

A Review of the Relationship between Wine Consumption and Type 2 Diabetes Mellitus

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Abstract: The potential health benefits of moderate alcohol consumption are not limited to a reduced risk of cardiovascular disease but are also observed for type 2 diabetes mellitus. The relationship appears to be J-shaped where moderate alcohol consumption reduces the risk of developing type 2 diabetes mellitus in both men and women, irrespective of age, and in those with a low and a high body mass index. The optimal amount of wine appears to be approximately two drinks per day, where a standard drink in Australia is considered to be 10 g alcohol. Given that the incidence of diabetes is projected to approximately double in the next 15 years, simple dietary supplementation to a healthy diet and lifestyle to reduce the risk will become increasingly important. This paper reviews the association between wine specifically and type 2 diabetes mellitus, and discusses biological mechanisms related to the association.

Keywords: Wine, alcohol, resveratrol, diabetes phenolic compound, consumption.

INTRODUCTION

The prevalence of diabetes mellitus is escalating worldwide. Its incidence is projected to increase from approximately 1.7 million now to 3.5 million in 2033 in Australia as an estimated 275 Australians develop type 2 diabetes mellitus per day [1]. The disease mainly develops in adults after the age of 45 years.

Type 2 diabetes mellitus, which accounts for more than 85% of all incidences of diabetes mellitus, is a disorder characterised by resistance to the effects of circulating insulin. This disorder leads to a substantial increase in risk of cardiovascular disease, which is the major cause of mortality, accounting for up to 80% of all deaths in individuals with type 2 diabetes mellitus [2-4]. The age-adjusted relative risk of death due to cardiovascular disease is approximately three-fold higher than in the general population. Approximately 30 to 60% of diabetics have hypertension [5,6]. In addition, individuals with type 2 diabetes mellitus have coexistent lipid disorders characterised by increased blood triglycerides and reduced HDL-cholesterol, as well as haemostatic and fibrinolytic abnormalities [4] similar to individuals with, or at risk of, cardiovascular disease.

In addition to those with the disease, an estimated 2 million Australians are pre-diabetic, which is defined as having an abnormally high blood glucose level (hyperglycaemia). Australians with pre-diabetes are at higher risk of developing type 2 diabetes in the following five years [7]. There is strong evidence from

international, randomised controlled trials that type 2 diabetes mellitus can be prevented in many of these high-risk individuals through weight loss, and changes to diet and exercise [8-11].

ALCOHOLIC BEVERAGES AND DIABETES

Apart from obesity and physical inactivity there are few well-established modifiable risk factors for type 2 diabetes mellitus. Recent evidence suggests, however, that alcohol consumption may be a potentially modifiable risk factor for type 2 diabetes mellitus. A J-shaped relationship has been observed between level of alcohol consumption and risk of developing diabetes in both men and women [12-21], where regular moderate alcohol consumption is associated with a 30-40% reduced risk of type 2 diabetes [22-26]. This is shown by Lim *et al.* (2012) in Figure 1 [107].

The most recent meta-analysis of 20 cohort studies by Baliunas *et al.* (2009) [25] suggested that for women, the risk of developing type 2 diabetes mellitus was observed to be most reduced at 24 g alcohol/day, with a risk reduction of 40% compared with lifetime abstainers. Alcohol consumption remained protective until approximately 50 g/day. For men, the protective effect of alcohol consumption was greatest at 22 g/day, with the risk of diabetes being 0.87 times that of lifetime abstainers, and remained protective until consumption of 60 g/day. Therefore, for both women and men, the protective effect of alcohol consumption on incident type 2 diabetes mellitus was greatest with the consumption of approximately two drinks/day. Similarly, for both men and women, higher amounts of consumption (above 50 g/day for women and 60 g/day for men) were no longer protective and increased the risk for diabetes. Indeed, as in the general population,

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Figure 1: The relationship between the relative risk of developing diabetes and average daily alcohol consumption compared with lifetime abstinence (Adapted and extracted from Lim *et al.* 2012) [107].

there is also a decrease in cardiovascular risk with moderate alcohol consumption in type 2 diabetics [16,27,28]. These 20 cohort studies did not necessarily differentiate, however, between beer, wine and spirits and an association with type 2 diabetes mellitus.

METHOD

This review paper discusses the available published literature on the relationships between diabetes and the consumption of alcoholic beverages, and specifically wine, through a systematic search of the electronic database PUBMED from January 1980 up to December 2014. The published literature included meta-analyses, case-control and prospective cohort studies, relevant reviews, experimental and clinical studies, and references of identified papers, but excluded letters, editorials, conference abstracts and commentaries. No language restrictions were applied. Articles were included if they fulfilled the following criteria: (a) epidemiological studies with a case-cohort or cohort study design; (b) studies on the association of diabetes incidence with wine consumption or with wine, beer and spirit consumption; (c) studies presenting the odds ratio, risk ratio, or hazard ratio estimates with the corresponding 95% confidence intervals (CIs); and (d) never and/or occasional (non/occasional) drinkers as the reference category or available data for non/occasional drinkers. Also articles on wine products were included but not those on wine components except where mechanistic material was provided.

RESULTS

Wine and Diabetes

A review of the literature provided 22 individual studies post 2000 which have specifically assessed the effect of wine consumption on the risk of type 2 diabetes (Table 1). Of these, 14 assessed the risk of developing type 2 diabetes mellitus and a further six assessed the risk of micro-vascular and other complications associated with type 2 diabetes mellitus as well as all-cause mortality. Population groups from at least nine different countries were included in the studies.

All studies consistently observed a decreased risk of developing type 2 diabetes mellitus with moderate wine consumption in both men [14,15,29] and women [21,30-32], although in some studies a decreased risk was observed at different amounts of wine consumption [33]. The optimal amount of wine appeared to be approximately two drinks/day, where a standard drink in Australia is considered to be 10 g alcohol [34]. Wine consumed with food, and especially as an integral component of Mediterranean-type diet, was inversely associated with type 2 diabetes mellitus [35-37]. The inverse association was particularly observed for overweight and obese individuals at higher risk of developing the disease [32,33,35], in middle-aged individuals [17,38] and in elderly individuals [30,39]. Above moderate amounts, the risk of developing type 2 diabetes mellitus generally

Table 1: Individual Studies Assessing the Effect of Wine Consumption on Type 2 Diabetes Post 2000

Study	Study, country and type	Population studied	Reduced risk of Type 2 diabetes or other related effects observed for wine	Amount of wine associated with reduced risk	Beverage differentiation observed	Gender differentiation observed
Marques-Vidal <i>et al.</i> 2015 [108]	CoLaus Study Switzerland cohort	4765 subjects followed for an average of 5.5 yr	yes	14-27 drinks/week	no	no
Blomster <i>et al.</i> 2014 [49]	ADVANCE Study 20 countries cohort	11,140 T2DM subjects	Yes for cardiovascular events and all-cause mortality	Moderate	Wine >beer, spirits	n/a
Fagherazzi <i>et al.</i> 2014 [32]	E3N-EPIC Study France cohort	66,485 female subjects	Yes in overweight women	≥2 drinks/day	n/a	n/a
Koloverou <i>et al.</i> 2014 [37]	ATTICA Study Greece cohort	1514 men and 1528 women followed for 10 yr	Yes ↓↓ for Mediterranean diet and no metabolic syndrome	1 drink/day	wine = beer > spirits	no
Rojo-Martinez <i>et al.</i> 2014 [50]	Study Spain case-control	1031 T2DM subjects	Yes for serum sCD163 levels associated with insulin resistance		n/a	no
Bauer <i>et al.</i> 2013 [35]	EPIC-NL Study The Netherlands cohort	20,835 subjects with a BMI ≥25 kg/m ²	Not associated with T2DM as part of Mediterranean-type diet		n/a	no
Fernemark <i>et al.</i> 2013 [36]	Peru <i>In vivo</i>	21 T2DM subjects	Yes for postprandial glucose elevations for Mediterranean-type diet	150-200 mL/day	n/a	no
Beulens <i>et al.</i> 2012 [33]	EPIC-InterAct Study 8 countries cohort	16,154 subjects	Yes ↓↓ for overweight subjects	24.1-96 g/day (men) 6.1-12 g/day (women)	Wine + fortified wine >beer, cider, spirits	Women>men 0.5-1 drink/day ↓ risk by 20% in women compared to 13% in men
Rasouli <i>et al.</i> 2012 [29]	HUNT Study Norway cohort	90,269 subjects followed for 11 or 22 yr	Yes for both T2DM and auto-immune diabetes in men	10-15 g/day binge and high alcohol consumption did not increase risk	wine >> beer, cider, spirits	Men> women
Beulens <i>et al.</i> 2010 [48]	SMART disease study The Netherlands	5447 subjects with DM or vascular disease followed for 4.7 yr	Yes for stroke, amputations, vascular all-cause mortality	1-2 drinks/day	Wine > beer, spirits	no
Beulens <i>et al.</i> 2008 [47]	EURODIAB study The Netherlands	3,250 T2DM subjects	Yes for all microvascular complications	Moderate	Wine>beer, spirits	no
Athyros <i>et al.</i> 2007 [106]	Greece cohort	4153 subjects	yes	Moderate	Wine>beers>spirits	no

(Table 1). Continued.

Study	Study, country and type	Population studied	Reduced risk of Type 2 diabetes or other related effects observed for wine	Amount of wine associated with reduced risk	Beverage differentiation observed	Gender differentiation observed
Djousse <i>et al.</i> 2007 [39]	Cardiovascular Health Study USA cohort	4655 elderly subjects followed for average of 6.3 yr	Yes	Light - moderate	no	no
Hodge <i>et al.</i> 2006 [38]	Melbourne Collaborative Cohort Study Australia Prospective cohort	36,527 subjects followed for 4 yr	Yes	Light - moderate	Wine>>beer, spirits	no
Marfella <i>et al.</i> 2006 [46]	USA Intervention	115 T2DM subjects post MI	Yes for ↓oxidative stress, pro-inflammatory cytokines, and cardiac function post MI	Regular, moderate with meals	n/a	no
Beulens <i>et al.</i> 2005 [30]	Dutch Prospect-EPIC Study The Netherlands cohort	16,330 elderly female subjects followed for averages 6.2 yr	Yes	Moderate	no	n/a
Lapidus <i>et al.</i> 2005 [31]	Sweden Longitudinal population	1,462 female subjects followed for 32 yr	yes	Moderate	no	n/a
Wannamethee <i>et al.</i> 2003 [21]	Nurses' Health Study USA Prospective cohort	109,690 female subjects followed for 10 yr	yes	Light to moderate	Wine=beer>spirits >30 g/day as spirits ↑ risk	n/a
Kao <i>et al.</i> 2001 [17]	ARIC Study USA Prospective cohort	12,261 middle-aged subjects followed for 3-6 yr	no	n/a	Spirits>wine=beer for ↑ risk at > 14 drinks/week	Men>women for ↑ risk at > 21 drinks/week
Ceriello <i>et al.</i> 2001 [45]	Italy intervention	20 T2DM subjects	Yes for ↓ postprandial LDL cholesterol and thrombotic activation	Moderate	n/a	no
Conigrave <i>et al.</i> 2001 [15]	Health Professionals Follow-Up Study USA Prospective cohort	46,892 male subjects followed for 12 yr	yes	Regular moderate	no	n/a
Carlsson <i>et al.</i> 2000 [14]	Stockholm Diabetes Prevention Program Study Sweden Cross-sectional population based	3,128 male subjects	no	n/a	Spirits=beer>wine for ↑ risk at > 12 drinks/week	n/a

increased with wine consumption [14,17,21] similar to the consumption of other alcoholic beverages, and likely related to a dose dependent elevation of blood glucose levels [40]. The increased risk with the heavy consumption of alcoholic beverages may also reflect increases in body weight and changes to the plasma concentration of certain fats such as triglycerides, as well as increases in blood pressure [41,42].

Concerning the effect of wine on risk of pre-diabetes, a reduced risk of progressing from normal to impaired fasting glucose and impaired glucose tolerance and to type 2 diabetes mellitus was observed with light to moderate wine consumption in women, where high wine consumption increased the risk of abnormal glucose regulation in men [43,44].

Micro-vascular and other complications of type 2 diabetes mellitus were also inversely associated with regular moderate wine consumption [24,29,36,45-50]. Beulens *et al.* (2010) [48], for example, suggested that one to two drinks/day as wine was associated with a reduced risk of vascular-related deaths such as from coronary heart disease, myocardial infarction and stroke as well as non-fatal events including amputations in diabetic individuals at high risk of cardiovascular disease compared to abstainers.

The literature also suggested that wine consumption may be more protective than beer and spirits for preventing type 2 diabetes mellitus [29,33,38,51], as well as the micro-vascular and other complications of type 2 diabetes mellitus [29,47-49].

Interestingly, Rasouli *et al.* (2012) [29] also observed that moderate wine consumption also decreased the risk of autoimmune diabetes. Other similar studies are shown Table 2. Autoimmune diabetes is caused by cellular-mediated autoimmune damage of the insulin-producing pancreatic β -cells and includes both Type 1 diabetics and those adults with latent onset autoimmune diabetes. The moderate consumption of alcoholic beverages such as wine has been previously associated with a reduced risk of other autoimmune diseases such as rheumatoid arthritis [51] and systemic lupus erythematosus [52].

Potential Mechanisms of Action

The development of insulin resistance is key in the pathogenesis of type 2 diabetes, where cells fail to respond, or become resistant, to insulin. Accordingly, the protective effect of alcoholic beverages on the

development of type 2 diabetes mellitus has been attributed to increasing insulin sensitivity [53-57], reduced postprandial glycaemic response [58,59] and increasing the concentration of circulating adiponectin, which is an adipocyte hormone associated with increasing insulin sensitivity [57,60-64].

A J-shaped relationship has also been observed between insulin sensitivity and level of alcohol consumption, where the moderate consumption of alcohol has been observed to improve insulin sensitivity, possibly by reducing the concentration of free fatty acids in blood [65,24]. This has been found in observational studies as well as in randomised controlled trials [13,54,60,66,67]. Short-term moderate red wine consumption has also specifically been observed to improve insulin sensitivity in type 2 diabetic individuals [68].

In turn, the improved insulin sensitivity lowers the concentration of insulin [69], glucose and triglycerides in the blood, and increases that of HDL, while LDL particles become less dense, less adherent and less easily oxidised. Altogether, this reduces the risk of developing type 2 diabetes mellitus, as well as improving control of blood glucose and reducing the risk of cardiovascular disease [70,71]. Following the consumption of 120 to 240 mL wine daily for 30 days fasting serum insulin concentration was also lowered [72].

Furthermore, the pre-dinner consumption of a moderate amount of wine may reduce fasting plasma glucose concentrations [73], peak blood glucose concentrations or the overall postprandial glycaemic response to a subsequent carbohydrate-containing meal. In lean healthy individuals, Brand-Miller *et al.* (2007) [59] observed that wine produced the greatest reduction in the postprandial glucose response compared to beer and spirits, despite contributing less alcohol. This suggests that wine could contain substances other than alcohol that are physiologically relevant.

In addition, adiponectin appears to be an important link between alcohol consumption, insulin sensitivity, type 2 diabetes and atherosclerosis [74,47]. High concentrations of adiponectin have been associated with lower risk of type 2 diabetes [75,76] and adverse cardiovascular events [77], where moderate alcohol consumption has been shown to increase adiponectin concentrations in healthy individuals, obese males, and women with impaired glucose tolerance and type 2

diabetes [60-62,78,79]. Adiponectin also has anti-inflammatory properties [80].

More recently, another protective mechanism has been suggested for moderate alcohol consumption related to glycaemic load (GL). The GL of food estimates how much the food will increase an individual's blood glucose concentration after consuming it, and represents the interaction between the quantity and quality of carbohydrate. One unit of glycaemic load approximates the effect of consuming one gram of glucose [81]. There is a positive dose-response relationship between GL and the incidence of type 2 diabetes mellitus [82]. As alcohol metabolises differently to carbohydrates, it was proposed that the consumption of alcohol with food might attenuate the adverse effects of high GL foods on the risk of type 2 diabetes mellitus by delaying the insulin glucose response. Alcohol consumption of at least 15 g/day was observed by Mekary *et al.* (2011) [83] to decrease the positive relationship between GL and the incidence of type 2 diabetes mellitus in healthy women. Moderate alcohol consumption may also modify the metabolism of carbohydrate by decreasing glycogenolysis [84], fat oxidation [85] and the hormonal response to hypoglycaemia [86].

Risk of Vascular Complications

Patients with diabetes mellitus have other risk factors for cardiovascular disease such as a decreased total antioxidant capacity of plasma and concomitant increased LDL oxidation post-prandially [87,88]. Ceriello *et al.* (2001) [45] observed, however, that the consumption of red wine with food in type 2 diabetic patients decreased LDL oxidation post-prandially [89]. Furthermore, the post-prandial hypoglycaemia experienced in diabetes mellitus, which activates coagulation [90], was decreased by the consumption of red wine. The consumption of red wine by fasting type 2 diabetic patients, however, did not decrease either LDL oxidation or coagulation. Landrault *et al.* (2001) [91] also investigated whether wine-derived phenolic compounds increased the total plasma antioxidant capacity in an insulin-deficient diabetic rat model, as well as affecting glycaemia or blood sugar concentration, the biomarker of diabetes. Following the medium-term administration of both phenolic-enriched white wine and de-alcoholised phenolic-enriched white wine, the total plasma antioxidant capacity of the diabetic rats was increased to the level of non-diabetic rats and the level of glycaemia reduced by 15 to 20%. This suggests that moderate wine consumption may

also attenuate the debilitating hyper- and hypoglycaemic symptoms of diabetes.

Increased inflammation via an increase in circulating pro-inflammatory cytokines has been observed in both diabetic and non-diabetic patients and to be involved in the pathogenesis of cardiovascular complications such as endothelial dysfunction after a myocardial infarction [92]. Wine-derived phenolic compounds have anti-inflammatory actions including inhibition of reactive oxygen species in neutrophils, monocytes and macrophages [93,94]. In subjects with diabetes, red wine consumption, taken with meals, significantly reduces oxidative stress and the circulating concentration of pro-inflammatory cytokines from lymphocytes and macrophages such as C-reactive protein, tissue necrosis factor-alpha and interleukin-6, as well as improving cardiac function after a myocardial infarction [46].

One of the most studied wine-derived phenolic compounds is resveratrol. A recent meta-analysis on clinical parameters where resveratrol was used as an adjunct to pharmaceutical interventions with type 2 diabetes mellitus, suggested that resveratrol consumption consistently increased the concentration of glycosylated haemoglobin (HbA1c) which is associated with a decreased risk of multiple complications and risk of death in diabetics [94]. It also decreased serum creatinine concentrations which are associated with kidney function. Increased serum creatinine concentrations (as well as HbA1c) are a biomarker for kidney dysfunction and associated with a risk of nephropathy and cardiovascular disease [95,96]. In addition, resveratrol appeared to reduce systolic blood pressure which is also associated with risk of nephropathy and cardiovascular disease [97]. These data need to be considered cautiously, however, as the resveratrol was consumed in the studies was in higher amounts than that observed naturally in wine.

CONCLUSIONS

As acknowledged by the World Health Organization (WHO) in 2014, regular moderate wine consumption is causally linked to reduced risk of type 2 diabetes [98]. This has been observed for both genders and for individuals with a low or high body mass index. Conversely, heavy consumption appears to increase the risk of type 2 diabetes mellitus, although sample sizes generally have been too small to draw firm conclusions.

Table 2: Studies Involving Type 1 Diabetes

Study	Type of study	Population studied	Type of reduced risk with wine	Amount of wine associated with reduced risk	Beverage differentiation observed	Gender differentiation observed
Harjutsalo <i>et al.</i> 2013 [105]	Finnish Nephropathy Study (FinnDiane)	3608 T1DM subjects	Yes for nephropathy and retinopathy microvascular complications compared to spirit drinkers	light	Wine<spirits	no
Beulens <i>et al.</i> 2010 [48]	SMART disease study The Netherlands	5447 subjects with DM or vascular disease followed for 4.7 yr	Yes for stroke, amputations, vascular all-cause mortality	1-2 drinks/day	Wine > beer, spirits	no
Beulens <i>et al.</i> 2008 [47]	EURODIAB study The Netherlands	3,250 T2DM subjects	Yes for all microvascular complications	moderate	Wine>beer, spirits	no
Koppes <i>et al.</i> 2006 [24]	Meta-analysis	T2DM	Yes for coronary heart disease and all-cause mortality	Light to moderate	no	no

The WHO's *Global Status Report on Alcohol and Health* – 2014 edition clearly states that for diabetes mellitus “a dual relationship exists, whereby a low-risk pattern of drinking may be beneficial while heavy drinking is detrimental”. It also states that “for diabetes mellitus, the alcohol attributable fraction (AAF) was negative, meaning that, overall, alcohol consumption exerts a beneficial effect on this disease”.

There are, however, specific areas of research that warrant further study as only approximately 30 to 50 percent of wine's protective effects on diabetes can be linked to the biomarkers studied to date, such as its overall effect on insulin sensitivity. Studies could be conducted to examine how wine consumption modifies the risk of type 2 diabetes mellitus based on lifestyle characteristics, such as diet, exercise and body mass index. Components of a healthy lifestyle include maintaining a normal body weight [16], being physically active [99], refraining from smoking [100] and eating a healthy diet [101]. Although several studies have shown that type 2 diabetes can largely be prevented through a healthy lifestyle [16,102], in individuals already at lower risk of type 2 diabetes on the basis of multiple low-risk lifestyle behaviors, moderate alcohol consumption has been associated with an approximately 40% lower risk compared with abstinence [103]. The association between moderate wine consumption and different dietary patterns, such as high versus low glycaemic loads, also requires further study. In addition, information on alcohol

metabolising and diabetes-related genes could also be utilised in examinations of interactions between wine, genetic predisposition and diabetes risk [104]. For example, the ADH1C genotype modifies the association between alcohol consumption and diabetes as the ADH1C*2 allele, which is related to a slower rate of alcohol metabolism, attenuates the lower diabetes risk among moderate to heavy alcohol consumers. This observation suggests that the association between alcohol consumption and diabetes may be causal but may also be mediated by metabolites such as acetate rather than alcohol itself. In addition, studies on any interactions between the alcohol and phenolic content of wine should be undertaken to tease out the different mechanism of the alcoholic beverages on reducing the risk of type 2 diabetes mellitus.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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