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REVIEW ARTICLE

Diabetes mellitus and alcohol

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Summary

Alcohol influences glucose metabolism in several ways in diabetic patients as well as in non-diabetic patients. Since alcohol inhibits both gluconeogenesis and glycogenolysis, its acute intake without food may provoke hypoglycaemia, especially in cases of depleted glycogen stores and in combination with sulphonylurea. Consumed with a meal including carbohydrates, it is the preferred fuel, which may initially lead to somewhat higher blood glucose levels and hence an insulin response in type 2 diabetic patients. Depending on the nature of the carbohydrates in the meal, this may be followed by reactive hypoglycaemia.

Moderate consumption of alcohol is associated with a reduced risk of atherosclerotic disorders. Diabetic patients benefit from this favourable effect as much as non-diabetic patients. Apart from effects on lipid metabolism, haemostatic balance and blood pressure, alcohol improves insulin sensitivity. This improvement of insulin sensitivity may also be responsible for the lower incidence of type 2 diabetes mellitus reported to be associated with light-to-moderate drinking. In case of moderate and sensible use, risks of disturbances in glycaemic control, weight and blood pressure are limited.

Excessive intake of alcohol, however, may not only cause loss of metabolic control, but also annihilate the favourable effects on the cardiovascular system.

Keywords alcohol; insulin sensitivity; hypoglycaemia; cardiovascular diseases; diabetes mellitus

Introduction

The use of alcohol in diabetes mellitus has always been controversial. With short-term risks such as hypoglycaemia, metabolic dysregulation and acidosis and long-term ones such as hypertension, weight gain and neuropathy, physicians and patients have been reserved regarding the consumption of this worldwide popular stimulant. However, an increasing number of epidemiological studies have shown an inverse relationship between light-to-moderate alcohol consumption and atherosclerotic disorders. Since diabetes mellitus, especially type 2, is associated with an increased risk for cardiovascular diseases, this raises the question whether diabetic patients in particular may benefit from moderate drinking. Apart from the use of alcohol in established diabetes, some studies report that even at an earlier stage, alcohol may decrease or retard the incidence of type 2 diabetes mellitus.

This review addresses this question by focussing on the data available on the acute and chronic effects of moderate alcohol use in diabetes mellitus.

Acute effects of alcohol on glucose metabolism

The effects of alcohol on carbohydrate metabolism are complex and not all completely understood. Some are directly related to the

influence of alcohol or its metabolic products, acetaldehyde and acetate, but others to an alcohol-induced increase within the liver cell of the NADH/NAD ratio (NAD for nicotinamide adenine dinucleotide). This so-called redox shift is the result of the oxidation of alcohol to acetaldehyde and of acetaldehyde to acetate by dehydrogenases [1]. The consequence of this shift is inhibition of the activity of the citric acid cycle and of β-oxidation of fatty acids, while the conversion of pyruvate to lactate is favoured. The increase of the NADH/NAD ratio and of the lactate/pyruvate ratio contributes to inhibition of gluconeogenesis. After the consumption of 48 g alcohol ($\approx$4 glasses), hepatic gluconeogenesis decreases about 45% [2]. Normally, when a shortage of glucose is impending, glucose will be released from glycogen stores in the liver, but glycogenolysis is also impaired by alcohol. In case of normal glycogen stores, hepatic glucose output decreases 12% after the consumption of a moderate amount of alcohol rarely causing hypoglycaemia. However, when stores are depleted, normal blood glucose levels cannot be maintained and hypoglycaemia may occur. Such depletion is not restricted to malnourished alcoholics, but can also be observed in people on a low-carbohydrate diet and in fasting people missing a meal or two while drinking [3].

Another type of hypoglycaemia described in relation to the use of alcohol is reactive hypoglycaemia. After a carbohydrate-rich meal combined with alcohol, the insulin response to rising blood glucose levels can be exaggerated resulting in hypoglycaemia about 2 to 3 h after the meal [4,5]. Although this suggests some stimulation of pancreatic β-cells by alcohol, studies do not show an increase of insulin or C-peptide after alcohol use, neither in normal volunteers nor in patients with non-insulin-dependent diabetes [6,7]. In an experimental setting in which both glucose and alcohol are given intravenously, alcohol proves to be the preferred fuel at the expense of carbohydrate oxidation, leading to an initial decrease in glucose utilisation and hence higher blood glucose levels and hyperinsulinaemia [8,9]. On the basis of a study in which the effects of two types of beer with the same alcohol content but differing in carbohydrate composition were compared, it has been suggested that the development of alcohol-induced reactive hypoglycaemia is largely determined by the nature of the carbohydrate [10]. While the alcohol component of the drink inhibits glucose disposal, the carbohydrate is responsible for the pace and extent of the blood glucose rise and thus the insulin response.

Short-term effects of alcohol in diabetes

Although in most studies the amount of alcohol is expressed in grams, some studies use glasses. Standard glasses for a specific drink such as beer, wine or spirits contain about 12 g of alcohol.

The effect of alcohol (1 g/kg) consumed with a meal on postprandial glucose homeostasis was studied by Koivisto *et al*. in both type 1 and type 2 diabetic patients [11]. In type 1 diabetic patients, blood glucose and insulin levels were virtually identical compared with the situation when participants were drinking mineral water. In type 2 patients, however, alcohol slightly enhanced meal-induced insulin secretion resulting in lower blood glucose levels the morning after. A similar observation was reported in a French study in which the consumption of two glasses of red wine with lunch was compared with the consumption of mineral water [12]. The insulin-treated diabetic patients showed no difference in insulin requirement while a slight decrease in glucose tolerance was observed in the non-insulin-treated patients. The French researchers later compared the effects of red wine consumed with a meal with those of ethanol and tannic acid in 30 non-insulin-dependent diabetic patients [13]. Significant lower glucose excursions were found 60 and 90 min after the meal with red wine and tannic acid compared to the meal with mineral water while no differences in glucose and insulin excursions were observed between water and ethanol. They concluded that ethanol itself consumed with a meal has no direct effect on plasma glucose or insulin levels. Even the use of 300 mL sweet white wine combined with a light meal or the same amount of dry white wine sweetened with glucose has no impact on glycaemic control [14]. Also, the combination of moderate exercise and moderate alcohol intake does not cause acute hypoglycaemia as has been tested in untrained, overweight type 2 diabetic subjects [15]. However, a significant reduction in non-esterified fatty acids can be observed after alcohol consumption.

The situation seems different when alcohol is consumed without food. An intake of about one litre beer consumed during the evening resulted in significant lower blood glucose levels and more hypoglycaemic episodes between 7 and 11 the next morning in an experiment on type 1 diabetic patients [16]. A comparable observation in type 1 diabetic patients has been described with lower blood glucose levels during the night and protracted hypoglycaemia the next morning after the consumption of 6 units of alcohol at 21.00 h [17]. The last study also analysed the influence of alcohol on hormones of counter-regulation and found no effect on cortisol and glucagon levels but a blunted nocturnal growth hormone response. In an experiment in which hypoglycaemia was induced by insulin in type 2 diabetic patients, alcohol did not modify recovery, although the glucagon response was decreased with normal counter-regulatory responses of catecholamines, cortisol and growth hormone [18]. When only small amounts of alcohol are taken by diet-treated type 2 diabetic patients, the risk of hypoglycaemia is small even if consumed without a meal [19]. However, the concomitant use of sulphonylurea predisposes, especially the elderly fasted patients, to low blood glucose levels [20].

It can, therefore, be concluded that a moderate amount of alcohol taken with a meal hardly has any influence on glucose homeostasis but alcohol consumed without food may be precarious even with intact counter-regulation.

Whether hypoglycaemia plays a role in alcohol related cases of sudden death is unknown.

Chronic moderate alcohol consumption and insulin sensitivity

In general, diabetic patients drinking in excess show poor metabolic control, which improves after withdrawal [21,22]. However, in these patients, dysregulation will not only be related to their alcohol consumption but also to other factors of their lifestyle and social and psychological stress. In contrast, there is now quite some evidence that chronic moderate use of alcohol has no deleterious effect on metabolic control and may even be associated with increased insulin sensitivity. One of the first studies that showed an inverse relationship between alcohol use and fasting and post-load insulin levels was the Kaiser Permanente Women Twins Study [23]. Within the range of light-to-moderate drinking habits, an increment of 12 g of alcohol a day was associated with 8% lower post-glucose insulin levels. Lower fasting insulin levels and increased insulin sensitivity have been reported in population studies from England [24], Italy [25] and France [26] as well as in selected groups of individuals such as young adults [27] and postmenopausal women [28]. Euglycaemic hyperinsulinaemic clamp studies also showed enhanced insulin-mediated glucose uptake in light-to-moderate drinkers compared to non-drinkers [29,30]. Studies including heavy drinkers indicate that the relationship between alcohol use and insulin sensitivity is J-shaped with the lowest fasting insulin levels and the lowest insulin resistance index values in moderate drinkers and higher values in both abstainers and heavy drinkers [24,31,32]. In one of these studies, this relationship could be largely explained by the confounding factors body mass index (BMI) and central adiposity [32].

Because of the close relationship between insulin resistance and type 2 diabetes mellitus, it is of no surprise that a correlation has been found between drinking pattern and the incidence of diabetes mellitus. In the Health Professionals' Follow-up Study, 41 810 US male physicians aged 40 – to 75 and free of diabetes, cardiovascular disease and cancer were followed-up for six years [33]. During that period, 509 men were newly diagnosed with diabetes. After controlling for known risk factors, smokers had a relative risk of diabetes of 1.94 compared with non-smokers while men, who drank 30 to 50 g alcohol daily had a significant reduced risk of diabetes (RR 0.61) compared to abstainers. Data after 12 years did not change the picture with the addition that the greatest protection was observed in daily drinkers and that similar associations were found for all types of alcoholic beverages [34]. The Nurses' Health Study reported on the association between alcohol use and incidence of diabetes in 85 051 healthy women followed-up for two to four years [35]. Compared with non-drinkers, moderately drinking women had a lower risk of diabetes. After adjustment for BMI, family history of diabetes, total energy intake and age, the relative risk of diabetes was 0.8 for women drinking 5 to 15 g per day and 0.6 for those drinking more than 15 g per day. Just as for insulin sensitivity, the relationship between alcohol use and the risk of developing diabetes seems J-shaped with heavy drinkers being at elevated risk [36,37]. Adjustment for BMI decreases the risk in heavy drinkers indicating that the adverse effect of heavy drinking is partially mediated through its effect on body weight [38]. In a Japanese study, heavy drinking was associated with an increased risk of type 2 diabetes in lean men (BMI < 22 kg/m^2) while moderate drinking proved protective in men with a BMI > 22 kg/m^2 [39].

Moderate drinking in diabetes and cardiovascular risks

Moderate drinking is associated with a reduced all-cause mortality, which is largely attributable to a favourable effect on atherosclerotic disorders, especially coronary heart disease (CHD). Mechanisms suggested to be involved are changes in lipid metabolism, haemostatic balance, blood pressure and insulin sensitivity [40]. Alcohol increases high-density lipoprotein (HDL) cholesterol, and influences platelet reactivity. Recently, a suppression of plasma non-esterified fatty acid concentrations during the post-prandial phase has been described when alcohol is used during a mixed meal contributing to the beneficial effects [41]. Alcohol has an acute and profound effect on fibrinolysis, which in light drinkers does not interfere with the circadian rhythm of this system but in heavy drinkers rather promotes atherothrombosis [42].

Chronic heavy drinking is associated with an increase in blood pressure and the prevalence of hypertension is two to three times higher in alcoholics than in moderate consumers [43]. The exact mechanisms involved are not very clear, but apart from a direct cardiac and vascular effect, changes in the sympathetic nervous system, the renin–angiotensin-aldosteron system and cortisol production have been observed. In contrast to moderation, excessive alcohol intake also causes elevated concentrations of triglycerides, mainly by an increase in very-low-density-lipoprotein cholesterol (VLDL) production [44]. Combined with a disturbed clearance of triglycerides, this may result in impressively high levels of triglycerides in type 2 diabetic patients.

Light drinking lowers blood pressure and improves insulin sensitivity. The question is, however, does the type 2 diabetic patient profit as much from moderate drinking as the non-diabetic patient?

In a sub-analysis of the Physicians' Health Study, similar reductions in CHD deaths were observed among non-diabetic and diabetic men [45] confirming the favourable outcome on CHD mortality rates found in another study from the United States [46]. Among men with diabetes at baseline, moderate but daily drinkers had a relative risk of 0.42 compared to non-drinkers.

Within the group of health professionals, 2419 men reported a diagnosis of diabetes at age 30 or older. During the 11 411 person-years of follow-up after this diagnosis, the relative risk of CHD, including fatal and non-fatal myocardial infarctions, was 0.59 for men having >two drinks/day compared to non-drinkers [47]. Comparable risk reductions in CHD (RR 0.48) were observed in moderately drinking diabetic women in the Nurses' Health Study and in a Swiss population of type 2 diabetic patients [48,49]. When using aortic pulse wave velocity as a surrogate marker for atherosclerosis in diabetic patients, preventive effects on atherosclerosis were only seen in light-drinking persons but not in heavy drinkers, again suggesting a J-shaped relationship [50].

Conclusions

Alcohol has acute effects on carbohydrate metabolism. Combined with a meal including carbohydrates, it is the preferred fuel, initially leading to an increase in blood glucose and hence an insulin response. In some cases, probably depending on the nature of the carbohydrate and individual characteristics, this can lead to reactive hypoglycaemia. However, in most cases, no change in glycaemic control will be noticed. When alcohol is ingested without food and glycogen stores are depleted, there is a chance of developing hypoglycaemia since alcohol inhibits gluconeogenesis.

Moderate drinking improves insulin sensitivity, and this may well be one of the mechanisms involved in the protective effect of alcohol with regard to atherosclerotic disorders. Diabetic subjects benefit from this effect as much as non-diabetic subjects. The mechanisms by which alcohol influences insulin sensitivity are unknown. Moderate alcohol use also has a protective effect against the development of type 2 diabetes mellitus, and it can be speculated that this is based on improvement in insulin sensitivity.

It can be concluded that there are no arguments to deny a diabetic patient the pleasure of an alcoholic drink. With moderate and sensible use, risks of disturbances in glycaemic control as well as in blood pressure and weight are limited.

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