

Meta-analysis of the Effects of Alcohol in Diabetes

Short and medium-term effects of moderate ethanol intake on glycaemic control in diabetes mellitus - a systematic review and meta-analysis

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Novelty of study:

- Guidelines suggest that drinking alcohol can result in hypoglycaemia in people with diabetes mellitus.
- Studies to date provide no evidence that drinking moderate amounts of alcohol in the short or medium term affects glycaemic control in people with diabetes mellitus

Abstract

People with diabetes are told that drinking alcohol may increase their risk of hypoglycaemia. This systematic review reports the effects of alcohol consumption on glycaemic control in people with diabetes mellitus. Medline, Embase, and the Cochrane library databases were searched in 2015 to identify randomised controlled trials comparing alcohol consumption and no alcohol use, reporting glycaemic control in subjects with diabetes. Data on blood glucose, HbA_{1c} and numbers of hypoglycaemic episodes were pooled using random effects meta-analysis. Pooled data from nine short-term studies showed no difference in blood glucose concentrations between those who drank alcohol in doses of 16–80 g (median 20 g or 2.5 units) compared with those who did not drink alcohol at times of 0.5, 2, 4, and 24 hours after alcohol consumption. Pooled data from four medium-term studies showed that there was no difference in blood glucose or HbA_{1c} concentrations at the end of the study between those who drank 11–18 g alcohol/day (median 12 g/day or 1.5 units/day) for 4–52 weeks and those who did not. We found no evidence of a difference in hypoglycaemic episodes or withdrawal rates between the randomised groups. Studies to date have not provided evidence that drinking moderate amounts of alcohol, with or without a meal, affects any measure of glycaemic control in people with diabetes mellitus. These results suggest that there is no need to advise people with diabetes to abstain from drinking moderate quantities of alcohol.

Introduction

Hypoglycaemia is of major concern to patients with diabetes mellitus [1], and there is a perception that alcohol consumption may increase the risk of hypoglycaemia. Patient-oriented websites from organisations such as the American Diabetes Association [2] and Diabetes UK [3] give mixed messages, advising that “most people with diabetes can have a moderate amount of alcohol” or “there is no need to give up alcohol”, and on the same page that “alcohol can cause hypoglycaemia” or “drinking alcohol makes hypoglycaemia ... more likely”, without citing supporting evidence [2, 3].

In considering the interpretation of “moderate” alcohol consumption in such statements, we note that the definition varies from country to country. In the UK, according to guidelines of the House of Commons Science and Technology Committee in 2011 [4] “men should not regularly drink more than three to four units a day and women no more than two to three units a day”, where “regularly” means every day or on most days of the week; this is described as “sensible drinking” and “moderate consumption” and elsewhere “lower risk drinking” [5]. The US Dietary Guidelines for Americans [6] define moderate alcohol consumption as “average daily consumption of up to one drink per day for women and up to two drinks per day for men, with no more than three drinks in any single day for women and no more than four drinks in any single day for men.”

During a patient consultation on a previous project [7], whether alcohol affects glycaemic control was the question raised by more patients than any other drug interaction. We have therefore carried out a systematic review of randomised controlled trials of short-term and medium-term effects of alcohol on glycaemic control in people with diabetes.

Patients and methods

We registered our protocol in advance on the Prospero database [8]. We sought eligible studies in Medline, EMBASE and the Cochrane database of registered controlled trials from 1946 to 5 May 2015. Additionally we scanned reference lists of reviews and relevant papers and searched Clinical trials.gov clinical trials registry. The Medline search strategy is shown in the on-line appendix, A1. Two reviewers independently screened all identified studies for eligibility and extracted the data. We included studies of any duration in which people with diabetes were randomised to alcohol or a control group and reported glycaemic control as an outcome. Glycaemic control, the primary outcome, was assessed from HbA_{1c}, blood glucose, and hypoglycaemic episodes. Secondary outcomes were lipid concentrations and adverse events. We also extracted data on study characteristics (alcohol type and dose, length of follow-up) and patient characteristics (age, sex, BMI, and diabetes duration). The dose of alcohol, where not reported, was estimated from the reported volume drunk using a nomogram [9]. We assessed the quality of included studies by recording randomisation method, blinding, intention-to-treat analysis, and attrition rates [10]. We wrote to the authors of studies to request unpublished data.

We separately analysed studies that involved short-term and medium-term alcohol use. The longest short-term study lasted 2 days and the shortest medium-term study lasted 4 weeks.

For short-term studies we combined data on blood glucose concentrations at 0.5, 2, 4, and 24 hours (or overnight) after alcohol consumption across the studies. For medium-term studies we pooled data on mean HbA_{1c}, blood glucose and lipid concentrations at the end of the study. We pooled the HbA_{1c} data only in studies that lasted 8 weeks or longer [11].

Statistical methods

Analyses were carried out using Stata 12.1SE (StataCorp, Tx). Blood glucose and lipid concentrations reported as mg/dl were converted to mmol/L. End-point blood glucose, HbA_{1c}, and blood lipids were pooled using a random-effects DerSimonian and Laird meta-analysis reporting mean difference. One short-term study which only reported change in blood glucose was also included [12]. Numbers of hypoglycaemic events were pooled using the Peto method to calculate odds ratio, because of cells with no events. Patient withdrawal rates were pooled using the Mantel Haenszel method to calculate risk ratio. We imputed standard deviations in studies in which they were not reported by averaging standard deviations from all the studies where they were reported for that comparison, as recommended in the Cochrane Handbook [10], and we approximated the geometric mean to the mean. In sensitivity analyses we excluded studies in which these approximations were made, and a single study in which it was unclear whether all the groups were randomised [13].

Results

The flow chart for searches is shown in Figure 1. We identified 1308 studies in our initial search, and a further four studies by scanning reference lists. We removed duplicates, leaving 1044 articles to review for eligibility based on titles and abstracts. We then reviewed 42 papers for full eligibility, and excluded 30, for the reasons shown in Figure 1. This left 12 studies for meta-analysis: eight were short-term studies [12, 14-20], three were medium-term studies [13, 21, 22], and one reported both short- and medium-term outcomes [23].

Characteristics of the included studies are shown in Table 1. Mean patient age was 54 years and mean duration of diabetes 9 years. In the medium-term studies the subjects were randomised to wine compared to no wine or “non-alcoholic” beer. In short-term studies patients were randomised to wine (3 studies), ethanol (6 studies) or vodka (2 comparisons). Comparator groups in the short-term studies were fruit juice, non-alcoholic beer, alcohol-free wine, water, or nothing. Two studies included a meal taken with the drink in both intervention and comparator groups [15, 16]. Three medium-term studies reported HbA_{1c} as an outcome, and three reported blood glucose. None of the included studies specified the method of randomisation used or whether patients or researchers were blinded to the randomised groups.

Short-term studies

All short-term studies were a cross-over design. The doses of alcohol were 16–80 g, median 20 g (2.5 units). Blood glucose concentration 30 minutes after alcohol, reported in 5 studies (8 comparisons) (Figure 2), was not significantly different in those who were randomised to alcohol and those in the comparator groups (mean difference 0.25 mmol/L, 95% CI –0.43 to

0.94). The results at 2, 4, and 24 hours after alcohol were similar (mean difference -0.12 , 95% CI -0.80 to 0.57 after 2 hours; -0.09 , 95% CI -0.50 to 0.32 after 4 hours; and 0.19 , 95% CI -0.56 to 0.94 after 24 hours; Figure 2).

Stratifying by insulin use and sensitivity analyses gave similar results (not shown). Of the six studies in which hypoglycaemia or other adverse events were reported, five reported no events in either study arm and one reported a total of three hypoglycaemic events, one in the control group and two in the alcohol group [20] (Appendix A2).

Medium-term studies

Three studies (including 257 participants) were included in the meta-analysis of end-point blood glucose (Figure 3a). The doses of alcohol were 11–18 g/day (median 12 g/day or 1.5 units/day) for 4–52 weeks. There was a non-significant mean difference in blood glucose concentration between those randomised to alcohol and those in the comparator groups: -0.39 mmol/L (95% CI -1.08 to 0.29).

The mean difference in HbA_{1c} in three studies (4 comparisons, including 292 participants) between those randomised to alcohol and those in comparator groups was 0.08% (95% CI -0.13 to 0.29) (Figure 3b).

Three studies reported numbers of hypoglycaemic episodes; one of the studies with two comparisons did not record any episodes of hypoglycaemia over the course of the study.[13] There was no significant difference between the alcohol and comparator groups (odds ratio = 0.63 , 95% CI 0.19 to 2.15 ; Appendix A2). Similarly, there was no difference in withdrawal rates between the groups (risk ratio = 0.94 , 95% CI 0.21 to 4.13 ; Appendix A3). There was no significant difference in lipid concentrations between the alcohol and comparator groups (mean difference HDL: 0.30 mmol/L, 95% CI -0.28 to 0.89 , LDL: -0.11 mmol/L, 95% CI -0.37 to 0.15 , TG: -0.12 mmol/L, 95%CI -0.27 to 0.03). Sensitivity analyses gave similar results (blood glucose mean difference = -0.62 mmol/L, 95% CI -1.74 to 0.49 , HbA_{1c} mean difference = 0.08% , -0.19 to 0.35)

Discussion

Summary of findings

This is the first systematic review and meta-analysis of randomised studies of the effect of alcohol on glycaemic control in people with diabetes mellitus. We have examined the effects of single doses of alcohol on blood glucose concentrations and the effects of medium-term moderate alcohol use on blood glucose and HbA_{1c}. Drinking moderate quantities of alcohol with or without a meal had no significant effect on any measure of glycaemic control in people with diabetes mellitus. We did not find an effect of alcohol on acute hypoglycaemic events, which were rare in both alcohol and control arms.

There is randomised trial evidence that drinking moderate amounts of alcohol in people with diabetes improves metabolic markers, with improvements in HDL cholesterol, triglycerides, and apoB101/apoA1 ratio[24] and a reduced cardiovascular risk[25] which is consistent with meta-analysis data in people without diabetes [26]. We have not been able to confirm this in

our review. There is a U-shaped relationship between alcohol use and the development of diabetes.²⁸ Light to moderate alcohol consumption may protect against type 2 diabetes [27-29]. Conversely, high alcohol consumption is reported to be a risk factor for diabetes [30, 31]. The mechanisms for this dual effect may be protection by improved insulin sensitivity at low to moderate doses [32] and pancreatic damage at high doses [33]; there may also be a contribution from obesity caused by long-term alcohol [34]. This work consolidates and extends previous literature [35, 36], providing the best available evidence that there is no effect of short-term or medium-term moderate alcohol consumption on glycaemic control.

Limitations

Most of the included studies did not specify whether and how long before entry the participants had abstained from alcohol. Thus, we cannot tell whether alcohol has different effects in drinkers and non-drinkers. However, that did not appear to be the case in 224 well-controlled alcohol abstaining patients with diabetes, and moderate alcohol consumption has beneficial effects on glycaemic control in these patients and on other markers of cardiometabolic risk [24]. We have not been able to assess very long-term use of alcohol in diabetes, as the longest study lasted only two years.

Clinical implications

Advice from patient-oriented websites that people with diabetes do not need to refrain from drinking alcohol in moderation is supported by the available evidence [2, 3]. Cautions from the same organisations that alcohol causes hypoglycaemia are not supported by the evidence base, which is strongest for low to moderate alcohol consumption. However, higher alcohol consumption and other risky behaviours may never be addressed by randomised studies in diabetes, and therefore caution about the potential dangers of excessive alcohol is likely to be the safest course.

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Author contributions

JH designed the study, performed literature searches, data extraction, oversaw the statistical analyses, and drafted the manuscript, BF contributed to screening of articles data extraction and interpretation of results, CM contributed to screening of articles, data extraction and statistical analysis, AF contributed to study design, interpretation of results, and discussion, JKA contributed to study design, interpretation of results, and discussion, RS contributed to study design, interpretation of results, and discussion and provided statistical support. All authors reviewed and edited the manuscript and approved the final version.

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Table 1 - List of included studies

Short-term studies											
Authors (ref)	Year	Total number	Intervention	n	Mean alcohol dose (approx)	Comparator	n	Times of BG measurement (hours)	Mean age	Insulin use	Length of study
Bantle [23]	2008	18	White wine	18	24 g	White grape juice	18	2, 4, 24	64	No	overnight
Christiansen [14]	1993	10	Ethanol + non-alcoholic beer	10	24 g	Non-alcoholic beer	0	0.5, 2, 4	66	No	4h
Christiansen [15]	1994	10	Ethanol + non-alcoholic beer + food	10	24 g	Non-alcoholic beer + food	10	0.5, 2, 4	55	No	4h
Dalgaard [16]	2004	11	40g ethanol + food	11	40 g	Food	11	0.5, 2, 4, 24	63	No	8h
Foot - placebo [17]	1997	12	Ethanol in orange juice	12	45 g*	Orange juice alone	12	0.5, 2, 4, 24	56	No	24 h
Foot - troglitazone [17]	1997	11	Ethanol in orange juice	11	45 g*	Orange juice alone	11	0.5, 2, 4, 24	64	No	24 h
Gin [12]	1999	10	Red wine + meal	10	16 g*	Water	10	0.5, 2, 4	53	No	5h
Gin [12]	1999	10	Ethanol + meal	10	16 g	No ethanol	10	0.5, 2, 4	53	No	5h
Kerr [18]	2009	12	White wine	12	48-80 g	Alcohol-free wine	12	2, 4	44	Yes	4 h
Kovisto [19]	1993	10	Vodka, red wine & cognac	10	61 g*	Mineral water	10	0.5	34	Yes	overnight
Kovisto [19]	1993	16	Vodka, red wine & cognac	16	61 g*	Mineral water	16	0.5, 2, 4, 24	34	No	overnight
Walsh [20]	1974	20	Ethanol + diet orange + and water	20	28 g	No drink	20	24	63	7/20	24 h

***Alcohol dose estimated using nomogram [9]**

Medium-term studies											
Authors (ref)	Year	Total number	Intervention	n	Mean daily alcohol dose	Comparator	n	Outcome	Mean age	Insulin use	Length of trial (weeks)
Bantle [23]	2008	17	Wine	17	18 g	No wine	17	Blood glucose	64	No	4
Marfella [21]	2006	131	A 4-oz glass of red wine each day	57	11 g	No red wine or other alcohol consumption	58	Blood glucose & HbA _{1c}	36	ns	52
Nakamura [13]	2009	36	Red wine	12	12 g	No wine	12	HbA _{1c}	55	36%	26
Nakamura [13]	2009	36	White wine	12	12 g	No wine	12	HbA _{1c}	55	36%	26
Shai [22]	2007	109	¾ Red wine, ¼ white wine	75	13 g	Non-alcoholic diet malt beer	34	Blood glucose & HbA _{1c}	61	some	12

Figure 1 – Flow chart of searches

Figure 2– Mean difference in blood glucose (mmol/mol) at 0.5, 2, 4 and 24 hours after randomisation to alcohol or comparator calculated by the DerSimonian and Laird random effects model in short-term studies. Horizontal bars and diamond widths represent 95% CIs and box sizes indicate relative weights in the analysis. Asterisks indicate studies in populations using insulin.

Figure 3 – Mean difference in (a) endpoint blood glucose (mmol/L) and (b) endpoint HbA_{1c} (%) with alcohol versus placebo (boxes) and pooled estimates (diamond) calculated by the DerSimonian and Laird random effects model in medium-term studies. Horizontal bars and diamond widths represent 95% CIs and box sizes indicate relative weights in the analysis

Figure 1 – flow chart

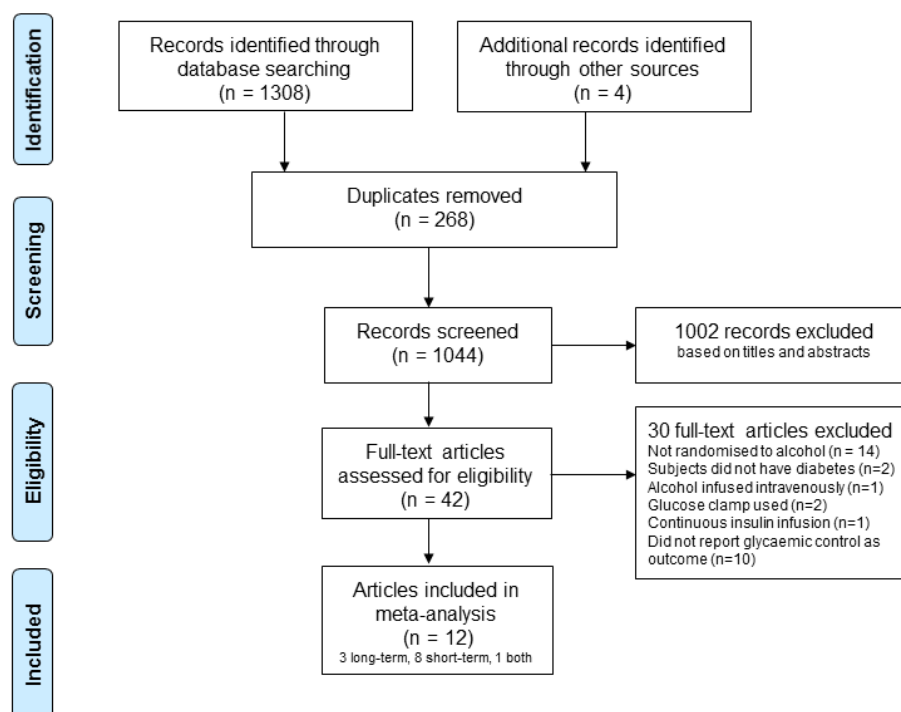


Figure 2

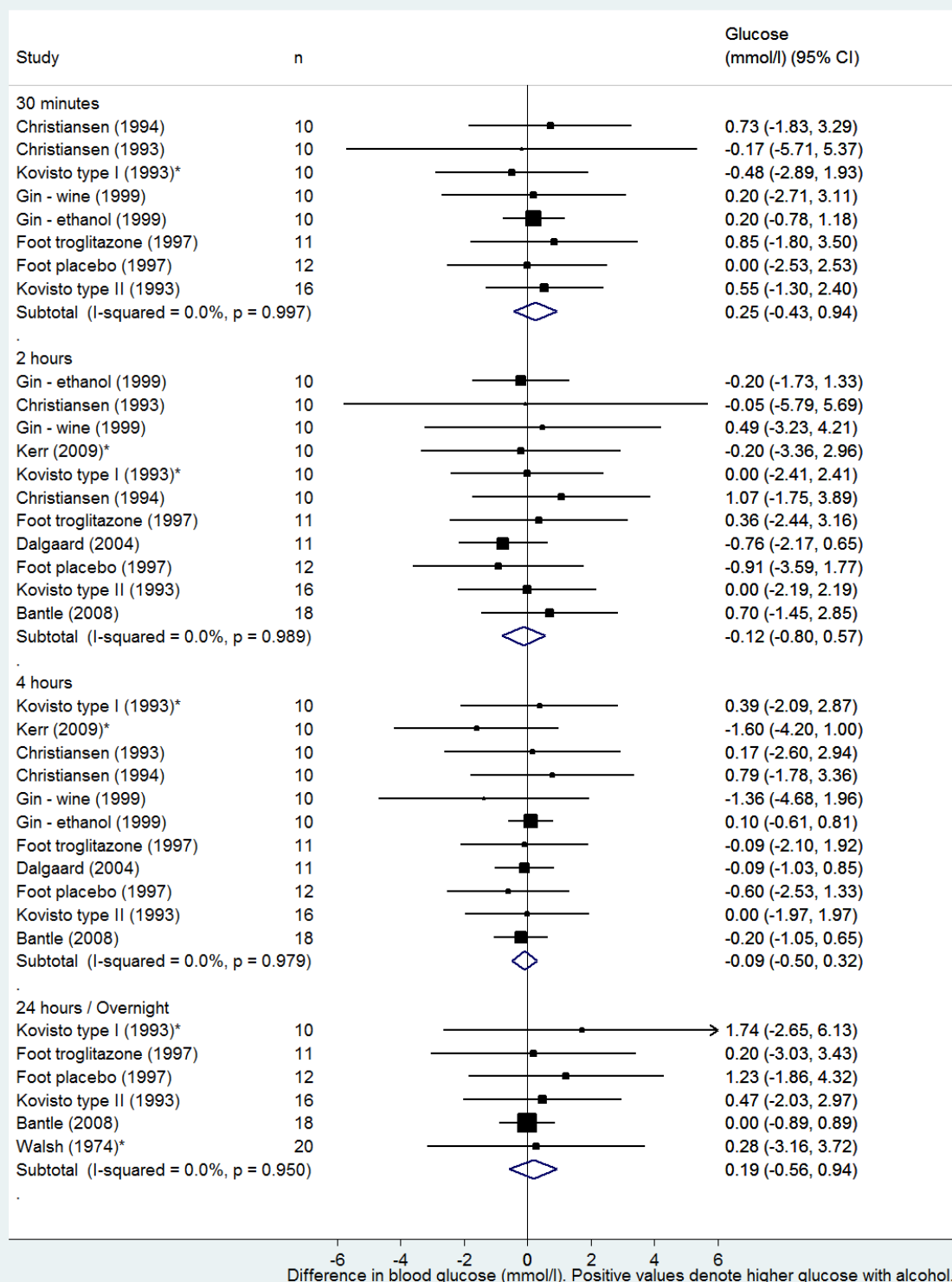


Figure 3

