rather disease aetiology[34] and is more prevalent in patients with cirrhosis than those who are not cirrhotic[33]. Increased all-cause mortality is associated with 25-OHD deficiency and specifically with increased mortality in patients with cirrhosis[35]. To date, an association between 25-OHD deficiency and HE has not been described. Therefore, we aimed to investigate the relationship between 25-OHD, cirrhosis and HE.

MATERIALS AND METHODS

Patient selection

All patients who present for assessment for liver transplantation routinely undergo a comprehensive series of tests and examinations prior to consideration of suitability for transplantation. A retrospective analysis of the results of 392 adult patients with chronic liver disease who were assessed for liver transplantation between 2006 and 2010 was undertaken. Approval to access medical records was granted by the Sydney Local Health District Ethics Review Committee (RPAH X15-0209).

Data collection

Data collated included primary diagnosis, demographic information, standard biochemical markers of liver function, disease severity scores model for end stage liver disease (MELD)[36] and Child Turcotte Pugh (CTP)[37], subjective nutritional assessment (SGA) scores[38], 25-OHD levels and the presence of HE assessed using the West Haven criteria[39]. Patients who presented with acute, fulminant or subacute disease were excluded from the analysis due to the acute nature of their illness. Patients with a primary diagnosis of liver cancer or who were undergoing assessment for re-transplantation or who did not have a 25-OHD measurement were also excluded from the analysis.

25-OH vitamin D status was defined as sufficient (> 75 nmol/L), insufficient (50-75 nmol/L), mild deficiency (25-50 nmol/L), moderate deficiency (12.5-25 nmol/L) and severe deficiency (< 12.5 nmol/L)[40,41].

During the study period, three different 25-OH D assay methods were used: (1) radioimmunoassay (RIA), referred to as the Diasorin-RIA® assay; (2) the electro-chemiluminescence immunoassay, referred to as the Roche Elecys® vitamin D_3 assay; and (3) the Liaison total automated direct competitive chemiluminescence immunoassay, referred to as the Diasorin Liaison® 25-OH vitamin D assay. 25-OHD levels are frequently overestimated with greater intra-assay variation when assessed by more recent methodologies[42]. As the Diasorin RIA® assay was regarded as the most accurate measure of 25-OHD[43] at the time of this investigation, the final analysis included only patients with 25-OHD levels measured using the Diasorin RIA® assay technique (Figure 1).

Statistical analysis

Results were analysed using Prism 6 for Mac (GraphPad Software Inc, La Jolla, CA, United States). Categorical values were analysed using χ^2 and quantitative continuous results were compared using the Mann-Whitney *U* test. Relationships between quantitative variables were assessed using Spearman correlation analysis. Multiple comparisons were made using One-way ANOVA, Kruskal-Wallis test and Dunn's multiple comparison test. The threshold for statistical significance is $P < 0.05$.

RESULTS

The patient selection process is outlined in Figure 1. After the exclusion criteria were applied 165 patients remained

Table 1 Population characteristics

	Total cohort (*n*)	Overt HE[1] (*n*)	No HE[1] (*n*)
Demographics	165	88	77
Gender			
Male	119	68	51
Female	46	20	26
Mean age (years ± SD)	53 ± 8	52 ± 7	54 ± 8
Primary indication for liver transplantation			
Viral hepatitis	91	52	39
Alcoholic cirrhosis	23	18	5
Cholestatic disease (PBC, PSC, autoimmune)	30	10	20
Non-alcoholic steatohepatitis	7	6	1
Other	14	2	12
Ethnicity			
Caucasian	130	75	55
Asian	22	6	16
Middle Eastern	8	4	4
Other	5	3	2
Clinical characteristics			
CTP score mean ± SD	9 ± 2.5	11 ± 1.7[a]	7 ± 2[a]
CTP stage			
A	41	0[a]	41[a]
B	47	22	25
C	77	66[a]	11[a]
Ascites			
None	51	7[a]	44[a]
Medically controlled	54	36[a]	18[a]
Poorly controlled	60	45[a]	15[a]
BMI (kg/m^2 ± SD)	27.4 ± 5.2	28.7 ± 5.4[a]	25.7 ± 4.2[a]
Nutritional status	104	65	39
SGA: A (well nourished)	12	9	3
SGA: B (moderately malnourished)	65	40	25
SGA: C (severely malnourished)	27	16	11
Biochemical characteristics			
25-OHD (vitamin D) (nmol/L) mean ± SD	36 ± 15	30 ± 13[a]	42 ± 16[a]
MELD score mean ± SD	17.1 ± 6.8	19.9 ± 6. 5[a]	13.9 ± 5.7[a]
Bilirubin (μmol/L) mean ± SD	114 ± 152	141 ± 167[a]	83 ± 128[a]
Creatinine (μmol/L) mean ± SD	84 ± 50	85 ± 35[a]	83 ± 63
Albumin (g/L) mean ± SD	33 ± 6	31 ± 5[a]	35 ± 6[a]
INR mean ± SD	1.6 ± 0.5	1.8 ± 0.6[a]	1.3 ± 0.3[a]
Sodium (mmol/L) mean ± SD	136 ± 5	135 ± 5[a]	138 ± 4[a]
Zinc (μmol/L) mean ± SD	8 ± 4	8 ± 3[a]	10 ± 5[a]

[a]$P < 0.05$. [1]Unless otherwise indicated there is no significant difference between HE and no HE. 25-OHD: 25-hydroxyvitamin D; HE: Hepatic encephalopathy; CTP: Child Turcotte Pugh; BMI: Body mass index; SGA: Subjective nutritional assessment; MELD: Model for end stage liver disease; INR: International normalized ratio.

in the study. Table 1 identifies the primary disease aetiology for liver transplantation assessment and the patient physical and biochemical characteristics.

The group was predominantly male with a mean age of 53.0 ± 8 years. Seventy nine percent of the group was Caucasian and there was no significant difference in 25-OHD levels identified across the different ethnic groups. The major cause of listing for liver transplantation was decompensated cirrhosis secondary to viral hepatitis. All patients had advanced disease as demonstrated by the CTP and MELD scores. OHE was present in 53% of patients. The majority of the cohort (69%) had ascites which was defined as grade 3-4 in 53% of patients[44]. Patients with OHE had a higher body mass index (BMI) ($P < 0.001$) with an associated significantly increased incidence of medically controlled and poorly controlled ascites ($P < 0.0001$) and significantly lower serum albumin levels ($P < 0.0005$).

Our results showed a strongly negative correlation between MELD score and 25-OHD levels ($P < 0.0001$) in all patients (Figure 2). Patients with OHE had significantly worse liver disease with a MELD score of 19.9 ± 6.5 whilst those who were not encephalopathic had significantly lower MELD score of 13.9 ± 5.7 ($P < 0.0001$) (Figure 3A). 25-OHD levels were lower in patients with OHE ($P < 0.0001$) (Figure 3B).

SGA of nutritional status was available for 104 patients. The majority of patients were either moderately or significantly malnourished (88%) and there was no significant correlation between nutritional status and 25-OHD levels (Figure 4). There is trend towards a higher incidence and increased severity of malnutrition in patients with OHE but this did not reach statistical significance. The correlation between RIA 25-OHD and the biochemical and physical parameters of the group are further outlined in Table 2.

Table 2 25-hydroxyvitamin D categories in patients assessed for liver transplantation

	25-OHD (nmol/L)	Total number	Overt HE[1] (n = 88)	No overt HE[1] (n = 77)
Sufficient	> 75	2	0	2
Insufficient	50-75	27	6	21
Mildly deficient	25-50	87	46	41
Moderately deficient	12.5-25	42	30[a]	12[a]
Severely deficient	< 12.5	7	6	1

[a]$P < 0.05$. [1]Unless otherwise indicated there were no significant differences between the overt HE and no-overt HE groups. 25-OHD: 25-hydroxyvitamin D; HE: Hepatic encephalopathy.

Table 3 Univariate 25-hydroxyvitamin D correlations with physical and biochemical markers determined by Spearman correlation

	Spearman r	P value	Significance
Age	0.1110	0.16	ns
Total bilirubin	-0.3493	< 0.0001	[f]
Albumin	0.3153	< 0.0001	[f]
ALP	0.0203	0.80	ns
GGT	0.2055	0.0081	[b]
ALT	0.0246	0.75	ns
AST	-0.1741	0.0253	[a]
Creatinine	-0.0687	0.38	ns
Na^+	0.2666	0.0005	[e]
Zn^+	0.2790	0.0004	[e]
RBP	0.2913	0.0002	[e]
Transferrin	0.3568	< 0.0001	[f]
INR	-0.4232	< 0.0001	[f]
Ca^{2+}	0.2370	0.0022	[b]
Ca^{2+} corrected	-0.1531	0.08	ns
PTH	-0.1824	0.0205	[a]
BMI	-0.2244	0.0055	[b]

[a]$P < 0.05$; [b]$P < 0.01$; [e]$P < 0.001$; [f]$P < 0.0001$. ns: Not significant; ALP: Alkalinephosphatase; GGT: Glutamyl transpeptidase; ALT: Alanine transaminase; AST: Aspartate transaminase; RBP: Retinol binding protein; INR: International normalized ratio; PTH: Parathyroid hormone; BMI: Body mass index.

Mild 25-OHD deficiency was not associated with an increase in OHE (Table 3). However, moderate and severe 25-OH D deficiency was significantly associated with the development of OHE ($P < 0.0001$). The relationship between 25-OH vitamin D and OHE is outlined in Figure 3B.

Using using χ^2 analysis lower 25-OHD levels were associated with a significant trend towards increasing levels of OHE ($P < 0.0001$). A significant difference between 25-OHD levels in patients with OHE and those without OHE was identified ($P < 0.0001$) and is demonstrated in Figure 5. Furthermore, there was a significant correlation between increasing OHE in patients with lower 25-OHD levels at the same level of disease severity as measured by the MELD scores.

DISCUSSION

Our results demonstrate that at the same level of disease severity patients with OHE have significantly lower 25-OHD levels than those who do not have OHE. This is the first description of this association.

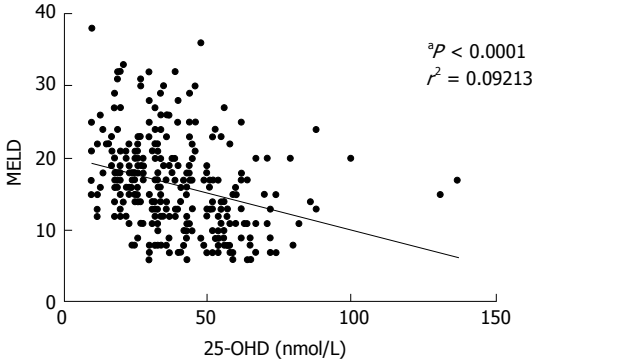

Figure 2 Vitamin D and severity of liver disease. 25-OHD levels fall with worsening liver disease. 25-OHD: 25-hydroxyvitamin D; MELD: Model for end stage liver disease.

When stratified into patients who have OHE and those who do not, our results show that, in patients assessed for liver transplantation, there is a statistically significant relationship between low 25-OHD levels and OHE. Importantly, a significantly higher incidence of OHE was observed in individuals with low 25-OHD levels at similar levels of disease severity. This association raises the possibility that vitamin D deficiency has an effect on the manifestation of HE or is associated with other unrecognised factors. Importantly, OHE rarely occurred with normal Vitamin D levels but individuals could have low vitamin D and not have OHE. This is a similar relationship to the association of elevated serum ammonia with the development of OHE[45]. Consequently, the presence of moderate to severe 25-OHD deficiency means OHE is more likely in patients with ESLD.

It was beyond the scope of this investigation to explore the relationship between covert HE and 25-OHD deficiency. A large proportion of patients with insufficient (78%) or mild 25-OHD deficiency (47%) were not diagnosed with OHE. It possible that in a proportion of patients with insufficient or mild 25-OHD deficiency reduced levels of 25-OHD could be associated with the development or presence of covert HE. This is analogous to ammonia levels in ESLD which are elevated in HE but elevation does imply the presence of HE either OHE or covert HE.

There is a significant relationship between worsening liver function and 25-OHD deficiency. This is consistent with the growing awareness of the association between

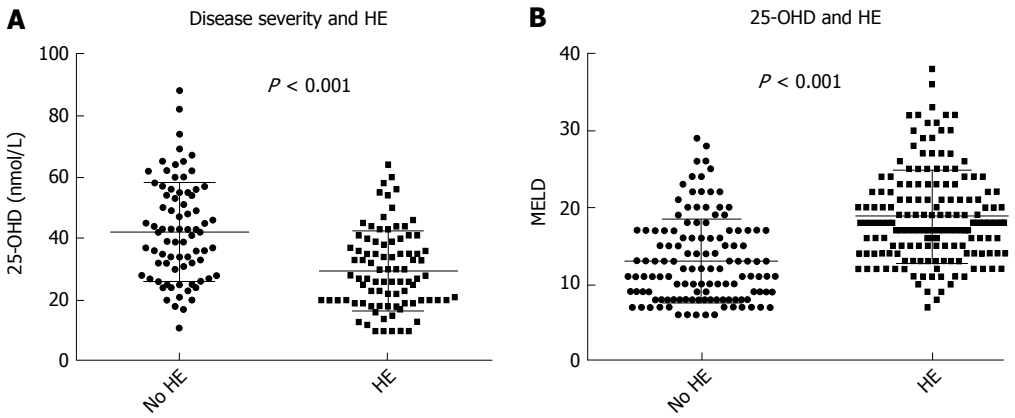

Figure 3 Disease severity, overt hepatic encephalopathy and vitamin D levels. A: Patients with overt HE have significantly higher MELD than patients without overt HE; B: 25-OHD levels measured by Diasorin-RIA and HE. Patients with overt HE have significantly lower 25-OHD levels than those without overt HE. 25-OHD: 25-hydroxyvitamin D; HE: Hepatic encephalopathy; MELD: Model for end stage liver disease.

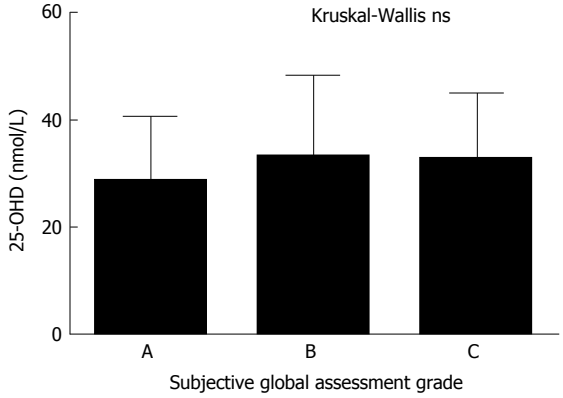

Figure 4 25-hydroxyvitamin D and nutritional status. 25-OHD levels are independent of nutritional status. 25-OHD: 25-hydroxyvitamin D; ns: Not significant.

disease severity and reduced levels of 25-OHD in patients with cirrhosis[25]. Less than 2% of patients assessed for liver transplantation in this group had adequate levels of 25-OHD which is comparable to a previous study which identified vitamin D deficiency in 96% of patients waiting for liver transplantation[46].

As liver disease progresses, patients become increasingly malnourished with an associated increase in HE[8]. Alterations in macronutrient requirements and reductions in oral intake are a feature of decompensated cirrhosis[8]. However, our results did not show a significant association between malnutrition and 25-OHD levels. This is consistent with changes in 25-OHD metabolism being a determinant of deficiency in CLD.

Vitamin D supplementation is now recognised as an important component of the management of patients with cirrhosis. Routine vitamin D supplementation for patients with chronic liver disease and insufficient levels of 25-OHD has become the standard of care in hepatology clinics to treat or prevent osteoporosis in CLD[47]. These results suggest a role for vitamin D supplementation in patients with CLD and reduced levels of 25-OHD.

There is growing evidence for an association between 25-OHD deficiency and the development of all-cause dementia and a reduction in cognitive capacity[48] which is not confined to older populations. A linear relationship between 25-OHD deficiency and cognitive impairment has been identified in younger adults (30-60 years) as well as adults older than 60 years[49]. A systematic review of vitamin D and cognitive impairment concluded that "25-OHD insufficiency likely negatively affects specific cognitive functions, such as explicit episodic memory"[31] but there is a need for robust clinical investigation in this area.

Although it is plausible that 25-OHD deficiency could impact on cognitive function in CLD, neither a causative relationship nor a mechanism for this has been demonstrated. The level at which 25-OHD deficiency adversely affects brain function is unknown. 25-OHD is associated with verbal fluency, a marker of executive function and therefore a marker of cognitive function. Individuals with supratherapeutic 25-OHD levels of > 100 nmol/L scored significantly higher on verbal fluency tasks than those with inadequate 25-OHD levels[50] further supporting the role of vitamin D in the development of cognitive decline.

Neurobehavioral abnormalities are the major clinical component of HE and have shown to be associated with increased levels of inflammatory cytokines[51]. Systemic inflammation and changes in hepatic metabolism (*i.e.*, increased ammonia levels) are increasingly recognised as a precipitants of HE and worsen existing HE[52]. Vitamin D has been shown to have anti-inflammatory properties[52]. It can be postulated that vitamin D deficiency is associated with an increase in systemic inflammation thereby giving rise to the development of HE.

It is unclear whether there is a steady decline in brain function as 25-OHD levels drop or whether there is a threshold from which point there is a significant reduction in brain function in patients with cirrhosis. To show a causative relationship of the vitamin D with HE it is now necessary to examine the effects of vitamin D supplementation on encephalopathy symptoms in

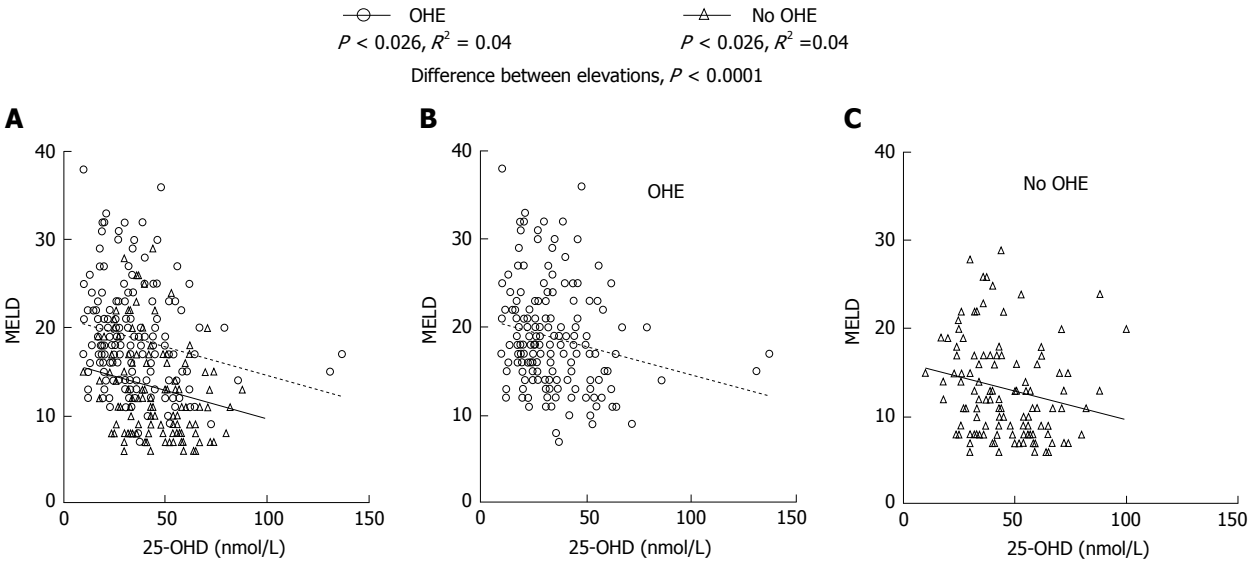

Figure 5 Overt hepatic encephalopathy, disease severity and 25-hydroxyvitamin D. Patients were stratified into those who had overt HE and those who did not. The combined data is presented in (A) and the sub groups of patients with OHE (B) and those without OHE (C). Vitamin D deficiency correlates with MELD score in both patients with and without OHE. Across the range of MELD scores from 10-30 patients with OHE (B) had significantly lower levels of 25-OHD than those who did not (C). 25-OHD: 25-hydroxyvitamin D; OHE: Overt hepatic encephalopathy; MELD: Model for end stage liver disease.

patients with CLD.

To date, the literature suggests association not causality. There is sufficient association between cognitive and behavioral changes associated with 25-OHD deficiency to suggest a role for vitamin D deficiency in the development of HE in patients with chronic liver disease. Further studies are required to investigate the relationship between 25-OHD levels and the development of HE in patients with CLD.

COMMENTS

Background

Hepatic encephalopathy (HE) describes a complex range of neuropsychiatric symptoms and is associated with the development and progression of hepatic cirrhosis. HE has been described as a form of dementia which is largely reversible. Low vitamin D levels [25-hydroxyvitamin D (25-OHD)] are associated with dementia and impaired cognition in the general population. The association between low 25-OHD levels and HE has not been previously investigated.

Research frontiers

It is not known whether the association between low 25-OHD levels and HE is causative. The association described requires further investigation to determine the precise role of 25-OHD deficiency in the development of HE. Historically, the assays used to determine 25-OHD levels have varied significantly. Consistent assay methodology should be implemented to investigate this relationship further.

Innovations and breakthroughs

It has been established that patients with chronic liver disease (CLD) have low levels of 25-OHD which are associated with overt HE. Monitoring of 25-OHD vitamin D levels and regular and appropriate vitamin D supplementation in patients with cirrhosis may help prevent the development of HE.

Applications

Monitoring 25-OHD levels and replacement therapy is an important aspect of the overall management of patients with CLD.

Terminology

Automated immunoassays are used for routine analysis of serum 25-OHD levels and there is wide variation between the different assay techniques. At the time of this investigation, the Diasorin RIA assay was identified as the most reliable method of measuring serum 25-OHD levels.

Peer-review

This is very interesting paper about the relationship between 25-OH deficiency and HE. Author concluded that there is a significant association between low-25-OHD levels and the development of HE.

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ORIGINAL ARTICLE

Prospective Study

Hepatic encephalopathy before and neurological complications after liver transplantation have no impact on the employment status 1 year after transplantation

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Abstract

AIM

To investigate the impact of hepatic encephalopathy

before orthotopic liver transplantation (OLT) and neurological complications after OLT on employment after OLT.

METHODS

One hundred and fourteen patients with chronic liver disease aged 18-60 years underwent neurological examination to identify neurological complications, neuropsychological tests comprising the PSE-Syndrome-Test yielding the psychometric hepatic encephalopathy score, the critical flicker frequency and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), completed a questionnaire concerning their occupation and filled in the short form 36 (SF-36) to assess health-related quality of life before OLT and 12 mo after OLT, if possible. Sixty-eight (59.6%) patients were recruited before OLT, while on the waiting list for OLT at Hannover Medical School [age: 48.7 ± 10.2 years, 45 (66.2%) male], and 46 (40.4%) patients were included directly after OLT.

RESULTS

Before OLT 43.0% of the patients were employed. The patients not employed before OLT were more often non-academics (employed: Academic/non-academic 16 (34.0%)/31 *vs* not employed 10 (17.6%)/52, $P = 0.04$), had more frequently a history of hepatic encephalopathy (HE) (yes/no; employed 15 (30.6%)/34 *vs* not employed 32 (49.2%)/33, $P = 0.05$) and achieved worse results in psychometric tests (RBANS sum score mean ± SD employed 472.1 ± 44.5 *vs* not employed 443.1 ± 56.7, $P = 0.04$) than those employed. Ten patients (18.2%), who were not employed before OLT, resumed work afterwards. The patients employed after OLT were younger [age median (range, min-max) employed 47 (42, 18-60) *vs* not employed 50 (31, 29-60), $P = 0.01$], achieved better results in the psychometric tests (RBANS sum score mean ± SD employed 490.7 ± 48.2 *vs* not employed 461.0 ± 54.5, $P = 0.02$) and had a higher health-related quality of life (SF 36 sum score mean ± SD employed 627.0 ± 138.1 *vs* not employed 433.7 ± 160.8; $P < 0.001$) compared to patients not employed after OLT. Employment before OLT ($P < 0.001$), age ($P < 0.01$) and SF-36 sum score 12 mo after OLT ($P < 0.01$) but not HE before OLT or neurological complications after OLT were independent predictors of the employment status after OLT.

CONCLUSION

HE before and neurological complications after OLT have no impact on the employment status 12 mo after OLT. Instead younger age and employment before OLT predict employment one year after OLT.

Key words: Hepatic encephalopathy; Employment; Neurological complications; Cognitive function; Health-related quality of life; Liver transplantation

Core tip: This prospective study is the first to consider hepatic encephalopathy prior to liver transplantation, neurological complications after liver transplantation as well as socio-economic factors as risk factors for unemployment 1 year after transplantation. Our data confirm that employment status before liver transplantation is most important in predicting the employment status 12 mo after transplantation. However, neither prior-liver transplantation hepatic encephalopathy nor neurological complications after liver transplantation are independent risk factors for unemployment 1 year after transplantation.

Pflugrad H, Tryc AB, Goldbecker A, Strassburg CP, Barg-Hock H, Klempnauer J, Weissenborn K. Hepatic encephalopathy before and neurological complications after liver transplantation have no impact on the employment status 1 year after transplantation. *World J Hepatol* 2017; 9(10): 519-532 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i10/519.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i10.519

INTRODUCTION

During the last 35 years specialized transplantation centres with outpatient clinics for follow-up and improvement of immunosuppressive therapy have significantly increased survival rates after orthotopic liver transplantation (OLT)[1]. Thus, additional indicators of treatment quality besides mortality, such as employment after OLT, emerged. Employment after OLT indicates reintegration into society, regain of cognitive and physical capability and increased health-related quality of life (HRQoL)[2]. Although reintegration of patients into work is pursued, actually, only about 50% of the patients work after OLT, and there are significant differences between different countries with rates ranging between 17% and 55%[3-8]. Reasons why patients do not work after OLT are believed to be manifold. Local social security insurance system, age, sex, level of vocational training, level of school education, type of work, disability, unemployment before OLT, underlying liver disease, high morbidity due to liver disease and complications after OLT have been discussed[4,9]. Hereof, employment itself and the type of employment before OLT were considered to be the most important predictors of post OLT employment[3]. Interestingly, neither hepatic encephalopathy (HE) before OLT nor neurological complications after OLT have been considered in this respect so far even though both can significantly impact patients' physical and mental ability before and after OLT.

HE is a frequent complication of liver cirrhosis caused by liver insufficiency and porto-systemic shunts[10]. It is based on neurochemical and neurophysiological disorders of the brain and although the pathogenesis of HE is not completely understood, ammonia is believed to be of major importance[11]. HE is characterized by deficits in motor accuracy and motor speed as well as cognitive impairment especially concerning attention, whereas verbal abilities maintain unaffected[12]. HE is

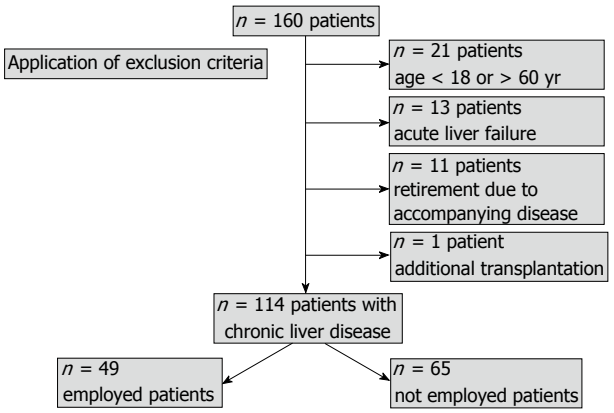

Figure 1 Patients' distribution. Flow chart showing loss of patients due to exclusion criteria and distribution into the groups "employed" and "not employed" before liver transplantation.

present in about 10%-50% of patients at the time of transplantation and about 35%-45% of OLT patients have a history of HE[13]. Neurological complications like encephalopathy, seizures, tremor, psychotic disorders and posterior reversible encephalopathy syndrome occur in about 30% of the patients after OLT[14]. They result in a high morbidity and prolonged in-hospital stay[15]. HE prior OLT and neurological complications after OLT have not been distinctly considered as risk factors for unemployment after OLT so far, probably because HE was considered to be completely reversible[16], and neurological complications after OLT - though frequent - are usually impairing the patients cognitive function only transiently[14,15,17].

However, HE is known to have an impact on patients' working ability before OLT, especially of blue collar workers[18], and neurological complications possibly impair recovery of working capability after OLT[15]. The main hypothesis of this prospective study was that hepatic encephalopathy before OLT and neurological complications after OLT are significantly associated with unemployment one year after OLT. Furthermore, we analysed whether employment status before OLT, occupation, underlying liver disease, health-related quality of life, quality adjusted life years (QALYs), age and sex are significantly associated with the employment status one year after OLT.

MATERIALS AND METHODS

Patients

All patients included into this study took part in a long-term prospective follow-up study of patients after liver transplantation (n = 160). Patients with liver cirrhosis, admission to the waiting list for liver transplantation, acute liver failure and age between 18 and 80 years were included into the follow-up study. For the present study patients with acute liver failure, neurological or psychiatric diseases not related to hepatic encephalopathy, additional transplantation of another organ, regular intake of medication with an effect on the central nervous system (CNS), age older than 60 years at OLT because of the high probability of age related retirement and the expected low probability of reintegration into employment after OLT, retirement due to conclusion of work life, accompanying disease or age were excluded. Finally, data of 114 patients with chronic liver disease were considered for the analysis (Figure 1). Sixty-eight (59.6%) patients were recruited before OLT, while on the waiting list for liver transplantation at Hannover Medical School [age: 48.7 ± 10.2 years, 45 (66.2%) male], and 46 (40.4%) patients were included directly after OLT [age: 44.9 ± 11.4 years, 27 (58.7%) male].

All subjects gave written informed consent. The study was approved by the local ethics committee and performed according to the World Medical Association Declaration of Helsinki (revised in 2008).

Methods

Patients recruited before OLT regularly underwent neurological examinations by a neurologist of the group before OLT if possible and all patients included underwent a neurological examination on day 1, day 7, day 90 and approximately 12 mo after OLT. If the examination was not possible 12 mo after OLT, it was done at a later point of time within the follow-up study. Additional neurological examinations were performed when necessary. Encephalopathy, posterior reversible encephalopathy syndrome, alterations of consciousness, seizures, hallucinations, confusion, infections of the CNS, intracerebral bleeding or stroke were classified as neurological complications. Neurological complications were assessed as a categorical variable independent from the time of occurrence within the immediate hospital stay after OLT.

If possible, a psychometric test battery for the assessment of attention, concentration, memory, speed of information processing, visuo-constructive abilities, motor speed and accuracy and executive functions comprising the PSE-Syndrome-Test, a battery that provides the psychometric hepatic encephalopathy score (PHES)[19], the critical flicker frequency (CFF)[20] and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[21,22] were applied by a neurologist of the group trained in these tests. The median interval between the psychometric testing before OLT and the transplantation was 4 mo (interquartile range 5 mo, min 0, max 33) and the median interval between OLT and psychometric testing after OLT was 12 mo (interquartile range 5 mo, min 10, max 62). Furthermore, the patients were asked to complete questionnaires concerning occupation and HRQoL [short form 36 (SF-36)][23]. The SF-36 evaluation was performed according to its scoring algorithm yielding 8 domain scores: Physical functioning (PF), physical role functioning (PRF), bodily pain (BP), general health perception (GHP), vitality (VIT), social role functioning (SRF), emotional role functioning (ERF) and mental health (MH) which were summated for the SF-36 sum score. The default summary measures physical health and mental health were not calculated because they are based on

Table 1 Self-reporting questionnaire occupation *n* (%)

n = 114	Before OLT	After OLT
Employed	36 (31.6)	33 (34.4)[1]
Retired	48 (42.1)	49 (51.0)[1]
Unemployed	7 (6.1)	2 (2.1)[1]
Certified unfit for work	10 (8.8)	2 (2.1)[1]
Homemaker	8 (7.0)	6 (6.3)[1]
Student	5 (4.4)	4 (4.2)[1]
Deceased	-	18 (15.8)

[1]Percent value is based on *n* = 96 survivors. OLT: Orthotopic liver transplantation.

American standard values.

The six-dimension health state short form (SF-6D)[24] was derived from the SF-36 by generating six multi-level dimensions that provide a health status which ranges from 1 (full health) to 0 (death). It is based on preference weights gained from the United Kingdom general population and estimates a preference-based single index measure for health to measure QALYs.

Individual test results were evaluated by comparison to norm values given in the test manuals. The scores of the psychometric batteries were adjusted for age and education. Reasons for missing data before OLT were language issues, inclusion of the patient after OLT or refusal by the patient to complete the tests or questionnaires. After OLT data is missing due to refusal by the patient to complete the tests or questionnaires, language issues or death after OLT.

Age, occupation, underlying liver disease, laboratory Model of End Stage Liver Disease (labMELD) score and medication were assessed and documented. The history of HE was taken from reliable case records in which HE was diagnosed and scored by physicians according to the West Haven criteria[25].

Self-reporting questionnaire occupation: The patients selected which of the following specifications applied to their situation: Employed, retired (receiving pension due to illness), unemployed, certified unfit for work, homemaker or in training at school or university. Patients on a full time or part time job, students and homemakers were classified as employed. Although Patients with the status "student" or "homemaker" were not working for a wage, they were classified as employed because the authors are convinced that studying or keeping the house requires physical and mental capability which equals the requirements that are needed to work for a wage. The not employed patient group consisted of patients that were unemployed, temporarily certified unfit for work or retired due to liver disease (Table 1). For subgroup analysis the patients were allocated according to their employment status before and after OLT into the groups employed before and after OLT, employed before but not employed after OLT, not employed before and after OLT as well as not employed before but employed after OLT. Patients with a university degree were classified as academics and patients with a vocational training for qualification were classified as non-academics. These data were surveyed retrospectively for patients included after OLT from case records or by anamneses.

Statistical methods: Normality of distribution was assessed by the Shapiro-Wilk test. Differences between the groups of employed and not employed patients concerning age, labMELD score, psychometric test results and SF-36 scores were evaluated with the Mann-Whitney test for not normal distributed values and Analysis of variance (ANOVA) for normal distributed values. The Wilcoxon test or the paired sample T-test was used to compare related values concerning psychometric test results and SF-36 scores surveyed before and after OLT. Categorical variables comprising sex, profession, history of HE and neurological complications were tested by Fisher's Exact Test and the underlying liver disease was tested by the χ^2 test. Binary logistic regression analysis (Method = Enter) was applied to identify independent prognostic factors for employment after OLT as the dependent variable considering employment before OLT, underlying liver disease, labMELD score, history of HE, neurological complications after OLT, age, sex, profession, SF-36 sum score before OLT and SF-36 sum score 12 mo after OLT as independent parameters. For the regression model the Omnibus Test of Model Coefficients, the -2 Log likelihood, the Nagelkerke R Square and the effects size Cohen's d values are shown. For the variables in the Equation significant at the 0.05 level, Wald statistic, *P* value, the Odds ratio [Exp(B)] and the confidence interval for the Odss ratio [Exp(B)] are given. Normally distributed values are shown as mean ± SD and not normally distributed values are shown as median with range. A *P*-value $\leqslant$ 0.05 was considered significant for all tests applied. The statistical methods of this study were reviewed by Prof Hecker, former Head of the Biostatistics Department at Hannover Medical School.

RESULTS

Before OLT

Forty-nine (43.0%) of the 114 patients were employed at the time of OLT compared to 65 (57.0%) who were not employed (Figure 2). The two patient groups did not differ with regard to age, sex, the severity of liver disease according to the labMELD score, or with regard to aetiology of liver disease. Patients who were not employed before OLT had significantly more often a positive history of HE, were more frequently non-academic (82% *vs* 66%) and showed a significantly lower value in the SF-36 domain score physical functioning, whereas all other SF-36 domain scores and the QALYs did not differ. Furthermore, they achieved significantly worse results in the PHES and the RBANS sum score (Table 2).

Twelve month after OLT

Twelve month after OLT 43 (44.8% of those who survived) patients were employed (including students and homemakers) and 53 (55.2%) patients were not employed. Eighteen of the included 114 patients died after OLT

Table 2 Characteristics of employed and not employed patients before orthotopic liver transplantation

n = 114	Employed (*n* = 49)	Not employed (*n* = 65)	*P* value
Age median (range, min-max)	49 (42,18-60)	50 (36, 24-60)	0.06
Sex (male/female)	30 (61.2%)/19	42 (64.6%)/26	0.85
Profession	16 (34.0%)/31	10 (17.6%)/52	0.04
Academic/non-academic	(NS 2)	(NS 3)	
labMELD median (range, min-max)	18 (33, 7-40)	18 (33, 7-40)	0.16
Aetiology of liver disease			0.44
PSC	16	14	
PBC	0	1	
Alcohol	5	10	
HCV	7	11	
HBV	5	13	
AIH	3	1	
M. Wilson	3	1	
Others	10	14	
History of HE (+/-)	15 (30.6%)/34	32 (49.2%)/33	0.05
PHES, median (min/max)	0 (-8/+5)	-2 (-18/+4)	0.04
	(*n* = 27)	(*n* = 37)	
CFF, mean ± SD	42.7 ± 3.9	42.3 ± 5.0	0.77
	(*n* = 26)	(*n* = 35)	
RBANS	92.2 ± 17.0	89.6 ± 18.6	0.59
Immediate memory, mean ± SD	(*n* = 24)	(*n* = 32)	
RBANS Visuospatial/constructional, median (range,	84 (60, 66-126)	84 (66, 60-126)	0.26
min-max)	(*n* = 24)	(*n* = 32)	
RBANS	99.3 ± 11.6	96.2 ± 14.4	0.40
Language, mean ± SD	(*n* = 24)	(*n* = 32)	
RBANS	91.8 ± 17.3	84.2 ± 16.6	0.10
Attention, mean ± SD	(*n* = 24)	(*n* = 32)	
RBANS	97 (36, 86-122)	94.5 (64, 44-108)	0.24
Delayed memory, median (range, min-max)	(*n* = 24)	(*n* = 32)	
RBANS	472.1 ± 44.5	443.1 ± 56.7	0.04
Sum score, mean ± SD	(*n* = 24)	(*n* = 32)	
RBANS	92.1 ± 11.6	84.9 ± 14.4	0.05
Total scale, mean ± SD	(*n* = 24)	(*n* = 32)	

P value ≤ 0.05 is considered significant. NS: Not specified; OLT: Orthotopic liver transplantation; labMELD: Laboratory Model of End Stage Liver Disease; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis; HCV: Hepatitis C virus; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; HE: Hepatic encephalopathy; PHES: Psychometric hepatic encephalopathy score; CFF: Critical flicker frequency; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

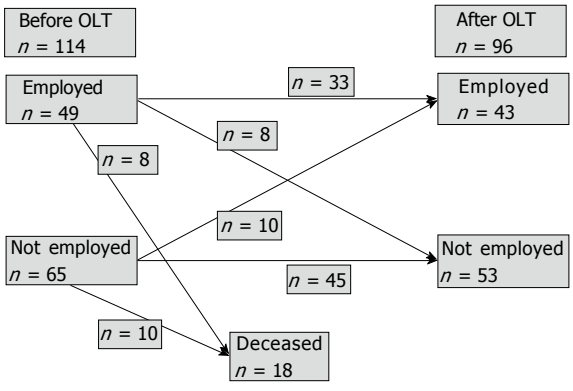

Figure 2 Employment status before and 12 mo after orthotopic liver transplantation. The distribution of patients into the groups "employed" and "not employed" before and 12 mo after OLT is displayed. *n* = 114 patients before OLT; *n* = 96 survivors 1 year after OLT; *n* = 18 patients deceased after OLT. OLT: Orthotopic liver transplantation.

(15.8%). The cause of death was multi-organ failure in 5 cases, sepsis, heart failure or abdominal bleeding in 3 cases each, subarachnoid haemorrhage in one case, meningitis/encephalitis in one case and unknown in 2 cases. Eight of these were employed (16.3%) and 10 (15.4%) were not employed before OLT. Eight of the patients who were employed before OLT did not return to employment after OLT (19.5% of those who survived, *n* = 41), while 33 (80.5% of those who survived) returned to work. Of those survivors who were not employed before OLT (*n* = 55), 10 (18.2%) returned to work within the year after transplantation, while 45 (81.8%) remained not employed (Figure 2).

Patients not employed 12 mo after OLT were significantly older and showed significantly worse results in the psychometric tests after OLT than the employed patients (Table 3).

HE (*P* = 0.10) before OLT and neurological complications (*P* = 0.11) after OLT were more frequent in not employed patients after OLT, but the difference did not reach statistical significance at the 0.05 level. Concerning the HRQoL, all SF-36 domain scores and the QALYs were significantly higher in the group of employed patients compared to the not employed patients after OLT (Table 4). There was no significant difference for all other parameters tested.

Patients employed before and after OLT (*n* = 33) other than patients employed before but not employed

Table 3 Characteristics of employed and not employed patients after orthotopic liver transplantation

n = 96	Employed (*n* = 43)	Not employed (*n* = 53)	*P* value
Age median (range, min-max)	47 (42, 18-60)	50 (31, 29-60)	0.01
Sex (male/female)	23 (53.5%)/20	36 (67.9%)/17	0.21
Profession	13 (31.0%)/29	8 (15.1%)/45	0.08
Academic/non-academic	(NS 1)		
labMELD median (range, min-max)	18 (33, 7-40)	19 (33, 7-40)	0.16
Aetiology of liver disease			0.41
PSC	15	13	
PBC	1	0	
Alcohol	4	8	
HCV	7	6	
HBV	3	12	
AIH	2	1	
M. Wilson	2	1	
Others	9	12	
History of HE (+/-)	13 (30.2%)/30	25 (47.2%)/28	0.10
Neurological complications (+/-)	17 (39.5%)/26	30 (56.6%)/23	0.11
PHES, median (min/max)	0 (-5/+2) (*n* = 30)	-1 (-10/+4) (*n* = 43)	0.10
CFF, mean ± SD	45.8 ± 4.0 (*n* = 29)	42.0 ± 4.1 (*n* = 40)	< 0.001
RBANS Immediate memory, mean ± SD	101.1 ± 15.1 (*n* = 30)	92.1 ± 17.7 (*n* = 41)	0.03
RBANS Visuospatial/constructional, median (range, min-max)	84 (64, 62-126) (*n* = 30)	89 (57, 64-121) (*n* = 41)	0.17
RBANS Language, mean ± SD	103.2 ± 13.9 (*n* = 30)	93.0 ± 16.5 (*n* = 41)	0.01
RBANS Attention, mean ± SD	101.2 ± 13.7 (*n* = 30)	89.3 ± 15.5 (*n* = 41)	0.001
RBANS Delayed memory, median (range, min-max)	98 (109, 10-119) (*n* = 30)	95 (44, 75-119) (*n* = 41)	0.13
RBANS Sum score, mean ± SD	490.7 ± 48.2 (*n* = 30)	461.0 ± 54.5 (*n* = 41)	0.02
RBANS Total scale, mean ± SD	97.4 ± 13.6 (*n* = 30)	89.6 ± 14.2 (*n* = 41)	0.02

P value ≤ 0.05 is considered significant. NS: Not specified; OLT: Orthotopic liver transplantation; labMELD: Laboratory Model of End Stage Liver Disease; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis; HCV: Hepatitis C virus; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; HE: Hepatic encephalopathy; PHES: Psychometric hepatic encephalopathy score; CFF: Critical flicker frequency; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

after OLT (*n* = 8) showed significantly better values in the CFF (*P* = 0.04) and higher scores in the RBANS domain scores immediate memory (*P* = 0.04) and attention (*P* = 0.04) after OLT (Table 5). Furthermore, the health related quality of life scores after OLT were significantly higher in patients reintegrated into employment after OLT compared to the patients not reemployed after OLT (Table 6).

In the subgroup of 10 patients (18.2%) that were not employed before OLT but returned to work within 1 year after OLT, 5 were male (50%) and the median age was 41 (range 34, min 26, max 60) years. The qualification was a vocational education in 8 and a university degree in 2 cases. The reason for OLT was primary sclerosing cholangitis (PSC) in 3 patients, primary biliary cirrhosis (PBC), alcoholic liver disease, hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, kryptogenic cirrhosis, biliary atresia and Budd-Chiari syndrome in 1 patient, respectively. The median labMELD score was 20 (range 24, min 8, max 32). Four patients had a history of HE before OLT and 6 patients had a neurological complication directly after OLT. All 10 patients returned to a job working for a wage after OLT. The comparison of the psychometric test results and the health related quality of life scores after OLT of this subgroup compared to patients that were not employed before and after OLT (*n* = 45) showed no significant group differences except that the patients reintegrated into employment after OLT were significantly younger (*P* = 0.03) and had significantly better CFF values (*P* < 0.01) after OLT than the patients that stayed not employed after OLT (Tables 7 and 8).

Paired comparison of psychometric tests and questionnaires surveyed before and 12 mo after OLT

Thirty-seven patients filled in the questionnaires before and 12 mo after OLT. Of these, 16 patients were employed and 21 patients were not employed one year after OLT.

The HRQoL and the QALYs significantly increased after OLT in the 16 patients that were employed after OLT (Table 9). In contrast, the patients not employed after OLT (*n*

Table 4 Short form 36 domain scores and six-dimension health state short form score of employed and not employed patients

SF-36 domain score	Before OLT		*P* value	After OLT		*P* value
	Employed (*n* = 27)	Not employed (*n* = 35)		Employed (*n* = 30)	Not employed (*n* = 41)	
PF, mean ± SD	70.7 ± 25.1	47.4 ± 27.4	0.001	82.3 ± 19.2	59.4 ± 28.2	< 0.001
PRF, median (range, min-max)	50 (100, 0-100)	25 (100, 0-100)	0.14	100 (100, 0-100)	25 (100, 0-100)	< 0.001
BP, median (range, min-max)	74 (100, 0-100)	51 (100, 0-100)	0.14	100 (69, 31-100)	74 (88, 12-100)	0.001
GHP, median (range, min-max)	40 (77, 10-87)	35 (82, 0-82)	0.71	69.5 (87, 10-97)	50 (87, 10-97)	0.01
VIT, median (range, min-max)	45 (80, 10-90)	40 (85, 0-85)	0.43	70 (75, 20-95)	45 (85, 5-90)	0.001
SRF, median (range, min-max)	87.5 (87.5, 12.5-100)	62.5 (87.5, 12.5-100)	0.52	100 (50, 50-100)	62.5 (87.5, 12.5-100)	< 0.001
ERF, median (range, min-max)	100 (100, 0-100)	100 (100, 0-100)	0.94	100 (100, 0-100)	33.3 (100, 0-100)	< 0.001
MH, median (range, min-max)	76 (60, 32-92)	64 (88, 8-96)	0.31	80 (56, 44-100)	68 (72, 28-100)	0.01
Sum score, mean ± SD	479.2 ± 193.9	419.7 ± 169.7	0.20	627.0 ± 138.1	433.7 ± 160.8	< 0.001
SF-6D QALYs, mean ± SD	0.71 ± 0.14	0.64 ± 0.15	0.06	0.8 ± 0.1	0.64 ± 0.12	< 0.001

P value ≤ 0.05 is considered significant. SF-36: Short form 36; SF-6D: Six-dimension health state short form; OLT: Orthotopic liver transplantation; PF: Physical functioning; PRF: Physical role functioning; BP: Bodily pain; GHP: General health perception; VIT: Vitality; SRF: Social role functioning; ERF: Emotional role functioning; MH: Mental health; QALYs: Quality adjusted life years.

Table 5 Comparison of patients employed before and after orthotopic liver transplantation to patients employed before but not-employed after orthotopic liver transplantation

n = 41	Employed before and after OLT (*n* = 33)	Employed before but not employed after OLT (*n* = 8)	*P* value
Age, median (range, min-max)	50 (42, 18-60)	54 (30, 29-59)	0.13
Sex (male/female)	18 (54.5%)/15	6 (75.0%)/2	0.43
Profession	11 (34.4%)/21	3 (37.5%)/5	1.00
Academic/non-academic	(NS 1)		
labMELD median (range, min-max)	18 (33, 7-40)	17 (31, 9-40)	0.91
Aetiology of liver disease			0.19
PSC	12	2	
PBC	0	0	
Alcohol	3	0	
HCV	6	0	
HBV	2	2	
AIH	2	1	
M. Wilson	2	0	
Others	6	3	
History of HE (+/-)	9 (27.3%)/24	2 (25.0%)/6	1.00
Neurological complications (+/-)	11 (33.3%)/22	5 (62.5%)/3	0.23
PHES after OLT, median (min/max)	1 (-4/+2) (*n* = 25)	0 (-7/+4) (*n* = 7)	0.93
CFF after OLT, mean ± SD	45.3 ± 3.7 (*n* = 24)	41.7 ± 5.0 (*n* = 7)	0.04
RBANS after OLT Immediate memory, mean ± SD	101.6 ± 14.1 (*n* = 26)	89.4 ± 10.0 (*n* = 7)	0.04
RBANS after OLT Visuospatial/ constructional median (range, min-max)	84 (64, 62-126) (*n* = 26)	89 (57, 64-121) (*n* = 7)	0.68
RBANS after OLT Language, mean ± SD	103.2 ± 14.6 (*n* = 26)	95.1 ± 24.2 (*n* = 7)	0.27
RBANS after OLT Attention, mean ± SD	100.8 ± 14.1 (*n* = 26)	87.1 ± 18.6 (*n* = 7)	0.04
RBANS after OLT Delayed memory, median (range, min-max)	98 (109, 10-119) (*n* = 26)	95 (17, 88-105) (*n* = 7)	0.16
RBANS after OLT Sum score, mean ± SD	492.0 ± 47.8 (*n* = 26)	457.0 ± 56.8 (*n* = 7)	0.11
RBANS after OLT Total scale, mean ± SD	97.7 ± 13.7 (*n* = 26)	88.3 ± 14.6 (*n* = 7)	0.12

P value ≤ 0.05 is considered significant. NS: Not specified; OLT: Orthotopic liver transplantation; labMELD: Laboratory Model of End Stage Liver Disease; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis; HCV: Hepatitis C virus; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; HE: Hepatic encephalopathy; PHES: Psychometric hepatic encephalopathy score; CFF: Critical flicker frequency; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

= 21) did not show a significant change concerning their HRQoL with the exception of the SF-36 domain scores physical functioning and general health perception, which both increased significantly after OLT (Table 10).

Forty-two patients completed the PHES (*n* = 16 employed after OLT), 36 patients the RBANS (*n* = 13 employed after OLT) and 38 patients the CFF (*n* = 15 employed after OLT) before and after OLT.

Table 6 Short form 36 domain scores and six-dimension health state short form score of patients employed before and after orthotopic liver transplantation compared to patients employed before but not-employed after orthotopic liver transplantation

SF-36 domain score	Before OLT		*P* value	After OLT		*P* value
	Employed before and after OLT (*n* = 17)	Employed before and not employed after OLT (*n* = 4)		Employed before and after OLT (*n* = 26)	Employed before and not employed after OLT (*n* = 7)	
PF, mean ± SD	75.9 ± 23.8	55.0 ± 31.6	0.15	84.6 ± 17.0	45.0 ± 23.5	< 0.001
PRF, median (range, min-max)	50 (100, 0-100)	62.5 (50, 25-75)	0.97	100 (100, 0-100)	25 (50, 0-50)	0.001
BP, median (range, min-max)	84 (100, 0-100)	81 (48, 52-100)	0.90	100 (49, 51-100)	52 (78, 22-100)	0.03
GHP, median (range, min-max)	50 (72, 10-82)	35 (42, 25-67)	0.64	72 (77, 20-97)	60 (72, 15-87)	0.31
VIT, median (range, min-max)	45 (80, 10-90)	42.5 (60, 20-80)	0.97	70 (75, 20-95)	50 (70, 10-80)	0.04
SRF, median (range, min-max)	87.5 (87.5, 12.5-100)	87.5 (50, 50-100)	0.70	100 (37.5, 62.5-100)	50 (62.5, 37.5-100)	< 0.01
ERF, median (range, min-max)	100 (100, 0-100)	66.7 (100, 0-100)	0.70	100 (100, 0-100)	33.3 (100, 0-100)	0.05
MH, median (range, min-max)	72 (60, 32-92)	74 (24, 56-80)	0.83	82 (48, 52-100)	76 (56, 44-100)	0.22
Sum score, mean ± SD	512.1 ± 193.4	487.1 ± 172.2	0.82	652.9 ± 100.7	418.5 ± 121.5	< 0.001
SF-6D QALYs, mean ± SD	0.72 ± 0.14	0.72 ± 0.15	0.94	0.83 ± 0.1	0.65 ± 0.10	< 0.001

P value ⩽ 0.05 is considered significant. SF-36: Short form 36; SF-6D: Six-dimension health state short form; OLT: Orthotopic liver transplantation; PF: Physical functioning; PRF: Physical role functioning; BP: Bodily pain; GHP: General health perception; VIT: Vitality; SRF: Social role functioning; ERF: Emotional role functioning; MH: Mental health; QALYs: Quality adjusted life years.

Table 7 Comparison of patients not employed before and after orthotopic liver transplantation to patients not employed before but employed after orthotopic liver transplantation

n = 55	Not Employed before and after OLT (*n* = 45)	Not employed before but employed after OLT (*n* = 10)	*P* value
Age, median (range, min-max)	50 (28, 32-60)	41 (34, 26-60)	0.03
Sex (male/female)	30 (66.7%)/15	5 (50%)/5	0.47
Profession	5 (11.1%)/40	2 (20%)/8	0.6
Academic/non-academic			
labMELD median (range, min-max)	19 (33, 7-40)	20 (24, 8-32)	0.74
Aetiology of liver disease			0.2
PSC	11	3	
PBC	0	1	
Alcohol	8	1	
HCV	6	1	
HBV	10	1	
AIH	0	0	
M. Wilson	1	0	
Others	9	3	
History of HE (+/-)	23 (51.1%)/22	4 (40%)/6	0.73
Neurological complications (+/-)	25 (55.6%)/20	6 (60%)/4	1.0
PHES after OLT, median (min/max)	-1 (-10/+4)	0 (-5/+2)	0.63
	(*n* = 36)	(*n* = 5)	
CFF after OLT, mean ± SD	42.0 ± 4.0	47.9 ± 5.2	< 0.01
	(*n* = 33)	(*n* = 5)	
RBANS after OLT	92.7 ± 19.0	97.8 ± 22.9	0.62
Immediate memory, mean ± SD	(*n* = 34)	(*n* = 4)	
RBANS after OLT Visuospatial/constructional,	90.5 (55, 66-121)	84 (11, 78-89)	0.32
median (range, min-max)	(*n* = 34)	(*n* = 4)	
RBANS after OLT	92.5 ± 14.8	103.5 ± 10.3	0.16
Language, mean ± SD	(*n* = 34)	(*n* = 4)	
RBANS after OLT	89.7 ± 15.1	104.0 ± 12.6	0.08
Attention, mean ± SD	(*n* = 34)	(*n* = 4)	
RBANS after OLT	96 (44, 75-119)	98.5 (34, 71-105)	1.0
Delayed memory, median (range, min-max)	(*n* = 34)	(*n* = 4)	
RBANS after OLT	461.9 ± 54.8	482.3 ± 57.6	0.49
Sum score, mean ± SD	(*n* = 34)	(*n* = 4)	
RBANS after OLT	89.9 ± 14.3	95.0 ± 14.5	0.51
Total scale, mean ± SD	(*n* = 34)	(*n* = 4)	

P value ⩽ 0.05 is considered significant. OLT: Orthotopic liver transplantation; NS: Not specified; labMELD: Laboratory Model of End Stage Liver Disease; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis; HCV: Hepatitis C virus; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; HE: Hepatic encephalopathy; PHES: Psychometric hepatic encephalopathy score; CFF: Critical flicker frequency; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

Table 8 Short form 36 domain scores and six-dimension health state short form score of patients not employed before and after orthotopic liver transplantation compared to patients not employed before but employed after orthotopic liver transplantation

SF-36 domain score	Before OLT		*P* value	After OLT		*P* value
	Not employed before and after OLT (*n* = 25)	Not employed before but employed after OLT (*n* = 6)		Not employed before and after OLT (*n* = 34)	Not employed before but employed after OLT (*n* = 4)	
PF, mean ± SD	48.2 ± 26.8	57.5 ± 26.0	0.45	62.4 ± 28.5	67.5 ± 28.4	0.74
PRF, median (range, min-max)	25 (100, 0-100)	62.5 (100, 0-100)	0.45	25 (100, 0-100)	25 (100, 0-100)	1.0
BP, median (range, min-max)	51 (100, 0-100)	56.5 (78, 22-100)	0.79	74 (88, 12-100)	52.5 (69, 31-100)	0.70
GHP, median (range, min-max)	35 (67, 15-82)	43.5 (52, 0-52)	0.64	46 (87, 10-97)	41 (70, 10-80)	0.73
VIT, median (range, min-max)	40 (80, 5-85)	45 (65, 0-65)	0.79	45 (85, 5-90)	42.5 (35, 40-75)	0.70
SRF, median (range, min-max)	62.5 (87.5, 12.5-100)	81.3 (50, 50-100)	0.42	62.5 (87.5, 12.5-100)	68.8 (50, 50-100)	0.77
ERF, median (range, min-max)	100 (100, 0-100)	66.7 (67.7, 33.3-100)	0.21	33.3 (100, 0-100)	66.7 (66.7, 33.3-100)	0.48
MH, median (range, min-max)	68 (88, 8-96)	68 (80, 16-96)	0.79	68 (68, 28-96)	54 (56, 44-100)	0.57
Sum score, mean ± SD	419.4 ± 166.3	480.8 ± 180.4	0.43	436.9 ± 169.1	458.5 ± 237.3	0.82
SF-6D QALYs, mean ± SD	0.64 ± 0.15	0.71 ± 0.14	0.35	0.64 ± 0.12	0.65 ± 0.14	0.87

P value ≤ 0.05 is considered significant. SF-36: Short form 36; SF-6D: Six-dimension health state short form; OLT: Orthotopic liver transplantation; PF: Physical functioning; PRF: Physical role functioning; BP: Bodily pain; GHP: General health perception; VIT: Vitality; SRF: Social role functioning; ERF: Emotional role functioning; MH: Mental health; QALYs: Quality adjusted life years.

Table 9 Paired analysis of the short form 36 domain scores and the six-dimension health state short form score of patients employed after orthotopic liver transplantation surveyed before and 12 mo after orthotopic liver transplantation

SF-36 domain score, *n* = 16	Before OLT	After OLT	*P* value
PF, mean ± SD	71.6 ± 26.8	84.1 ± 18.6	0.04
PRF, mean ± SD	50.0 ± 47.4	82.8 ± 35.0	0.02
BP, mean ± SD	70.7 ± 34.5	88.8 ± 18.8	0.04
GHP, mean ± SD	46.9 ± 24.0	66.8 ± 24.0	0.01
VIT, mean ± SD	45.9 ± 23.8	68.4 ± 15.2	0.01
SRF, mean ± SD	70.3 ± 33.2	90.6 ± 15.5	0.06
ERF, mean ± SD	70.8 ± 43.7	91.7 ± 19.3	0.10
MH, mean ± SD	70.8 ± 18.7	80.0 ± 13.6	0.17
Sum score, mean ± SD	497.0 ± 191.7	653.2 ± 128.6	0.01
SF-6D QALYs, mean ± SD	0.71 ± 0.12	0.81 ± 0.10	0.02

P value ≤ 0.05 is considered significant, no correlation between first and second measurement. SF-36: Short form 36; SF-6D: Six-dimension health state short form; OLT: Orthotopic liver transplantation; PF: Physical functioning; PRF: Physical role functioning; BP: Bodily pain; GHP: General health perception; VIT: Vitality; SRF: Social role functioning; ERF: Emotional role functioning; MH: Mental health; QALYs: Quality adjusted life years.

Table 10 Paired analysis of the short form 36 domain scores and the six-dimension health state short form score of patients not employed after orthotopic liver transplantation surveyed before and 12 mo after orthotopic liver transplantation

SF-36 domain score, *n* = 21	Before OLT	After OLT	*P* value
PF, mean ± SD	48.1 ± 28.3	65.5 ± 29.0	0.03
PRF, mean ± SD	38.1 ± 40.0	41.6 ± 39.0	0.76
BP, mean ± SD	61.1 ± 31.3	70.0 ± 24.8	0.25
GHP, mean ± SD	41.8 ± 15.6	56.8 ± 22.2	0.01
VIT, mean ± SD	44.3 ± 20.0	51.2 ± 22.2	0.14
SRF, mean ± SD	65.5 ± 29.3	67.3 ± 21.1	0.80
ERF, mean ± SD	55.6 ± 45.1	57.1 ± 44.9	0.91
MH, mean ± SD	66.3 ± 16.3	69.1 ± 18.7	0.53
Sum score, mean ± SD	420.7 ± 163.8	478.6 ± 148.0	0.21
SF-6D QALYs, mean ± SD	0.64 ± 0.15	0.66 ± 0.10	0.46

P value ≤ 0.05 is considered significant, no correlation between first and second measurement. SF-36: Short form 36; SF-6D: Six-dimension health state short form; OLT: Orthotopic liver transplantation; PF: Physical functioning; PRF: Physical role functioning; BP: Bodily pain; GHP: General health perception; VIT: Vitality; SRF: Social role functioning; ERF: Emotional role functioning; MH: Mental health; QALYs: Quality adjusted life years.

In the group of patients employed 12 mo after OLT, the PHES and the RBANS did not change significantly whereas the CFF increased significantly after OLT (PHES: *n* = 16; median 1.0, range 19 (min -14, max 5) before OLT, median 1.0, range 7 (min -5, max 2) after OLT, *P* = 0.26; CFF: *n* = 15; before OLT mean 43.3 Hz ± 3.8, after OLT mean 45.6 Hz ± 4.6, *P* = 0.04; RBANS: *n* = 13; immediate memory *P* = 0.08, visuospatial/constructional *P* = 0.17, language *P* = 0.21, attention *P* = 0.34, delayed memory *P* = 0.44, sum score *P* = 0.70, total scale *P* = 0.79 (Figure 3).

The patients not employed 12 mo after OLT showed a significant increase in the PHES (*n* = 26, *P* = 0.04) whereas the CFF (*n* = 23, *P* = 0.28) did not change significantly [before OLT PHES median -1.0, range 22 (min -18, max 4), CFF mean 41.0 Hz ± 4.4; after OLT PHES median -1.0, range 13 (min -9, max 4), CFF mean 41.9 Hz ± 4.1]. The RBANS domain score Attention increased significantly 12 mo after OLT (*n* = 23, *P* < 0.01, mean 82.9 ± 16.2 before OLT, 91.2 ± 15.6 after OLT) whereas all other RBANS domain scores did not change significantly (Figure 4).

Binary logistic regression

Using binary logistic regression analysis (Method enter, Omnibus Test of Model Coefficients χ^2 = 52.840, *P* < 0.001, -2 Log likelihood = 77.581, Nagelkerke R Square= 0.571, Cohen's d = 0.70), employment status before OLT [Wald statistic = 21.5, *P* < 0.001, odds ratio (OR) = 19.64, confidence interval for OR 5.58 to 69.14] and age in years (Wald statistic = 8.17, *P* < 0.01, OR = 0.90, confidence interval for OR 0.84 to 0.97) were independent predictors of the employment status 12 mo after OLT (*n* = 95, *n* = 1 excluded due to missing value

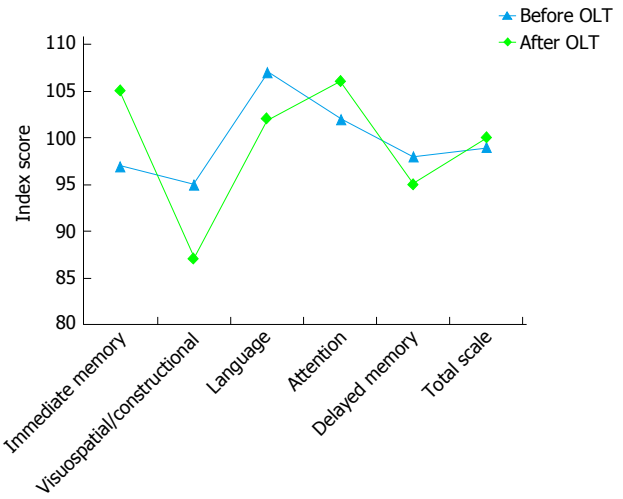

Figure 3 Paired comparison of repeatable battery for the Assessment of Neuropsychological Status domain scores of patients employed after liver transplantation surveyed before and 12 mo after orthotopic liver transplantation. Thirty-six patients completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test before and 12 mo after orthotopic liver transplantation (OLT). Of these 13 patients (36.1%) were employed after liver transplantation. This figure shows the paired analysis of the RBANS results of the patients employed after OLT achieved before and 12 mo after OLT. The RBANS Total scale and the domain scores Immediate memory, Visuospatial/constructional ability, Language ability, Attention and Delayed memory are displayed.

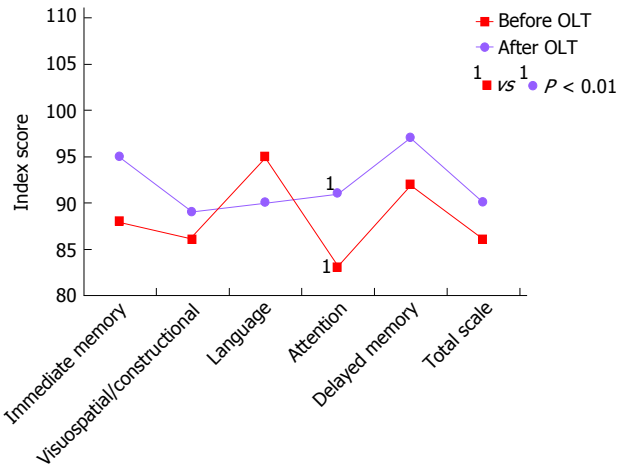

Figure 4 Paired comparison of repeatable battery for the Assessment of Neuropsychological Status domain scores of patients not employed after orthotopic liver transplantation surveyed before and 12 mo after orthotopic liver transplantation. Thirty-six patients completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test before and 12 mo after orthotopic liver transplantation (OLT). Of these 23 patients (63.9%) were not employed after OLT. This figure shows the paired analysis of the RBANS results of the patients not employed after OLT achieved before and 12 mo after OLT. The RBANS Total scale and the domain scores Immediate memory, Visuospatial/Constructional ability, Language ability, Attention and Delayed memory are displayed. [1]Indicates a statistical significant increase in the RBANS domain score Attention after OLT at the $P < 0.01$ level.

concerning profession). No significant effects were found for the underlying liver disease, history of HE before OLT, labMELD score, profession, sex, SF-36 sum score before OLT and neurological complications after OLT. In a subgroup of patients who filled in the SF-36 after transplantation (Method enter, Omnibus Test of Model Coefficients $\chi^2 = 50.579$, $P < 0.001$, -2 Log likelihood = 46.137, Nagelkerke $R^2 = 0.685$ and Cohen's d = 0.94, $n = 71$) the employment status before OLT (Wald statistic = 11.84, $P < 0.001$, OR = 20.13, confidence interval for OR = 3.64-111.27) and the SF-36 sum score after OLT (Wald statistic = 7.18, $P < 0.01$, OR for increment of 10 points = 1.10, confidence interval for OR = 1.03 -1.17) were independent predictors of the employment status after OLT.

DISCUSSION

This prospective study evaluated the impact of hepatic encephalopathy before OLT and neurological complications after OLT on the employment status 12 mo after liver transplantation. Moreover, health-related quality of life, age, sex, employment status before OLT and professional category were registered to identify factors which might be significantly associated with the employment status one year after OLT.

In contrast to our hypothesis, we did not find a significant impact of HE before or neurological complications after OLT on the employment status 12 mo after OLT, though the not employed patients after OLT showed a trend towards a higher frequency of HE before OLT and neurological complications after OLT in comparison to patients employed after OLT. Instead, the employment status after OLT was independently predicted by the employment status before OLT, age and health-related quality of life after OLT.

Hepatic encephalopathy is associated with high morbidity and has a direct impact on health-related quality of life before liver transplantation[26]. Impairment of motor and cognitive function lead to premature retirement of patients with HE[18]. Blue collar workers with liver cirrhosis are more frequently considered unfit for work than white collar workers, probably due to the fact that HE significantly affects motor function while language ability is preserved[18]. In accordance herewith, our patients who were not employed before OLT had more frequently a history of HE and had predominantly a vocational education for qualification compared to employed patients.

The credo that HE is completely reversible has been put into question recently, since it was shown that patients who had suffered HE before OLT, had an incomplete recovery of their cognitive function about 1 year afterwards[13,27,28]. This could well interfere with the patients' working ability. However, we did not find a significant impact of a HE history upon the employment status after OLT in our patients. Instead, like others, we observed an improvement in cognitive function in our patients after OLT with only a few patients showing abnormal test results 12 mo after OLT, for example, in the PHES (9 of 73 examined; 12.3%)[13,27]. Of these, only one patient was employed whereas 8 patients were not employed. There was no relation to any specific underlying cause of liver disease, such as alcoholism.

Neurological complications affecting the CNS are frequent in the first weeks after OLT and are known to prolong the in-hospital stay[14,15]. Although the distinctive impairment of cognitive function by neurological complications in the first weeks after OLT might only be transient[17], long term impairment might occur and influence the working capability. Nevertheless, our results did not indicate that neurological complications significantly impair the working capability 1 year after OLT and thus underline the good prognosis of neurological complications in the first weeks after OLT as long as they are promptly diagnosed and treated sufficiently. Our results still showed a trend indicating a higher frequency of neurological complications after OLT in the group of patients not employed 12 mo after OLT.

Eighty point five percent (n = 33) of the surviving patients employed before OLT (n = 41) returned to work afterwards, indicating the importance of the pre transplant working status upon a patient's occupational fate. This is in accordance with the findings of other studies[2-5,8,29] which came to similar results, irrespective of the country or continent where the study was performed[9].

It is no surprise that age was a predictor for post OLT employment status as well, since it may be hypothesized that younger patients have a higher physical and cognitive health resource than older patients, facilitating the return to work. Additionally, social insurance companies might be more eager to reintegrate young patients into work because of the costs of early retirement. Also, employers might have a higher confidence in young patients to be capable of working compared to older patients[8].

In our study, patients who were working 1 year after OLT had a significantly higher SF-36 and SF-6D score than those who did not, and the subgroup of patients that returned to their pre OLT job after transplantation had significantly better health related quality of life scores than patients who were employed before OLT but did not return to employment after OLT. Furthermore, the SF-36 score at 12 mo after OLT was an independent predictor for employment after OLT in the subgroup of patients who filled in this form. Aberg *et al*[2] assessed HRQoL in 354 patients after OLT [age at OLT (mean) 48 years, 42% male] compared to 6050 age and gender matched controls. They showed that the employed OLT patients had significantly higher HRQoL scores than retired patients and concluded that employment is an indicator of HRQoL. Our data do not allow a decision, whether the scores are higher due to the fact that the patients were able to return to a normal life and therefore perceived themselves as physically and mentally fit, or if better physical and mental condition facilitated the return to employment after OLT. However, it is conceivable that patients who have reached independence and the economic status they had before OLT have more confidence in their physical and cognitive functions than those who are not. In consequence, reintegration of patients after OLT into employment should be considered an important tool to achieve patients' well-being. The significant difference between patients who are working and those who are not employed after OLT and additionally between the subgroup of patients that were employed before and after OLT compared to patients that did not return to employment after OLT with regard to cognitive function (RBANS) in this study, however, indicates that besides socio-economic factors also medical factors must be considered (Tables 3 and 5).

In contrast to some other studies[8,30] and in accordance with Hunt *et al*[31] we did not find a significant gender difference with regard to employment status after OLT. The differing results between the studies may be due to lacking comparability of the classification of "work" especially as not all studies classified "homemakers" as employed.

Education has also been reported to have an impact on employment after OLT[3,4]. Our results were not able to confirm this assumption probably due to the low number of patients with a university degree (21 of 96 survivors; 21.9%). Nevertheless, a trend (P = 0.06) towards a higher frequency of vocational training in the group of patients not employed after OLT was observed. But the effect of education on post OLT employment was not observed by all authors[31], and obviously it is not exclusively the level of education that affects the probability to return to work after OLT, but also the type of work done before OLT. Adams *et al*[32] as well as Weng *et al*[6] showed that patients working in non-office jobs were less likely to return after OLT than patients working in an office. This may be due to different physical demands[29]. However, considering the observation that blue collar workers with chronic liver disease are more often not employed than white collar workers might as well be just a sequel of the pre OLT health status.

Contradictory results have been achieved considering the effect of the underlying liver disease - especially alcoholism[7,8,33-35] and hepatitis C[3] - upon the proportion of subjects employed after OLT. Alcoholic liver disease was estimated to have no effect[33,34], to increase[7] or to decrease[8,35] the probability of resuming work after OLT. In our study the underlying liver disease had no effect on the employment status after OLT.

Patients with chronic liver disease are not employed before OLT due to various reasons. Cirrhosis-associated morbidity might be the most frequent because being frequently certified unfit for work might lead to unemployment and employers as well as social insurance companies might aspire the patients' retirement. This assumption includes the hypothesis that patients staying employed before OLT might be less impaired and might have a shorter period of time of severe liver disease. It might alleviate returning to work after OLT and achieving the economic status as well as the financial independence they had before OLT. The employer might be more eager to reintegrate these patients after OLT because the circumstances signal that work capability exists. Still, our data do not support this assumption, if the labMELD score is considered representative for patients' health status.

Although patients who were not employed after OLT differed with regard to psychometric test results from those who were employed, the majority of the not employed patients achieved results within the normal range. The PHES, for example, was only abnormal in 8 of 43 patients (18.6%). Resuming work after OLT for patients who were not employed before OLT seems quite unlikely as only 10 (18.2%) of the not employed patients of our cohort returned to work after OLT. Similar results were described in other studies[9]. Probably the time off work is too long, determining low confidence in patients and employers that reintegration is possible. Furthermore, bureaucracy and fear of losing pension claims might play a role. Additionally, our data (Tables 3-6) and that of others[9] indicate that returning to the pre OLT job might be impaired by poor physical or impaired mental functioning. Achieving an occupational retraining, however, is extensive and support for patients might be low. To solve these problems, interventions based on the individual needs and obstacles of each single patient are needed to facilitate reemployment after OLT. Although so far data about the efficiency of interventions before and after OLT to facilitate reemployment after OLT are missing, the main aim seems to be to keep the patients with chronic liver disease employed before OLT[36]. To achieve this aim, liver related complications like hepatic encephalopathy and ascites need to be prevented or if applicable treated as soon as possible. The patients' mobility might be maintained by regular physiotherapy. Furthermore, education programs for employers about working capabilities of patients with chronic liver disease might prevent loss of employment before OLT. Such interventions might also increase the health related quality of life. After OLT, rehabilitation programs that focus on the individual physical and mental job requirements for each patient might be conducive to reintegrate the patient into the pre OLT job and to increase the health related quality of life. In addition, employers need to be educated about the working capabilities of patients after OLT. If the reintegration into the pre OLT job is not possible, collaboration with social workers and employment support agencies might be needed to match the patient to an appropriate alternative job. In this respect, the reduction of bureaucratic barriers seems to be particularly important concerning the encouragement of patients to resume work after OLT while at the same time, if needed, providing them with full medical coverage[36].

Limitations of our study are that our results can only be compared to studies that also classified "homemakers" and "students" as employed, because some studies only classified subjects as employed if they were working for a wage. Furthermore, 46 patients (40.4%) were included after OLT. Data for the psychometric tests and quality of life scores before OLT were missing for these patients. However, all other variables were available because all patients included underwent neurological examination after OLT and detailed case records were available for all patients including the HE history, occupation, underlying liver disease, labMELD score and medication. Finally, our results are only based on patients within the German health-care system, which might limit the transferability to other countries. Nevertheless, our findings are well in line with those of former studies, indicating the effect of the pre transplant employment status upon the post transplant working career, independent of the different health care systems.

As a result, our data confirm that employment status before OLT is most important in predicting the employment status 12 mo after OLT. Neither prior-OLT HE nor neurological complications after OLT are independent risk factors for unemployment 1 year after OLT. However, our results show a trend for both values to be more frequent in patients not employed after OLT, indicating the need to analyse a larger sample to finally answer the question if HE before OLT and neurological complications after OLT affect working ability after transplantation.

In conclusion, education of patients, employers and social insurance companies is needed to emphasise that it is worth analysing, on a single subject basis, if a patient is capable of being reintegrated into work after OLT. Obstacles should be identified in every single case because resuming work after OLT might improve the post OLT care and increase the health-related quality of life in patients after OLT.

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COMMENTS

Background

Specialized transplantation centres and improvement of immunosuppressive therapy have significantly increased survival rates after orthotopic liver transplantation (OLT). Thus, besides mortality other indicators of treatment quality emerged. Employment after OLT is considered to indicate treatment quality and socio-economic factors before OLT are esteemed crucial in this respect. However, currently only about 50% of patients are reintegrated into employment after OLT and the reasons for not returning to the pre OLT job are not well described. The relevance of hepatic encephalopathy (HE) before OLT and neurological complications after OLT has not been considered so far although both can significantly impact patients' physical and mental ability before and after OLT. This prospective study was designed to evaluate the impact of HE before and neurological complications after OLT in addition to socio-economic factors upon the employment status 1 year after OLT.

Research frontiers

Outcome of patients after OLT improved during the last 35 years and thus the focus on the patients' mental and physical well-being after OLT increased. Especially reintegration into employment was identified as an important factor as it is important for the physical and mental health after OLT. However, only about 50% of the patients return to their jobs after OLT. This study contributed to this research field by evaluating whether hepatic encephalopathy before OLT or neurological complications after OLT have an impact on the employment status of the patients 1 year after OLT.

Innovations and breakthroughs

The available studies identified employment before OLT, the type of employment and younger age as the main predicting factors for reintegration into employment

after OLT. This study contributed by showing that neither prior-OLT hepatic encephalopathy nor neurological complications after OLT are independent risk factors for unemployment 1 year after OLT. Furthermore, their study confirmed that employment status before OLT is most important in predicting the employment status 12 mo after OLT.

Applications

This study showed that neither hepatic encephalopathy before OLT nor neurological complications after OLT increase the probability of unemployment one year after OLT. Especially employment before OLT predicts the reintegration into employment after OLT and thus interventions should focus on how to keep patients with liver cirrhosis employed before OLT. Furthermore interventions are needed during the rehabilitation after OLT that focus on the physical and mental needs required for the pre OLT job of each patient.

Terminology

Hepatic encephalopathy: A frequent complication of liver cirrhosis caused by liver insufficiency and porto-systemic shunts. It is based on neurochemical and neurophysiological disorders of the brain and ammonia is believed to be of major importance. It is characterized by deficits in motor accuracy and motor speed as well as cognitive impairment especially concerning attention, whereas verbal abilities maintain unaffected. Neurological complications: encephalopathy, seizures, tremor, psychotic disorders and posterior reversible encephalopathy syndrome occur in about 30% of the patients after OLT.

Peer-review

In this well-written article, Pflugrad *et al* explore factors associated with employment after OLT, which is essential for quality of life and meaningful transplant outcomes. They found that hepatic encephalopathy before or central nervous system complications after OLT were not independent predictors of employment, unlike pre-OLT employment, age and post-OLT functional status.

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