LITERATURE REVIEW

Type 2 Diabetes Mellitus and Alcoholic Liver Disease: a literature review

Dannica Velasco[1], Felanita Hutani[2], Nathan Kuk[3], Rajeswari Ward[3], Ja Hyuk Koo (Brian)[1], Linda Kelly[3], Aditya Tedjaseputra[2]

[1]*Deakin University*

[2]*University of Melbourne*

[3]*Monash University*

Abstract

Introduction
Alcoholic liver disease (ALD) and type 2 diabetes mellitus (T2DM) are two important chronic diseases in Australia, both of which are emerging epidemics. As a result, patients presenting with both conditions may become increasingly more common. However, not much is known about how each affects the other in terms of clinical outcomes.

Methods
Evidence from studies exploring the relationship between T2DM and ALD, including those pertaining to liver function tests (LFT) and hepatocellular carcinoma (HCC), was reviewed and summarised.

Results
There are studies which show that high alcohol intake and chronic liver disease (CLD) are risk factors of developing T2DM. Conversely, having impaired glucose tolerance has been shown to promote progression of CLD. There is also some evidence of increased risk of HCC in patients with T2DM and who consume alcohol in the context of other liver disease. However, no studies that looked into how T2DM directly affects LFT results in ALD were found.

Discussion
There seems to be a bidirectional relationship between T2DM and ALD, although it is not explicitly cause-and-effect in nature. Hence, there is a need for a comprehensive management plan that utilises a multidisciplinary approach to minimise the risk of complications for patients with either or both diseases. Currently, this is not available and both diseases are treated as separate entities. Therefore, further research must be done to elucidate the relationship between the two, so that effective strategies to manage co-existing T2DM and ALD can be developed.

Introduction

Alcoholic liver disease (ALD) is an important chronic disease in Australia, which is characterised by long-standing hepatocellular damage as a result of excess alcohol consumption. ALD represents a spectrum of alcohol-related liver diseases of increasing severity - alcoholic steatosis (alcoholic fatty liver disease), alcoholic steatohepatitis and alcoholic liver cirrhosis as well as acute alcoholic hepatitis[1]. The prevalence of ALD itself is difficult to determine as most cases are diagnosed late in the course of the disease. In 2012, it was estimated there were at least 6,203 alcohol-related liver disease cases in Australia. There is an increasing trend of ALD and an addition of more than 1,000 new cases are expected by 2030[2].

Two key mechanisms of damage due to chronic alcohol consumption have been proposed. Firstly, ethanol molecule causes oxidative stress and hepatocyte inflammation, leading to liver damage[3]. This is mediated by the generation of reactive oxygen species as a by-product of ethanol metabolism, which causes mitochondrial glutathione depletion, and thus in sensitization of hepatocytes to injury.

Secondly, alcohol consumption, by promoting enteric bacterial overgrowth and increasing gut mucosal permeability, facilitates translocation of endotoxin to the bloodstream, and subsequently to the liver. These result in endotoxin-mediated complement cascade and Kupffer cell activation with the generation of TNF-α, a pro-inflammatory cytokine, which induces hepatocyte injury[4]. While Kupffer cells are also known for their role in initiating hepatoprotective and anti-inflammatory responses through the same pathway, these mechanisms seem to be inhibited in chronic alcohol consumption[4]. This imbalance between anti-oxidative mechanisms and oxidative stress imposed on hepatocytes in chronic alcoholism, in association with the release of inflammatory mediators due to endotoxemia are the principal mediators for the progression of ALD.

A few established risk factors for ALD have been documented in the literature. Non-modifiable risk factors include sex, with women developing more severe disease than men even with lower absolute amounts of alcohol consumption, and genetic variations such as the PNPLA3 variant[3, 5]. Modifiable risk factors include smoking[6] and most importantly,

aggressive drinking behaviours such as binge drinking and chronic high dose consumption[3].

On the other hand, Type 2 Diabetes Mellitus (T2DM) is considered to be an epidemic in Australia, with an estimated 848,000 Australians currently suffering from the condition. Furthermore, from 1989 to 2012, the number of diabetes diagnoses (T1DM and T2DM) has almost tripled[7].

The Australian Bureau of Statistics have reported that up to 10.7% of Australians with T2DM display high-risk alcohol drinking behaviour[8]. Increasing prevalence of T2DM and ALD may eventually translate to more patients being diagnosed with both conditions. Their co-existence in one patient may prove to be catastrophic, as they independently increase the risk of poor liver outcomes [3, 9].

Only a single study has been documented in the literature which examines the relationship between ALD and T2DM. Kotronen et al.[10] found that the prevalence of T2DM in alcoholic fatty liver disease patients approximates that in non-alcoholic fatty liver disease (NAFLD) at ~25%, which is much higher than that in the general population. The objective of this paper is to review the relationship between T2DM and ALD by examining liver outcomes in terms of liver function tests (LFTs) and a subsequent complication of hepatocellular carcinoma (HCC). Improved management options will be discussed in relation to an anticipated worse prognosis in patients with dual diagnosis.

Methodology

A comprehensive literature search for relevant articles from inception to December 2013 was performed on MEDLINE, Scopus and Discovery (The University of Melbourne) for original research and review articles using the key words: “Liver Diseases, Alcoholic” and “Diabetes Mellitus, Type 2”. Quantitative studies that explored the relationship between ALD and T2DM were included. Exclusion criteria include studies qualitative studies, duplicate articles, conference abstracts and non-English articles. In addition, a manual search was performed via Google Scholar and for the reference lists of relevant studies and reviews. Initial search yielded 1243 articles for abstract screening. Of these, 12 studies were included in our review following assessment of abstracts and full-text articles. Studies selected for analysis were further divided by topic: data on liver function tests (LFTs), hepatocellular carcinoma (HCC) and articles presenting known data on comorbidity between ALD and T2DM.

Researcher triangulation was achieved through having four investigators appraise and synthesise the evidence from each article.

Results

1. Liver Function Tests (LFTs) of ALD and T2DM patients

A. Gamma-GlutamylTransferase (GGT)

Whilst GGT levels are only moderately correlated with excessive alcohol consumption[11], GGT was found to be markedly elevated in ALD as an established diagnosis[12]. Compared to non-alcoholic steatohepatitis (NASH), the average GGT level in ALD is significantly higher (NASH: 68.7 IU/L vs ALD: 496.9 IU/L)[12]. Furthermore, it has been found that in people with baseline obesity, GGT increases with just mild alcohol consumption[11].

B. The Transaminases - Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT)

AST is more specific to the liver than ALT by histopathological evidence. Across the spectrum of ALD, alcoholic steatosis only causes minimal elevation, while in alcoholic steatohepatitis, the value goes up to 500 U/L[11]. This is also supported by another study in which aminotransaminases were found to be only slightly elevated in patients with alcoholic steatosis (mean AST 54.1 U/L, ALT 72.8 U/L), but were grossly increased in those with alcoholic steatohepatitis (mean AST 668.2 U/L, ALT 399.8 U/L). On the other hand, NASH exhibits a similar pattern of mild elevation of aminotransaminases as alcoholic steatosis (mean AST 67.2, ALT 117.6). However, in advanced disease with liver cirrhosis, these markers are not reliable in indicating liver damage[11].

In a study where patients with T2DM were screened, up to 28% of patients demonstrated generalised elevation of LFT results. Of these, 65% were subsequently diagnosed with non-alcoholic steatosis and 87% demonstrated steatosis by ultrasound criteria[13].

Our search did not retrieve studies that directly looked at how T2DM influences LFT results in ALD.

2. Hepatocellular Carcinoma (HCC)

Daily ethanol consumption of ≥80mL and ≥160 mL results in an exponential increase in the risk of a person developing HCC 5-fold and 25-fold, respectively[14]. Whilst the impact of T2DM alone on the risk of HCC is not well-documented, there is some evidence to support the notion of excess risk of HCC in patients with liver disease and co-morbid T2DM. A study has reported a 10-fold increase in the risk of progression to HCC when T2DM is combined with chronic viral hepatitis and hazardous drinking[9]. Balbi et al.[15] further documents an increased risk of HCC in the presence of both T2DM and alcohol consumption (OR = 49.0 with (95% CI 21.5−111.8; P < 0.0001)) compared to alcohol consumption alone (OR = 3.7 with (95% CI 2.5−5.4; P < 0.0001). Finally, Hassan et al.[14] reports a synergy index between alcohol consumption and diabetes in increasing HCC risk of 2.9 (1.3-4.6).

3. The Relationship between T2DM and ALD

It has been noted that there are some associations between ALD and T2DM[9].

Garcia-Compean et al.[16] reported a 2-fold increase of T2DM risk in patients who consume ≥270 grams of alcohol/week compared with those who consume ≤120 grams/week. Not surprisingly, patients with chronic liver disease (CLD) are prone to developing diabetes, as demonstrated by the following two studies. Holstein et al.[17] found that 96% of their patients with cirrhosis have impaired glucose tolerance, of which 75% suffer from T2DM. In another CLD study, where 74.3% of participants had a diagnosis of ALD (of variable degree of disease severity), impaired glucose tolerance was also demonstrated. In patients with severe disease, 69.8% were found to have impaired glucose tolerance, with 17.4% having diabetes[18].

Conversely, there exists some evidence in the literature that elucidate the impact of T2DM on liver function and development of ALD. One study showed that high blood glucose level is a risk factor for hepatic fibrosis ($p<0.05$). This applies both in ALD patients with ($r = 0.11 +/- 0.05$; $P = .027$) or without ($r = 0.115 +/- 0.045$; $P = .011$) cirrhosis[19]. This is consistent with Garcia-Compean et al.[16]; Hickman & Macdonald[9] and Picardi et al.[20] who

emphasized that the presence of insulin resistance is a risk factor in the progression of any liver disease.

Discussion

The results of our literature review support the notion that there may indeed be a bidirectional relationship between ALD and T2DM, with both conditions having the potential to exert an influence in the development of the other. Of particular importance is the evidence regarding the prevalence of liver enzyme dysfunction in T2DM, the prevalence of prediabetes in ALD patients, and the synergistic relationship between T2DM and alcohol consumption in the context of other liver disease in the development of HCC. With evidence showing high prevalence of T2DM in ALD patients[10], it is highly likely that patients will present with clinical features of both ALD and T2DM. Left untreated, numerous consequences can occur which will necessitate comprehensive management. Hence a holistic approach is recommended, incorporating facets of pharmacotherapy, social support, lifestyle modifications and most importantly, patient education.

Currently, the management of ALD and T2DM as individual conditions is multi-faceted and dependent on disease severity. For ALD, alcohol abstinence is the key to preventing cirrhosis progression. Principal issues that must be addressed include both physiological and psychological dependence and the breakdown of daily routine of alcohol drinking[21]. This is achieved primarily through psychological support, psychotherapy and adjunct pharmacotherapy. Nutritional supplementation, notably B-vitamins, folate and protein, is also recommended[22] as protein-calorie malnutrition is correlated with increased mortality, severity of liver disease and hepatic dysfunction. For patients with ALD that progresses to liver failure, the only cure that remains is liver transplantation. However, potential recipients are only eligible if they demonstrate 6 months of alcohol abstinence and have a low risk of continued alcohol abuse[23].

For T2DM management, the key objectives include symptom relief, prevention of disease progression and/or complications, as well as maintenance of quality of life[24]. Lifestyle modifications remain arguably the most effective treatment, with recent statistics revealing 80% of Australians with diabetes are overweight[25]. Referral to a dietician and consumption of a low-calorie, low-fat, low

glycaemic index and high-fibre diet should be encouraged. As an adjunct to dietary control, regular exercise has also been shown to improve blood glucose levels[26], however care is necessitated to avoid resultant hypoglycaemia[24]. When these measures prove to be unsuccessful, medications such as metformin and sulfonylureas are considered. Insulin therapy is implemented if the treatment target for blood glucose levels is still not achieved[24]. In addition to glycaemic control, other cardiovascular disease (CVD) risk factors such as hypertension, dyslipidaemia, smoking and excess alcohol consumption need to be addressed simultaneously using conservative and/or medical treatments[26].

Additionally, due to the multiple complications that can arise from T2DM, close monitoring by a dedicated team of specialists is essential. These include regular follow-up for retinopathy and nephropathy by an ophthalmologist and a GP/nephrologist respectively. Neurologists are only necessary in cases of neuropathy. Allied health professionals are also recommended to partake in T2DM management. Close follow-up of foot health by a podiatrist is recommended for all T2DM patients, as peripheral vascular disease, in conjunction with peripheral neuropathy, is responsible for diabetic foot disease[27]. Finally, patient education is crucial for the success of diabetes management. Ideally carried out from the first diagnosis of T2DM, self-monitoring of blood glucose levels on an agreed frequency and appropriate use of a diabetes diary are simple but effective methods of diabetes monitoring[24]. Furthermore, as there is an increased risk of death in T2DM patients during hypoglycaemic events[28], educating patients about what to do when medication side effects occur is of great importance. The delegation of care to a diabetes nurse specialist, who can assist with patient self-management, is an established practice in Australia[29].

In patients with co-existing ALD and T2DM, disease management becomes even more complicated. Preventing progression through alcohol abstinence is fundamental in such patients. However, in patients with ALD, alcohol abstinence continues to be a challenge due to many having a long history of dependence[30]. In addition, there are many socio-cultural factors that influence alcohol consumption, such as the use of alcohol in social events and the prevalence of alcohol advertisements in our society.

In patients with progressive ALD,

pharmacotherapy, such as glucocorticoids, may be used to reduce inflammation. However, in patients with concurrent T2DM, they may be relatively contraindicated due to their potential to exacerbate blood glucose levels[31]. Furthermore, they can precipitate new-onset hyperglycemia in patients with subclinical diabetes[32]. Its alternative, pentoxifylline, has also been reported to potentially aggravate pre-existing T2DM in patients[33]. Hence, there is no ideal pharmacotherapy for ALD with comorbid T2DM.

Finally, in patients with liver failure, liver transplantation is complicated by the presence of CVD due to long-standing T2DM. Evidence has shown that the presence of pre-existing CVD and T2DM leads to poor prognosis post-transplant[34]. This underlines the need of aggressive management of T2DM in the form of primary prevention through education and risk recognition, as well as achieving good control in patients with already established T2DM. Despite this, there is no standardisation of management of CVD available in the pre-transplant period[34].

It is imperative that clinicians are aware of how treatment for one condition may impact on the other. A fine balance must be achieved to ensure minimal detriment to other comorbidities. However, currently there is not enough known about how those two diseases interact to achieve such fine balance. Therefore, more studies need to be done to better elucidate the effect of these diseases on each other. Further research on how to best manage these implications is also essential. Ultimately, a multidisciplinary team management is recommended, consisting of specialist clinicians well versed in treating T2DM and ALD, pharmacists, dieticians, along with nurse educators for patient education. In doing so, this maximises the chance of recovery whilst minimising risks of complications in patients who suffer from both conditions.

Conclusion

Currently, there is good evidence to suggest that there may be a bidirectional relationship between T2DM and ALD. Evidence in the literature has shown that ALD may influence the development of T2DM and vice versa. However, there is much less information regarding the effects of these two conditions on liver function when they occur together. This is a notable gap that is of significant importance, given the potential for worse liver outcomes

occurring in these patients in the face of epidemics of both conditions in Australia. As such, further research in the area needs to occur in order to develop well-defined strategies to prevent and manage the combined effects of T2DM and ALD should they occur concurrently.

References

1. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Hepatology (Baltimore, Md). 2010 Jan;51(1):307-28. PubMed PMID: 20034030. Epub 2009/12/25. eng.
2. Gastroenterological Society of Australia. The economic cost and health burden of liver diseases in Australia. Sydney: Deloitte Access Economics, January 2013.
3. Testino G. Alcoholic hepatitis. Journal of medicine and life. 2013 Jun 15;6(2):161-7. PubMed PMID: 23904876. Pubmed Central PMCID: PMC3725441. Epub 2013/08/02. eng.
4. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011 Nov;141(5):1572-85. PubMed PMID: 21920463. Pubmed Central PMCID: PMC3214974. Epub 2011/09/17. eng.
5. Tian C, Stokowski RP, Kershenobich D, Ballinger DG, Hinds DA. Variant in PNPLA3 is associated with alcoholic liver disease. Nature genetics. 2010 Jan;42(1):21-3. PubMed PMID: 19946271. Epub 2009/12/01. eng.
6. Altamirano J, Bataller R. Cigarette smoking and chronic liver diseases. Gut. 2010 September 1, 2010;59(9):1159-62.
7. Australian Institute of Health and Welfare. Prevalence of diabetes Australia: Australian Institute of Health and Welfare; 2013 [6 December]. Available from: http://www.aihw.gov.au/diabetes-indicators/prevalence/.
8. Australian Bureau of Statistics. Table 2.4 Persons aged 35 years and over, Health risk factors by Prevalence of Type 2 Diabetes, 2007-08. In: Lifestyle risk factors for Type 2 diabetes, editor. Microsoft Excel. Australia: Australian Government; 2011.
9. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. The American journal of medicine. 2007 Oct;120(10):829-34. PubMed PMID: 17904449. Epub 2007/10/02. eng.
10. Kotronen A, Yki-Jarvinen H, Mannisto S, Saarikoski L, Korpi-Hyovalti E, Oksa H, et al. Non-alcoholic and alcoholic fatty liver disease - two diseases of affluence associated with the metabolic syndrome and type 2 diabetes: the FIN-D2D survey. BMC public health. 2010;10:237. PubMed PMID: 20459722. Pubmed Central PMCID: PMC2873937. Epub 2010/05/13. eng.
11. Conigrave KM, Davies P, Haber P, Whitfield JB. Traditional markers of excessive alcohol use. Addiction (Abingdon, England). 2003 Dec;98 Suppl 2:31-43. PubMed PMID: 14984240. Epub 2004/02/27. eng.
12. Kojima H, Sakurai S, Uemura M, Takekawa T, Morimoto H, Tamagawa Y, et al. Difference and similarity between non-alcoholic steatohepatitis and alcoholic liver disease. Alcoholism, clinical and experimental research. 2005 Dec;29(12 Suppl):259S-63S. PubMed PMID: 16385233. Epub 2005/12/31. eng.

13. Hickman IJ, Russell AJ, Prins JB, Macdonald GA. Should patients with type 2 diabetes and raised liver enzymes be referred for further evaluation of liver disease? Diabetes research and clinical practice. 2008 Apr;80(1):e10-2. PubMed PMID: 18187226. Epub 2008/01/12. eng.
14. Hassan MM, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology (Baltimore, Md). 2002 Nov;36(5):1206-13. PubMed PMID: 12395331. Epub 2002/10/24. eng.
15. Balbi M, Donadon V, Ghersetti M, Grazioli S, Della Valentina G, Gardenal R, et al. Alcohol and HCV Chronic Infection Are Risk Cofactors of Type 2 Diabetes Mellitus for Hepatocellular Carcinoma in Italy. International Journal of Environmental Research and Public Health. 2010;7(4):1366-78. PubMed PMID: doi:10.3390/ijerph7041366.
16. Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. World journal of gastroenterology : WJG. 2009 Jan 21;15(3):280-8. PubMed PMID: 19140227. Pubmed Central PMCID: PMC2653324. Epub 2009/01/14. eng.
17. Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. Journal of gastroenterology and hepatology. 2002 Jun;17(6):677-81. PubMed PMID: 12100613. Epub 2002/07/09. eng.
18. Mukherjee. S, Sarkar. BS, Das. KK, Banerjee. A. A cross-sectional study on occurrence of type 2 diabetes among patients admitted with chronic liver diseases in a medical college in Kolkata. International Journal of Medicine and Public Health. 2013 January - March 2013;3(1):44-7.
19. Raynard B, Balian A, Fallik D, Capron F, Bedossa P, Chaput JC, et al. Risk factors of fibrosis in alcohol-induced liver disease. Hepatology (Baltimore, Md). 2002 Mar;35(3):635-8. PubMed PMID: 11870378. Epub 2002/03/01. eng.
20. Picardi A, D'Avola D, Gentilucci UV, Galati G, Fiori E, Spataro S, et al. Diabetes in chronic liver disease: from old concepts to new evidence. Diabetes/metabolism research and reviews. 2006 Jul-Aug;22(4):274-83. PubMed PMID: 16506276. Epub 2006/03/01. eng.
21. Enoch MA, Goldman D. Problem drinking and alcoholism: diagnosis and treatment. American family physician. 2002 Feb 1;65(3):441-8. PubMed PMID: 11858627. Epub 2002/02/23. eng.
22. Duggan. A, RACGP. Alcoholic Liver Disease, Assessment and Management. Australian Family Physician. 2011 August 2011;40(8):590-4.
23. Transplant Society of Australia and New Zealand. Liver Protocol Sydney: The Transplantation Society of Australia and New Zealand; 2011 [updated February 2007; cited 2013 4 December]. Available from: http://www.tsanz.com.au/organallocationprotocols/liverprotocol.asp.
24. International Diabetes Federation. Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation, 2012. Contract No.: 1.
25. Australian institute of Health and Welfare. Risk factors for diabetes and its complications. Australia: Australian Institute of Health and Welfare,, Australian Institute of Health and Welfare; 2008.
26. McCulloch D. Initial management of blood glucose in adults with type 2 diabetes mellitus. In: UpToDate [Internet]. Wolters

Kluwer Health. 2013. [cited 1 December 2013]. Available from: http://www.uptodate.com/contents/initial-management-of-blood-glucose-in-adults-with-type-2-diabetes-mellitus.

27. Cheer K, Shearman C, Jude EB. Managing complications of the diabetic foot. BMJ (Clinical research ed). 2009;339:b4905. PubMed PMID: 19955124. Epub 2009/12/04. eng.
28. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ (Clinical research ed). 2010;340:b4909. PubMed PMID: 20061358. Pubmed Central PMCID: PMC2803744. Epub 2010/01/12. eng.
29. Diabetes Australia. Diabetes Management in General Practice. Canberra: Diabetes Australia Limited, 2013 March. Contract No.: 1.
30. Friedman. S. Alcoholic hepatitis: Natural history and management. In: UpToDate [Internet]. Wolters Kluwer Health. 2013. [cited 1 December 2013]. Available from: http://www.uptodate.com/contents/alcoholic-hepatitis-natural-history-and-management.
31. Saag. K, Furst. D. Major side effects of systemic glucocorticoids. In: UpToDate [Internet]. Wolters Kluwer Health. 2013. [cited 1 December 2013]. Available from: http://www.uptodate.com/contents/major-side-effects-of-systemic-glucocorticoids.
32. Mukamal. K. Overview of the risks and benefits of alcohol consumption. In: UpToDate [Internet]. Wolters Kluwer Health. 2013. [cited 1 December 2013]. Available from: http://www.uptodate.com/contents/overview-of-the-risks-and-benefits-of-alcohol-consumption.
33. Massart J, Robin MA, Noury F, Fautrel A, Letteron P, Bado A, et al. Pentoxifylline aggravates fatty liver in obese and diabetic ob/ob mice by increasing intestinal glucose absorption and activating hepatic lipogenesis. British journal of pharmacology. 2012 Mar;165(5):1361-74. PubMed PMID: 21740407. Pubmed Central PMCID: PMC3372722. Epub 2011/07/12. eng.
34. Ripoll C, Yotti R, Bermejo J, Banares R. The heart in liver transplantation. Journal of hepatology. 2011 Apr;54(4):810-22. PubMed PMID: 21145840. Epub 2010/12/15. eng.

ISSN: 2226-3403 J Asian Med Stud Assoc. 2015;4:14-24

Correspondence author: Dannica Velasco, dvelasco@deakin.edu.au