ARTICLE

Is it scientifically justifiable to exclude grapes and their derivatives from the diet of consumers with or at risk of developing type-2 diabetes?

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The abuse of alcoholic beverages has been associated with an increased risk of chronic-degenerative diseases, including diabetes mellitus, so that there is a general diffidence towards the moderate consumption of wine by individuals with type-2 diabetes (T2D) or at risk of developing it. This narrative review investigates by critical revision of the scientific literature, whether alcoholic beverages must be excluded from the diet of T2D individuals or if their light to moderate consumption could be part of their daily diet. Grapes and their unfermented derivatives are also considered here as, due to their sugar content, they are commonly not recommended in T2D. Although further intervention studies on the consumption of alcoholic beverages and the development or control of T2D are needed, the burden of evidence suggests that moderate wine consumption has beneficial effects. No scientific study supports the dietary exclusion of grapes and their unfermented derivatives for T2D individuals or those at risk of developing it.

Introduction

The prevalence of type-2 diabetes (T2D), which accounts for more than 85% of all incidences of diabetes mellitus, is increasing worldwide. According to the WHO the number of individuals with diabetes has increased from 108 to 422 million in the period 1980-2014, with a global prevalence of 8.5% among adults in 2014. In 2016, 1.6 million people died from the consequences of diabetes, and thus, represents the seventh leading cause of death.[1] T2D is a chronic disease characterized by a double defect: insufficient insulin secretion to meet the body's needs (insulin secretion deficit), or insufficient insulin action (insulin resistance). The result, in both cases, is the consequent increase in blood glucose levels (hyperglycaemia). Individuals with a pre-diabetic condition, that is, an abnormally high blood glucose level, have a higher probability of developing T2D in later life,[2] and they increasingly become a vulnerable target for associated risk factors. T2D is associated, for example, with several other disorders and in particular, an increased risk of cardiovascular disease, which is the major cause of mortality among individuals with T2D, accounting for up to 80% of deaths.[3,4] The age-adjusted relative risk of death due to cardiovascular disease is approximately three-fold higher than in the general population, and 30 to 60% of individuals with T2D have hypertension.[5,6] In addition, individuals with T2D have often coexistent lipid disorders characterized by increased blood triglycerides and reduced HDL-cholesterol, as well as hemostatic and fibrinolytic abnormalities,[4] which is similar to individuals with, or at risk of, cardiovascular disease. The strategy for the prevention of the onset of T2D or the delay of its development involves a balanced diet and lifestyle which includes the maintenance of a normal body weight through physical activity, and abstention from smoking.[1,7,8] Clinical and intervention studies have made progress in identifying factors associated with T2D but solidifying the scientific basis for prevention and control of this disease, as well as the implementation at a national and indeed international level, is still a challenge.[9]

Scientific evidence suggests that alcohol consumption may be a potentially modifiable risk factor. A J-shaped relationship has been observed between level of alcohol consumption and risk of developing diabetes in both men and women,[10–17] whereas regular moderate consumption of alcoholic beverages is associated with a 30-40% reduced risk of the disease.[11,18–20] Although ethanol is considered as one of the most active molecules in alcoholic beverages, there is convincing evidence that beneficial health effects observed in T2D individuals, as well as a reduction in T2D prevalence, could be attributed to the synergistic effects of ethanol and other bio-active molecules present. This narrative review aims to confirm whether there is

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a difference between alcoholic beverages in inducing beneficial health effects in T2D individuals and whether the consumption of alcoholic beverages can be included in the daily diet of diabetics, when consumed in light to moderate amounts. Grapes and their unfermented derivatives are also considered since due to their sugar content, these products are commonly not recommended in T2D, although there is no clear scientific basis to support their exclusion.

Methods

The most important scientific databases of references and abstracts on life sciences (PubMed, MEDLINE, Embase, CAB-Abstract) were systematically searched (from database inception to June 2020) using the terms "wine", "*Vitis vinifera*", "wine polyphenols", "grape", "grape polyphenols", "grape juice" in combination with "diabetes", "type-2-diabetes", "diabetes mellitus" and refining the results for "human studies" and "controlled trials".

The search by title and abstract allowed the collection of 237 publications relevant to the association between grape/grape derivatives and diabetes. By removing the duplicates, papers considering alcohol as such, and papers not relevant, the final number of publications included in this review was 39.

Results and Discussion

Grape and its non-fermented derivatives

Because of their sugar content (approximately 16 g/100 g), the consumption of grapes and their derivatives are commonly not recommended for individuals with T2D. Studies reported in this review indicate that many of these considerations are not scientifically based (see papers listed in **Table 1**). Banini et al. (2006) showed that the moderate consumption of muscadine juice (MJ), muscadine grape “wine” (MW) and de-alcoholised muscadine “wine” (Dz-MW) did not induce an increase of blood glucose, insulin and glycate hemoglobin in T2D individuals.[21] On the contrary, there was a downward trend, although the statistical significance was reached only for insulin in Dz-W group. The statistical significance observed only with the dealcoholized product suggests that the effect is not attributable to ethanol. Even though further studies are necessary, these data suggest improved glycemia control in T2D individuals receiving certain grape derivatives.

Generally, raisins are considered particularly unsuitable for the T2D individuals’ diet, but this was not confirmed by Kanellos et al. (2013, 2014), who evaluated the effects of the consumption of dried grapes on glycemic control.[22,23] In the 2014 publication, the daily consumption of 36 g of raisins was shown not to modify glycemic control in T2D individuals, as compared to the control group. In the 2013 publication which compared the consumption of 74 g raisins (RG) with the equivalent glucose amount (50 g) (GG), the area under the curve (AUC) for both glucose and insulin, was statistically lower in RG versus GG. This decrease was observed similarly in healthy and T2D individuals. Kanellos et al. (2013, 2014) attributed the beneficial health effects of raisins to their phenolic compounds and fiber content, promoting the dietary inclusion of raisins for T2D individuals.[22,23] Consequently, the long-term administration of dried fruit such as raisins and the potentially associated elevated level of circulating phenolic compounds, could be beneficially increase the antioxidant capacity for diabetics.

Wine

As in the case of unfermented grape derivatives, wine is usually considered an unsuitable inclusion in the diet of individuals with, or at risk of developing, T2D. The scientific literature, however, does not support the dietary exclusion of alcoholic beverages and in particular of wine. None of the 24 papers reviewed reported a negative association between light to moderate wine consumption and T2D, although the influence of bias cannot be underestimated (**Table 2**). Lapidus et al. (2005), when considering all covariates in statistical analysis, found a lower inverse correlation between alcoholic beverage consumption and T2D risk.[24]

Summarizing the results from the publications included in this review:

- Ten investigations reported a reduced risk of T2D when light to moderate wine consumption was compared to.[24–32] Tresserra-Rimbau et al. (2015) reported a similar inverse trend for the metabolic syndrome;[33]
- Two investigations reported a comparable risk of T2D between moderate consumers and lifetimes abstainers; [10,34]
- In some studies, differences were observed between men and women,[26,28,29,32,35] and between body mass index (BMI).[32,36] Holst et al (2017) observed a non-linear (U-shaped) correlation between T2D risk and consumption of alcoholic beverages, where the lowest T2D risk was observed at 14 drinks/week in men and 9 drinks/week in women. There were gender differences in T2D risk, however, for the joint effect of frequency of alcohol consumption and average weekly alcohol amount, and regarding beverage type.[29] Beulens et al. (2012) reported that the relationship between moderate alcohol consumption and a lower T2D risk was observed only in women and was stronger in overweight individuals (BMI>25);[36]
- When different alcoholic beverages were compared, more beneficial health effects were reported for moderate wine consumption;[10,26,28–30,32,35,37]
- When dealcoholized wine was included in investigations, the effect of the ethanol was comparatively negligible;[38,39]
- In some studies, the beneficial health effects were enhanced when wine consumption was also associated with a strict adherence to a Mediterranean-style diet;[30,40,41]
- Unlike light to moderate consumption, the heavy consumption of alcoholic beverages (and in particular spirits) was often associated with an increased T2D risk.[10,28,34,42]

Investigators have also used specific biomarkers and/or clinical indications to assess the beneficial health effects of light to moderate wine consumption on the development of T2D, or the lack of contraindications for T2D individuals.

Table 1 – Consumption of grape or non-fermented grape derivatives and metabolic effects in T2D patients

Cohort and study details	Grape derivatives included and doses	Objectives of the study	Main outcome	Ref
29 T2D patients (16M, 13F) 23 healthy subjects (11M, 12F) Intervention trial Period: 28 days	Groups received 150 mL/day of: 1) Muscadine (*Vitis rotundifolia*) grape juice -MJ (n= 10); 2) muscadine grape wine - MW (n=10); 3) dealcoholized muscadine grape wine - Dz-W (n = 9) Healthy subjects received MJ (n= 8) or no test drink (n=15)	To evaluate the effects of different drinks consumed with meals on glycemic indices	Compared to MJ, MW and Dz-W produced a reduction of blood glucose, insulin, and glycated hemoglobin levels, although the difference was statistically significant only for insulin levels in T2D patients receiving Dz-W	21
15 T2D patients (age: 55-68 years; 9M, 6F) 15 healthy people (age 20-30 years; 8M, 7F) Intervention study	74 g raisins or 50 g glucose (equivalent amount of sugar)	To evaluate the metabolic response measuring glucose and insulin levels in blood samples collected before starting the study, 30, 60, 90, 120, 150 and 180 min after raisin or glucose intake	No significant difference in baseline glucose and insulin value between raisins and reference groups. The difference at glucose peaks between raisins and reference was significant in healthy and in diabetics. Glycemic and insulinemic responses were decreased after raisin consumption compared to reference	22
48 T2D patients with similar dietetic habits according to a weekly food-frequency questionnaire (age 40-65 years; 25 M, 23 F) Two-armed, randomized, controlled, prospective intervention trial Period: 24 weeks	Intervention group: 36 g/day Corinthian Raisins (CR) (n=26; 15M, 11F), Control group: usual diet (n=22, 10M, 12F)	To assess the effects of CR on fasting glucose and glycated hemoglobin (HbA1c)	Glycemic control was not affected in either arms	23

Legend: M= Males; F= Females; T2D= Type-2 diabetes

Table 2 – Studies performed in humans where the consumption of wine was correlated to type-2 diabetes

Cohort and study details	Beverages included and doses	Objectives of the study	Main outcome	Ref
49,377 US adults (median age: 55 years; range: 21–102 years; 46% M, 54% F) Cohort study 2011-12	Self-reported alc. purchaser from 2007-2012 (National Consumer Panel data). Alcohol-type preference was based on expenditures. Unit drink: 12.5 oz (370 mL) of beer, 5 oz (148 mL) of wine, and 1.5 oz (44 mL) of spirits.	To estimate the effects of diet, alc., and lifestyle choices on the prevalence and incidence of T2D.	Many types of alcohol-related purchases were associated with a lower prevalence of T2D. Purchasers of the highest volumes of wine and beers (but not spirits) were less likely to report being diagnosed with T2D than non drinkers	25
18 patients T2D (mean age: 64 years; range: 45-82 years; 11F, 7 M) Intervention study	Acute effects: inpatients subjects received for two days, randomly, 240 mL wine or grape juice with their evening meal. Chronic effects: consumption for 30 d in random order, 120-240 mL/d wine or abstained from alc.	To evaluate possible beneficial metabolic effects of intervention	Acutely, 240 mL wine (24 g alc.) had no effect on plasma glucose or serum insulin. Chronically, a mean wine consumption (18 g/day alc.) for 30 days compared to abstinence determined no significant change in plasma glucose and a significant reduction of serum insulin.	43
24 T2D patients (age 59.3±1.1 years) 22 healthy volunteers (age: 54.1±1.4 years) Three periods, 4-week each (no wash out)	Consumption at dinner of: Red wine (RW) (Shiraz Cabernet, 13% alc.) Dealcoholized red wine (DRW) or water (F: 230 mL/day; M: 300 mL/day)	To assess the effects of RW on plasmatic mediators of inflammation (SPMs) typically associated with T2D, such as 18-HEPE, 17-HDHA, E- and D-series resolvins, and Maresin 1	Moderate consumption of RW does not modify SPMs values in T2D patients when compared to groups receiving DRW or water. The observed elevation of SPM compared with healthy volunteers may be a homeostatic response to counter ongoing inflammation	44
Random baseline sample= 15,258 (729 cases T2D) Incident cases T2D= 11,559 (mean age 52.9 years; 37.8% M; 62.2% F) Multicenter prospective case–cohort study. Average follow-up of 9.9 years	Wine intake was calculated by validated dietary questionnaire. Drinking was classified in g/day of alc.: light- 0.1-6.0 and moderate 6.1-24.	To investigate the association between alc. consumption and T2D, and possible role of sex, body mass index (BMI) and beverage type	Moderate alc. consumption was associated with a lower risk of T2D amongst women only, partially explained by fat distribution. The relationship between alc. consumption and T2D was stronger for overweight (BMI > 25) than normal-weight women and men. Wine and fortified wine consumption were most clearly associated with a reduced risk of diabetes.	36
67 M at high CV risk (age 55-75 years) Randomized crossover trial. Period: 4 weeks	After a run-in period, all participant received 30 g alc./day in randomized order: 1) red wine; 2) equivalent amount of dealcoholized red wine, and 3) gin	To compare the effects of moderate consumption of red wine, dealcoholized red wine, and gin on fasting plasma glucose and insulin levels, and on homeostasis model of insulin resistance (HOMA-IR)	No change was observed on fasting glucose level throughout the study, while mean adjusted plasma insulin level and HOMA-IR decreased after red wine and dealcoholized red wine.	38

Table 2 – Studies performed in humans where the consumption of wine was correlated to type-2 diabetes (*continue*)

Cohort and study details	Beverages included and doses	Objectives of the study	Main outcome	Ref
5,128 subjects with normal glucose tolerance (age 35-56 years; 2,070M, 3,058F) 111 T2D patients (age 35-56 years; 70 M, 41F) Cohort study follow up 8-10 years	Alcohol intake was calculated by baseline questionnaire. Classification of consumption (g/day total alc.): Males 0.01-6.79 occasional; 16.8-13.01 low; 13.02-22.13 medium; > 22.14 high. Females <0.32 occasional; 0.33-1.65 medium; >1.66 high Pure alc. content per mL: 0.035-0.055 mL for beers; 0.12 mL for wine; 0.19 mL for dessert wine; 0.4 mL for spirits.	To investigate the influence of alc. consumption and type of beverage on the risk of developing pre-diabetes and T2D in middle-aged Swedish men and women.	Total alc. consumption correlated with the risk of pre-diabetes or T2D in men. Higher risk of pre-diabetes and T2D was observed with high beer and high spirits intake, respectively. In women, high wine intake decreased pre-diabetes risk, while medium intake of both wine and spirits decreased the incidence of T2D. An increase of pre-diabetes was observed with high consumption of spirits.	26
4,655 subjects (41% M; age 73.2±5.2 years 59% F age 72.4±5.3 years Prospective study Mean follow-up: 6.3 years	Patients were classified according to the usual alc. consumption: Never (n=1808); Former (n=346); <1 drinks/week (n=944); 1 to 7 drinks/wk (n=858); >7 drinks/wk (n=699)	To assess the role of total and beverage-specific alc. consumption on the incidence of T2D among elderly men and women.	During the follow-up period there were 234 new cases of T2D with a reduced risk observed in participants with light to moderate alc. consumption, independently from the types of beverage consumed.	27
66,485 F from a French prospective cohort (age 52.7±6.6 years) Cohort study from 1993 to 2007	Classification of drinking habit: Never (< 1 drink/week); Regularly (>1 drinks/week) Standard glasses =10 mL alc. (250 mL for beer, 70 mL for fortified wine and 40 mL for spirits)	To evaluate the associations between T2D risk and both baseline wine consumption and trends of wine consumption frequency throughout life	1,372 case of T2D were diagbnosed. The average consumption of wine, among alc. consumers, was 0.81 drinks/day. Associations between wine and T2D risk was restricted to overweight women, showing an inverted association between wine consumption and T2D risk. Women who started drinking at age 10–15 were at a significantly lower risk than lifetime abstainers	35
395 T2D patients (age: 65.9±10.4 years; M=253, 142F) Diabetic retinopathy (DR)=235; Non-vision threatening (VT)DR =130; VTDR= 105 Alc. consumers=188 Cross-sectional study	Classification of consumption (previous 12 months): Never, <1SD/week; moderate 1-14 SD/week; high >14SD/week Standard drink (SD): 1 bottle beer=1.4 SD; 150 mL wine/champagne=1.5 SD	To explore the association between alc. consumption and diabetic retinopathy (DR).	Compared to abstainers, moderate consumption of white wine/champagne (1-14 SD/week) was significantly associated with reduced DR, non-VTDR and VTDR in T2D patients.	37
48 T2D patients (age: 57±6.6 years; 41M, 7F) 2-year randomized controlled trial	150 mL of: Red wine (16.9 g ethanol with 270.1 mg of total polyphenols as gallic acid equivalent) (n=27) Water (n=21)	To evaluate the effect on weight gain and abdominal fat accumulation and distribution in T2D patients	Compared to control group, moderate wine consumption, as part of a Mediterranean diet, in T2D patients was not responsible of weight gain or abdominal adiposity accumulation	40

Table 2 – Studies performed in humans where the consumption of wine was correlated to type-2 diabetes (*continue*)

Cohort and study details	Beverages included and doses	Objectives of the study	Main outcome	Ref
174 abstainers T2D patients (age: 52-66 years; 117 M, 57F); 2-year randomized controlled trial	150 mL of: red wine (n=53); white wine (n=43); water (n=64)	To evaluate the effect of moderate wine consumption on the progression of carotid total plaque volume, TPV	No significant progression in carotid-TPV was observed. Subgroup having the greatest plaque burden and drinking wine showed a small regression of plaque burden.	45
3,608 T1D patients (age 28.9 – 46.8 years; 1898 M, 1,710F) Cross-sectional study	Groups were based on the amount of alc. and the type of beverage consumed (beer, wine and spirits). Consumption: Men: lifelong abstainers 0 g/week; light 0–83.9 g/week; moderate 84–287.9 g/week; heavy ≥ 288 g/week. Women: lifelong abstainers 0 g/week; light 0–59.9 g/week; moderate 60–191.9 g/week; heavy ≥192 g/week	To evaluate the effect of alcohol consumption and the type of beverage on the risk of nephropathy and severe retinopathy	There is no direct association between alc. consumption (from beer and wine) and both T1D associated nephropathy and retinopathy. Abstainers and former users showed a higher risk of both diseases.	46
1,650 Japanese men (age 26-80 years) Prospective study with a follow-up period of 10.2 years	Alcohol consumption: Lifetime abstainers (n=153); Past drinkers (n=40); 8–54 g alc./week (n=234); 55-98 g alc./week (n=245); 99-160 g alc./week (n=244); 161-229 g alc./week (n=260); 230-287 g alc./week (n=273); 288-748 g alc./week (n=201) Drink= 23 g alc.	To investigate the role of alc. amount and drinking frequency in the development of T2D.	In the period considered, 216 people developed T2D. Moderate consumers (1 drink per occasion over 6 times/week) had an incidence comparable to lifetimes abstainers. Higher quantity of alcohol increased the risk independently from drinking frequency	34
36,527 adults (age 40 – 69 years) Prospective study	Alcohol intake classification: Men: abstainers as control; <10.0 g/day; 10.0–19.9 g/day; 20.0–29.9 g/day; and ≥30.0 g/day. Women: abstainers as control; <10.0 g/day; 10.0–19.9 g/day; and ≥ 20.0 g/day. Pattern of alc. consumption in the last week: 0, 1–3, 4–6 and 7 drinks.	To assess associations between amount and frequency of alcohol consumption and incidence of T2D after 4 years from enrollment.	Moderate consumption of alc. is not involved in an increased risk of T2D and could reduce it in women. Among beverages, wine appears the most active in reduce T2D risk in both sexes, although a high daily consumption could promote its appearance.	28

Table 2 – Studies performed in humans where the consumption of wine was correlated to type-2 diabetes (*continue*)

Cohort and study details	Beverages included and doses	Objectives of the study	Main outcome	Ref
76,484 participants (28,704 M – age 18-98 years; 41,847 F - age 18-99 years) Cohort study with median follow-up of 4.9 years	Self-reported questionnaires on frequency of alc. drinking, frequency of binge drinking, and beverage used (wine, beer and spirits). Alc. consumption as days in a week: lifetime abstainers; current abstainers; <1; 1-2; 3-4; 5-7. One standard drink corresponds to 12 g alc.	To examine the association between alcohol drinking pattern and diabetes risk in men and women from the general Danish population.	There is a non-linear correlation between alc. intake and risk of T2D. Consumption of alc. over 3-4 days/week is associated with the lowest risk of T2D, even considering the average alc. intake. Lowest risk of T2D was observed with 14 and 9 drinks/week in men and women, respectively. A lower T2D risk was associated with moderate to high wine intake, and among women an increase of T2D risk with high intake of spirits. There was no clear evidence of higher T2D risk in association with binge drinking.	29
12,261 participants (45-64 years; 5423 M, 6,838 F) Prospective Study (3 to 6 years)	Alc. consumption (wine, beer and spirits): <1 drink/week; 1.1-7 drinks/week; 7.1-14 drinks/week; 14.1-21 drinks/week; >21 drinks/week 1 drink=12 g alc.	To evaluate the association between alc. consumption and the risk of T2D with special attention payed to sex difference	High alc. intake (>21 drinks/week) increases T2D risk in middle-aged men, while moderate consumption does not in both sexes. The increased diabetes risk among men was mainly due to spirits rather than to beer or wine consumption.	10
3,042 participants (1,514M age 18–89 years, and 1,528F age 18–87 years) Prospective study with 10 years follow-up	Alc. consumption: abstainers; low 0-1 drink/day; moderate 1–2 drink/day; high > 2 drink/day One drink= 12 g of EtOH	To investigate the effect of type (wine, beer, whisky, traditional Greek drinks, spirits) and amount of alc. consumption on the 10-year diabetes incidence.	Moderate alc. consumption shows protective effect on T2D incidence, and in particular in subject with strict adherence to the Mediterranean diet and metabolic syndrome free. The protective effect was more evident consuming wine and beer compared to other beverages and spirits.	30
1,462 Females participants (38 – 60 years) Longitudinal population study with follow-up over 32 years.	The intakes of beer, wine, and strong spirits were studied as three separate variables. 1 wine serving= 140 mL (13% alc.) 1 beer serving= 330 mL (3% alc.) 1 liquor serving= 40 mL (40% alc.)	To explore the predictive value of women's alcohol habits in relation to incidence of diabetes and all-cause mortality	The study supported previous researches, where a protective effect of alc. on T2D was observed. On the other hands, the authors indicate that a lower inverse correlation could be found, when all variables are included in statistical elaboration.	24
4,765 participants without T2D at baseline (age 51.7 ± 10.5 years; 2,152M, 2,613 F) Prospective study with follow-up of an average period of 5.5 years	Participants' classification: abstainers: 0 drink/week; moderate 1–13 drinks/week; drinkers at risk (14–34 drinks/week) and -drinkers at very high risk ≥35 drinks/week Standard drink: 10-12 g alc.	To assess the effect of alcohol consumption and type of beverage on the incidence of T2D and T2D + Impaired fasting glucose (IFG)	During the period considered 99 M and 185 M developed T2D and 639 IFG. Moderate-high alcohol consumption correlates negatively with risk of T2D, but not when IFG is considered in association. Wine consumption is associated with a lower risk of T2D, while no association was found between type of beverage and co-occurrence of T2D and IFG.	31

Table 2 – Studies performed in humans where the consumption of wine was correlated to type-2 diabetes (*continue*)

Cohort and study details	Beverages included and doses	Objectives of the study	Main outcome	Ref
24 subjects with controlled T2D (age 59.5±5.6 years; 19M, 5F) Three-period, 4 weeks each, randomized crossover study	Intake of red wine: Women 230 mL/day (~24 g alc./day) Men 300 mL/d (~31 g alc./day), or equivalent volumes of dealcoholized red wine (DRW) or water	To evaluate the effects of alcohol consumption on glycemia measured twice weakly	Red wine did not affect fasting and post-prandial glycemia and insulin resistance	39
17 T2D patients (age 48-72 years, 15 M, 2 F) Intervention study	Groups: Red wine for 2 weeks (360 mL/day, WTD) (n=9) Control (n=8)	To evaluate the effect of red wine consumption on insulin resistance and explore the relationship between insulin sensitivity and endothelial function	Red wine consumption for two weeks markedly reduced insulin resistance in T2D patients versus controls. No change in vascular reactivity or nitric oxide production	47
807 Male participants (age 70 years) from the Uppsala Longitudinal Study Population-based cohort study with follow-up of 20 years	Seven-days self-reported alc. intake was collected by a questionnaire. Alc. consumption classification: lowest tertile (<28 g/week); middle tertile (28 to 81 g/week); highest tertile (>81 g/week)	To verify if moderate and high alcohol intake could be associated with decreased and increased risk of T2D, respectively	No association was found between wine intake and insulin sensitivity (measured by clamp technique) or insulin secretion. There was a strong correlation between high wine intake and increased abdominal fat distribution, mainly in BMI normal subject. Since abdominal obesity is an independent risk factor for T2D and could precede insulin resistance, high wine consumption could be a risk factor for T2D	42
514 T2D subjects (age 64.9±11.7; 280 M, 234F) 517 controls (age 64.9±11.8, 282M, 235F). Cross-sectional, matched case-control study	Study was based on an annual food frequency questionnaire (red wine < 1 drink/day and red wine > 1 drink/day)	To correlate alc. consumption with the level of potential biomarkers of insulin resistance in T2D setting	Results showed that the ratio between TNF-like weak inducer of apoptosis (sTWEAK) and its scavenger receptor sCD163 as well as the sCD163 concentration are increased in T2D patients. Coffee and red wine consumption was inversely associated with serum level of sCD163 suggesting a possible protective role through an anti-inflammatory pathway	48
109 T2D abstainer patients (age 41–74 years) 3-month randomized multicenter trial	Patients received daily: - 150 mL wine (13 g alc.) or - nonalcoholic beer (control)	To study the effect of daily moderate alc. intake on glycemic control in the fasting and postprandial period in patients who previously had abstained from alcohol	Fasting plasma glycemia after 3 months was significantly lower in T2D patients consuming wine versus control. No effect was shown in 2-h post-prandial glycemia. No adverse effect was observed and participants in wine group showed an improvement in falling asleep	49

Table 2 – Studies performed in humans where the consumption of wine was correlated to type-2 diabetes (*continue*)

Cohort and study details	Beverages included and doses	Objectives of the study	Main outcome	Ref
62,458 adults from ten European cohort studies (age >24 years) Prospective multi-country cohort study Follow-up average period: 4.3-20.8 years	Preference for beer, wine or spirits was established if one beverage represented 70% or more of the total alc. consumption in grams per day. Portion sizes were standardized: - 330 mL for a bottle of beer (4.5% alc.), - 175 mL for a glass of wine (12% alc.) - 25 mL for a shot of spirit (37.5% alc.)	To verify the association between alcoholic beverage preference and T2D incidence	Preference for beer, wine or spirit was similarly associated with T2D risk compared with having no preference. Absolute wine intake, adjusted for total alc., was associated with a lower T2D risk. A spirit preference was related to a higher diabetes risk in those with a higher body mass index, in men and women separately, but not after excluding persons with prevalent diseases.	[32]

Legend: alc. = alcohol; BMI= Body Mass Index; d=day; F=females; HEPE=hydroxyeicosapentaenoic acid; HDHA=hydroxydocosahexaenoic acid; M=males; RW=red wine; SPM=specialized pro-resolving mediators of inflammation; T1D=Type-1 diabetes; T2D=Type-2 diabetes

Glycemia, serum insulin level and insulin resistance. Generally, after a minimum four-week intervention, individuals consuming light to moderate amounts of wine compared to abstainers reported:

- No significant change in fasting,[38,39,43] and post-prandial glycemia;[39]
- A reduction of serum insulin level.[38,43]

Shai et al (2007), however, observed a reduction of fasting glycemia after three months of moderate daily wine consumption, while no effect was recorded in two-hour post-prandial glycemia.[49] It was suggested that the mechanisms for this effect probably involve enhanced insulin secretion and the effect of alcohol metabolism, which, by increasing the hepatic cytosolic NADH-to-NAD+ ratio, inhibits gluconeogenesis, a process largely controlling fasting, rather than post-prandial, glycemia. The non-significant increase of post-prandial glucose levels was suggested to be a consequence of increased consumption of simple carbohydrates in the evening meal. It was also suggested that the dose of alcohol, 13 g/day, may have been a less than optimal dose to achieve maximal effects in T2D individuals.

Other parameters or functions considered. No significant change or beneficial effects of moderate wine consumption were observed on: 1) plasma mediators of inflammation;[44,48] 2) diabetic retinopathy[37,46] 3) nephropathy;[46] and 4) progression of carotid total plaque volume.[45] Considering that no negative effect was observed in these parameters, the exclusion of moderate wine consumption from the diet of T2D individuals does not seem justifiable.

Molecules responsible of the beneficial effect of grapes and their derivatives on T2D

Studies conducted to evaluate the role of various active molecules contained in grapes and their derivatives have mainly considered ethanol and phenolic compounds, particularly resveratrol (**Table 3**). Nine of 11 studies showed a beneficial effect of resveratrol, irrespective of source, on diabetes control (both glycemic control and associated pathologies), where the dose of resveratrol varied from 10 mg to 2 g/day and the administration period ranged from four weeks to one year. In contrast, however, Bo et al. (2016) showed no beneficial effects on T2D after resveratrol supplementation for six months at doses ranging from 40 to 500 mg/day,[50] and neither did Thazhath et al. (2016) after 1 g/day resveratrol supplementation for five weeks.[51]

Conclusions

For centuries, the habit of consuming alcoholic beverages has been an integral part of the culture of many countries and, in particular, in the Mediterranean area, where wine is the most preferred alcoholic beverage, normally consumed with meals. Unfortunately, the excessive consumption of alcoholic beverages is a serious public health problem in certain countries, especially among the younger generations. The misuse of alcoholic beverages has been associated with an increased risk of chronic degenerative diseases, including diabetes mellitus.[52] The plausible mechanisms behind this observation could be attributed either to the increase in body weight and changes to the plasma concentration of certain lipids such as triglycerides, or to the increase in blood pressure.[53]

Contrary to common thinking, grapes and their derivatives (including raisins) are not contraindicated for individuals with T2D (**Table 1**). The scientific literature suggests that wine consumption may be protective in preventing the development of T2D mellitus, as well as in modulating glycemic control and related complications in individuals (**Table 2**). Comparing different types of alcoholic beverages, the results of moderate wine consumption seem to be superior to beer and spirits. Moreover, the literature showed that the beneficial health effects of moderate wine consumption were associated with the non-alcoholic fraction, and in particular with its phenolic content.[38]

The studies examined in this review suggest the following:

- Used in limited amounts, grapes, its juice and raisins are not contraindicated for individuals with T2D;
- Light to moderate wine consumption (one to three glasses/day) does not contribute to an increased incidence of T2D;
- Light to moderate wine consumption is associated with an improved metabolic control in T2D individuals, so they should not be discouraged from the moderate consumption of wine during meals;
- When searching for bioactive molecules involved in the protective effects of wine, most authors suggest non-alcoholic polyphenols, such as resveratrol. The studies included in this review indicate that given the high doses of resveratrol required for the positive metabolic modulation (up to 2 g/day versus few mg supplied by the diet) and its low bioavailability, this molecule is only one of many molecules responsible for beneficial health effects associated with grapes and wine in T2D individuals. Thus, further research is warranted in the field of non–nutritive phytochemicals of grapes and derivatives and their synergistic effects.

Conflicts of interest

There are no conflicts of interest to declare.

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Table 3 – Studies performed in humans where molecules from grapes/wine were associated with T2D

Cohort and study details	Molecule used and doses	Objective of the study	Main outcomes	Ref.
71 overweight T2D patients (age 30-60 years) Randomized controlled trial Period: 8 weeks	Treated group: 1g/day trans-RES (n=35) Control group: methyl cellulose (n=36)	To evaluate the effect of RES supplementation on glycemic status, lipid profile and body composition	Compared to placebo group, RES decreased fasting glycemia and increased high density lipoprotein level	54
57 T2D patients with or without comorbidities, $\geq$ 6 months of ongoing oral hypoglycemic treatment and 3 years duration of the disease (age 30-70 years, 21 M and 36 F) Prospective, open-label, randomized, controlled study Period: 3 months	Treated group: 250 mg/once day RES with oral hypoglycemic treatment (n=28) Control group: only oral hypoglycemic agents (n=29)	To evaluate the effect of RES in improving the glycemic control and the associated risk factors.	Three months of supplementation significantly reduced mean hemoglobin A_{1c}, systolic blood pressure, total cholesterol, and total protein. No significant changes in body weight and HDL and LDL cholesterol	55
192 T2D patients (age ≥ 40 years) Double-blind, randomized, placebo-controlled trial Period: 6 months	Treated RES 40 mg/day (n=65) Treated RES 500 mg/day (n=65) Control group: inert micro-cellulose (n=62)	To determine whether RES supplementation could modulate positively the concentration of C-reactive-protein (CRP) and metabolic pattern	The supplementations with RES (both doses) did not show any improvement in parameters considered	50
19 T2D male patients (age 40-70 years) Double-blind, randomized, controlled study Period: 4-week with previous 4-week washout	Treated group: 2 x 5 mg/die RES (n=10) Control group (n=9)	To determine whether RES modulates insulin sensitivity, obtaining some data on mechanism of action Parameters measures: 1) Urinary ortho-tyrosine excretion (UTE) as a marker of oxidative stress 2) Ratio Phosphorylated protein kinase B/Protein kinase B (pAkt:Akt) in platelet as markers of insulin signaling	RES reduced significantly insulin resistance and UTE, and increased pAkt:Akt. No effect on parameters related to β-cell function.	56

Table 3 – Studies performed in humans where molecules from grapes/wine were associated with T2D (*continue*)

Cohort and study details	Molecule used and doses	Objective of the study	Main outcomes	Ref.
10 overweight-obese subjects with impaired glucose tolerance (IGT) (age 72±3 years, 3M and 7F) Open-label study Period: 4 weeks	Random distribution among: Treated group 1: RES 1 g/day Treated group 2: RES 1.5 g/day Treated group 3: RES 2 g/day	To test the effect of RES on glucose metabolism and vascular function	At doses of 1-2 g/day RES improves insulin sensitivity, and post-prandial but not fasting glycemia. Weight, blood pressure, and blood lipid profile were unchanged.	57
56 T2D patients with coronary heart disease Randomized, double-blind placebo-controlled trial Period: 4 weeks	Treated group: RES 500 mg/day (n=28) Control group: placebo (n=28)	To investigate the effects of RES on metabolic status	In comparison with placebo, RES determined positive effects on glycemic control (reduction of fasting glycemia, insulin level and insulin resistance; improvement of insulin sensitivity)	58
108 T2D patients under pharmacological control (at least 3 months) (age: 59.03±8.21 years; 40-78 yrs; 58 M and 50 F) Randomized (1:2:2), multicentric, double-blind trial Period: up to 12 months	Treated group 1: calcium dobesilate (CD) (750 mg/day; n=42), Treated group 2: Grape seed pro-anthocyanidin extract (GSPE) (150 mg/day; n= 41) Placebo (n=25)	To evaluate the efficacy and safety of GSPE in patients with non-proliferative diabetic retinopathy (NPDR) and retinal thickening with hard exudate (HE)	GSPE supplementation for one-year improved HEs in patients with NPDR. The efficacy of GSPE was higher than that of CD, a usual pharmaceutical drug	59
64 T2D patients with hypoglycemic treatment (at least 6 months) and without any antioxidant supplementation (age 20-65 years) Randomized placebo-controlled double-blinded parallel clinical trial Period: 45 days	Treated group: 1 g/day RES (2x500 mg) (n=31) Control group: 1 g/day inert micro-cellulose) (n=33)	To evaluate the effect of RES on diabetes biomarkers in the presence of standard antidiabetic treatment	RES significantly decreased systolic blood pressure, fasting blood glucose, glycated hemoglobin, insulin, and insulin resistance, while HDL was significantly increased.	60
60 T2D patients with albuminuria (age 40-60 years) Randomized, double-blind, placebo-controlled clinical trial Period: 90 days	Treated group: RES 500 mg/day (n=30) Control group: placebo (n=30) All subjects received Losartan (12.5 mg/day), an angiotensin receptor blocker	To evaluate the effects of RES on diabetic nephropathy	In association with Losartan, RES was effective in reducing urinary albumin excretion versus pre-treatment situation	61

Table 3 – Studies performed in humans where molecules from grapes/wine were associated with T2D (*continue*)

Cohort and study details	Molecule used and doses	Objective of the study	Main outcomes	Ref.
14 overweight T2D patients (age: 67.5±1.6 years; 10=M, 4F) Double-blind, randomized, crossover study Period: two periods of 5 weeks each with washout in between	Treatment period: RES 500 mg twice daily Placebo period: microcrystalline cellulose	To evaluate the effects of RES on glucagon-like peptide 1 secretion, gastric emptying, and glycemic control	Results do not support an improvement of glycemic control due to RES supplementation	[51]
35 T2D male patients with hypertensive medication (age: 60±11 years) Randomized placebo-controlled, triple-blind, dose–response, Period: 1-year follow-up with three parallel arms	One-year daily intake of: Treatment 1: Grape extract – GE (n=13) Treatment 2: Grape extract containing resveratrol (8 mg) - GE-RES (n=13) Placebo (n=9)	To investigate the molecular changes in peripheral blood mononuclear cells (PBMCs)	Data indicate a possible beneficial immunomodulatory effect of GE-RES compared to other groups	[62]

RES= resveratrol

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