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Alcohol consumption and insulin resistance in young adults

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Abstract

Background Alcohol may have a cardioprotective effect. One possible mechanism is by reducing insulin resistance, a known cardiovascular risk factor**.** The aim of this study was to assess the relationship between alcohol consumption, insulin resistance and other parameters determining glucose tolerance in 154 young men and women.

Subjects and methods Subjects completed a questionnaire documenting weekly alcohol consumption. Insulin sensitivity and glucose tolerance were measured using the intravenous glucose tolerance test with minimal model analysis. Height, weight, usual level of exercise, smoking habits and socio-economic status were also recorded.

Results Insulin sensitivity correlated inversely with body mass index ($r = -0{\cdot}529$, $P < 0{\cdot}001$) but not with level of physical fitness. Women were significantly less insulin sensitive than men (4·19 and 5·63 10^4 min^{-1} $pmol^{-1}$ L^{-1}, respectively; $P < 0{\cdot}001$). Insulin sensitivity correlated positively with alcohol consumption and this trend remained significant allowing for body mass index and gender ($\beta = 0{\cdot}17$, $P < 0{\cdot}014$). First-phase insulin secretion showed a weak but non-significant trend in the opposite direction. Fasting glucose, fasting insulin and glucose tolerance showed no relationships with alcohol consumption.

Conclusion These data suggest a close relationship between alcohol consumption and insulin resistance in young adults. Regular alcohol consumption is associated with decreased insulin resistance and this may partly explain the cardioprotective effect of alcohol.

Keywords Alcohol, insulin sensitivity, minimal model.
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Introduction

Modest amounts of alcohol appear to have a beneficial effect on reducing the risk of cardiovascular disease [1,2]. The effect of higher doses of alcohol is less clear, but the consensus of opinion is that mortality increases in this group, producing a U-shaped curve. Several investigators have noted the strikingly low rate of mortality from ischaemic heart disease in France compared with other Westernized countries [3]. France has the highest alcohol intake and the lowest rate of coronary heart disease mortality of any of the countries studied [4]. While some evidence suggests that non-alcoholic constituents of wine may be of cardiovascular benefit [5], other studies have suggested that alcohol consumption *per se* may be associated with a reduction in death from ischaemic heart disease [6].

Resistance to the metabolic actions of insulin is commonly associated with type 2 diabetes, but insulin resistance plays an important role in the pathogenesis of a number of other disease processes, including hypertension, dyslipidaemia and cardiovascular disease. The insulin resistance syndrome (Syndrome X) is a term used to describe the association of glucose intolerance, hypertension, dyslipidaemia, central obesity, hyperinsulinaemia and insulin resistance [7], and is in itself a risk factor for cardiovascular disease. The effect of alcohol on insulin resistance is

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complex but recent studies have suggested that moderate alcohol consumption is associated with reduced fasting or stimulated insulin levels [8–10]. From this it is inferred that alcohol consumption is associated with decreased insulin resistance. We therefore sought to explore the relationship between regular alcohol consumption and insulin resistance measures, using the intravenous glucose tolerance test with minimal model analysis, in a group of young men and women within a narrow age range.

Subjects and methods

This study sample was drawn from an existing cohort of young adults known as the Adelaide Children's Hospital Family Heart Study, Adelaide, Australia [11]. The subjects represent a subset of a previous epidemiological study to determine the relationship between foetal growth and glucose tolerance [12]. Computer-generated random samples were drawn for each sex to obtain a subset of approximately 150 subjects, which a priori power calculation indicated would be sufficient for the present analyses. Intravenous glucose tolerance tests (IVGTT) were performed on 163 subjects and data on alcohol consumption were available on 154 of these subjects. The study was approved by the Human Ethics Committee of the Women's and Children's Hospital, Adelaide. Informed written consent was obtained from each of the subjects. Subjects were requested to consume more than 200 g day^{-1} carbohydrate for 3 days. They were then asked to fast overnight and to refrain from smoking and drinking alcohol overnight before attending the department between 08:00 and 09:00. Exclusion factors included current diabetes or other current illness. Medical history and smoking habits were recorded. Area of residence was used to define current socioeconomic status. Alcohol consumption was estimated using a supervised questionnaire. Subjects were asked two questions: How often do you usually drink alcohol? On a day when you drink alcohol, how many drinks do you usually have? Alcohol consumption was converted into the total number of units (1 unit = 8 g ethanol) and a composite variable was then created reflecting how much alcohol was consumed per week. Subjects were divided into groups according to their total alcohol units per week: group 1 = no alcohol; group 2 = less than 8 units $week^{-1}$; group 3 = 8–12 units $week^{-1}$; group 4 = 12–20 units $week^{-1}$; group 5 = greater than 20 units $week^{-1}$. Subjects were categorized as either not doing exercise, doing less than three sessions of aerobic exercise, or three or more sessions per week. Measurements of the subjects' weight using an electronic scale (A.N.D. Weighing Equipment Ltd, Adelaide, Australia) and height using a stadiometer (Holtain Ltd, Crymych, Dyfed, UK), were used to calculate the body mass index (BMI), defined as weight divided by the height squared.

Subjects then underwent a 15-point frequently sampled IVGTT. Each subject received a glucose dose of 0·5 g kg^{-1} body weight as 50% w/v dextrose, via an antecubital vein, over 3 min. Blood was sampled from the opposite arm at the following time points: − 30, − 5, 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120 and 180 min. Plasma samples were analysed for glucose by the hexokinase method and insulin by two-site immunometric assays with alkaline phosphatase as label [13]. The within-assay coefficient of variation of the insulin measurements was less than 10%.

Data analysis

Basal insulin and basal glucose were calculated as the mean of the two fasting samples taken prior to the IVGTT. The area under the insulin concentration profile was analysed using the trapezoidal rule. The first-phase insulin response to glucose (AIRglucose) was calculated as the increment above the fasting insulin level in area under the IVGTT insulin concentration profile from 0 to 10 min. The intravenous glucose tolerance index (Kg) was used as the measure of overall glucose tolerance. This is a measure of the rate of decay of glucose following the glucose bolus. Kg was determined as the least-square slope of the log of the glucose concentrations between 20 and 60 min following the glucose bolus. Insulin sensitivity (Si) and glucose effectiveness (Sg) were determined from the IVGTT glucose and insulin profiles using the minimal model of glucose disappearance [14], with programs written in Fortran 77 run on a PDP-11/83 microcomputer. The IVGTT protocol employed in the present study differs from that traditionally used with mathematical modelling analysis in two respects. First, following glucose injection, a reduced sample schedule of 15 rather than 26 samples is followed, the reduced schedule being more useful for relatively large studies. Secondly, a glucose load of 0·5 g kg^{-1} rather than 0·3 g kg^{-1} is employed, which provides for a sufficient endogenous insulin response in non-diabetic volunteers without recourse to additional augmentation of pancreatic insulin secretion. The validity and effectiveness of the IVGTT protocol employed in the present study, with regard to measurement of insulin sensitivity (Si), is apparent in the high rate of model identification and good correlation with measures of insulin sensitivity derived from the euglycaemic clamp ($r = 0{\cdot}92$) that it provides [15,16]. Net insulin-dependent glucose elimination depends both on insulin sensitivity and the accompanying plasma insulin concentration, the latter being largely dependent on beta cell function. The relationship between these variables is hyperbolic and may be expressed as Si × AIRglucose = a constant [17,18]. The constant may then be taken as an index of net insulin-dependent glucose elimination. This constant was calculated for each individual. The sum of Sg + (Si × AIRglucose) was also calculated as a measure of the net effectiveness of glucose elimination. Kg is the direct measure of overall glucose disposal and correlates highly significantly ($r = 0{\cdot}81$, $P < 0{\cdot}001$) with the sum of Sg + (Si × AIRglucose).

Table 1 Baseline data on the subjects studied. Mean (SD)

	Men	Women	*P* for difference
n	81	73	
Age (years)	20·9 (0·29)	20·9 (0·28)	0·602
Body mass index (kg m^{-2})	24·0 (4·1)	23·3 (4·7)	0·310
Exercise level score (0–2)	1·24 (0·84)	1·01 (0·89)	0·116
Alcohol consumption score (0–5)	1·5 (1·1)	0·96 (0·67)	0·001
Fasting glucose (mmol L^{-1})	5·61 (0·32)	5·31 (0·31)	0·000
Fasting insulin (pmol L^{-1})	41·6 (25·0)	53·9 (33·6)	0·001
Glucose tolerance, Kg (10^{-2} min^{-1})	1·7 (0·41)	1·8 (0·51)	0·172
Insulin sensitivity, Si (10^{-4} min^{-1} $pmol^{-1}$ L^{-1})	5·63 (3·09)	4·19 (2·56)	0·001
Insulin secretion, AIRglucose (pmol L^{-1} min^{-1})	2984 (2620)	3367 (2241)	0·061
Glucose effectiveness, Sg (10^{-2} min^{-1}	1·77 (0·91)	1·91 (0·92)	0·377

Statistical methods

Where necessary, the data was transformed to normality using logarithms (AIRglucose) or square-root transformation (Si and Sg), and the means are therefore presented as the back-transformed means values. Independent sample *t*-tests were used to compare means in Table 1. We analysed the data using multiple linear regression; all analyses were undertaken using continuous variables.

Results

Table 1 compares baseline variables for the 81 men and 73 women. There was no significant difference in age, BMI or degree of physical fitness between the men and women. Women drank significantly less alcohol than the men. Women had lower fasting glucose than the men. Women were less insulin sensitive, and in keeping with this had higher fasting insulin levels. There was a weak but non-significant trend towards a higher first-phase insulin response in the women. There was no significant gender difference in glucose tolerance (Kg).

Si correlated inversely with BMI ($r = -0{\cdot}529$, $P < 0{\cdot}001$) but not with level of physical fitness ($r = 0{\cdot}053$, $P < 0{\cdot}518$). AIRglucose correlated positively with BMI ($r = 0{\cdot}486$, $P < 0{\cdot}001$). Fasting glucose, Kg and Sg did not show associations with BMI. Alcohol consumption showed a linear relationship with insulin sensitivity in this relatively young group of subjects. Si increased with increasing levels of weekly alcohol consumption (Fig. 1). In multiple regression analysis with Si as the dependent variable, the effects of alcohol consumption ($P = 0{\cdot}015$), gender ($P = 0{\cdot}003$) and BMI ($P = 0{\cdot}001$) were each statistically significant (Table 2a). AIRglucose showed a weak but non-significant trend with insulin secretion, AIRglucose falling as alcohol consumption increased (Fig. 2 and Table 2b). Fasting glucose and Kg did not correlate with alcohol consumption. The ability of glucose to promote its own disposal, Sg, showed no relationship with alcohol consumption. In other multiple regression analyses the influence of alcohol consumption on Si was independent of current smoking habits, level of physical fitness or current socio-economic status.

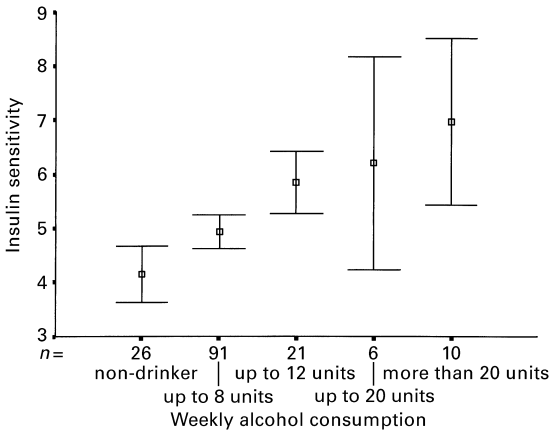

Figure 1 Mean (± SEM) insulin sensitivity (10^4 min^{-1} $pmol^{-1}$ L^{-1}) according to weekly alcohol consumption (units) for the 154 men and women.

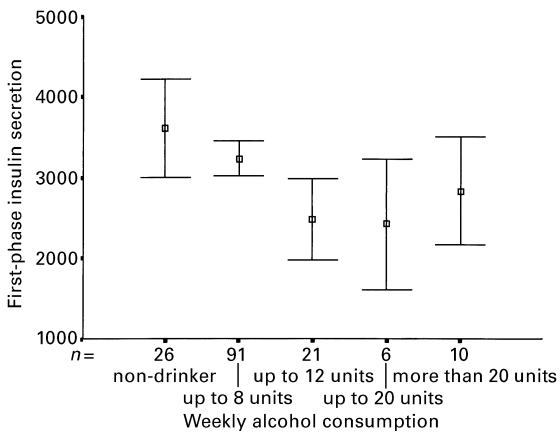

Figure 2 Mean (± SEM) first-phase insulin secretion (pmol L^{-1} min^{-1}) according to weekly alcohol consumption (units) for the 154 men and women.

Table 2 Multiple linear regression model for variables predicting insulin sensitivity (a) and first-phase insulin secretion (b) in the 154 men and women. (β = estimated regression coefficient)

Variable	β	95% confidence interval	*P*-value
Insulin sensitivity*			
Body mass index (kg m^{-2})	−0·08	−0·11 to −0·06	0·001
Gender	−0·28	−0·46 to −0·10	0·003
Alcohol consumption, group(0–5	0·11	0·02–0·21	0·015
Insulin secretion†			
Body mass index (kg m^{-2})	0·03	0·02–0·04	0·001
Gender	0·08	0·01–0·17	0·046
Alcohol consumption, group 0–5	−0·04	−0·08–0·01	0·088

*Insulin sensitivity is square root transformed in this regression.

†Insulin secretion is natural log transformed in this regression.

Table 3 shows the combined effect of alcohol consumption and BMI on Si for the men and women studied. With increasing BMI Si fell, but with increasing alcohol consumption Si increased, thus those subjects with a low BMI but a high alcohol consumption showed the highest level of insulin sensitivity, and subjects with a high BMI but low alcohol consumption showed the lowest level of insulin sensitivity.

Discussion

We have shown that increasing alcohol consumption is associated with increasing insulin sensitivity in a group of young men and women. First-phase insulin response to glucose showed the opposite trend with alcohol consumption; insulin secretion tended to fall with increasing alcohol consumption, although this trend was non-significant. However, there was no relationship between alcohol consumption and overall glucose tolerance. The effect was not due to confounding relationships between alcohol consumption and degree of physical fitness, gender, measures of obesity or smoking. Neither was it influenced by the socio-economic status of the subjects studied.

A major problem of studies dealing with self-reported alcohol consumption is that of under-reporting and inaccuracy. However, the study was primarily designed to look at the relationship between birth size and glucose metabolism. This makes it less likely that selection bias occurred from heavy drinkers not participating.

The effects of alcohol on insulin resistance are complex, with evidence suggesting that the acute and chronic effects of alcohol are quite different. Studies using the euglycaemic clamp technique have shown that the acute administration of alcohol decreases insulin-mediated glucose disposal [19]. In contrast, three recent epidemiological studies of chronic alcohol consumption have shown that moderate alcohol drinkers have the lowest indices of insulin resistance [8–10]. In these studies fasting insulin levels or insulin levels following an oral glucose challenge were taken as a surrogate of insulin resistance, although this does not allow for a direct effect of alcohol on insulin release [20,21]. The influence of alcohol on insulin resistance was not restricted to a particular type of alcohol. Two of the three studies showed a U-shaped relationship between alcohol consumption and insulin resistance, mirroring the effect on cardiovascular mortality. The third showed a linear relationship. Our finding of a linear relationship between alcohol consumption and insulin sensitivity may be a reflection of the relatively young age of the subjects studied. The period over which high levels of alcohol are being consumed may have an influence on insulin resistance. The study subjects are likely to have been drinking alcohol for a relatively short period of time. A second factor may be the level of alcohol consumption. Few subjects in this study consumed large amounts of alcohol on a regular basis, and it is this group that seems to be at risk of increasing insulin resistance. A case control study comparing subjects consuming moderate amounts of alcohol with non-drinkers using the modified insulin tolerance test supports our findings, with increased insulin-mediated glucose disposal in the drinkers [22].

The biological mechanisms underlying the association between alcohol consumption and insulin sensitivity are not known. Suggested mechanisms include alterations in hepatic glucose metabolism with decreased hepatic gluconeogenesis [23]. It is also possible that alcohol mediates its effect by altering the action of the counter-regulatory hormones. A number of studies have shown acute and

Table 3 The combined effect of alcohol consumption and body mass index on insulin sensitivity on men and women aged 20 years. Number of subjects in parentheses

	Body mass index (kg m^{-2})			
Alcohol consumption	−22	22–26	>26	Total
0 units week^{-1}	5·77 (10)	4·34 (9)	1·54 (7)	4·14 (26)
0–8 units week^{-1}	5·62 (43)	4·17 (23)	3·66 (24)	4·73 (90)
>8 units week^{-1}	7·55 (17)	5·38 (12)	4·11 (9)	6·05 (38)
Total	6·10 (70)	4·54 (44)	3·39 (40)	4·96 (154)

Standard deviation for Si = 2·9.

chronic effects of alcohol on growth hormone [24], glucocorticoid [25,26] and catecholamine [27] production. While these hormonal axes have been studied in the situation of acute alcohol ingestion or in pathological states of alcohol excess, little is known about the influence of moderate alcohol consumption.

A further possible mechanism is by a direct effect of alcohol on the beta cell. Studies of the acute effects of alcohol on insulin secretion have given conflicting results, some showing that acute alcohol administration has a direct stimulatory effect on insulin secretion [20] and others showing a non-significant increase in insulin release [28].

In conclusion, alcohol consumption is associated with increased insulin sensitivity and these patterns are already established by the age of 20 years. As insulin resistance is a known cardiovascular risk factor this has important public health implications. The underlying mechanisms require further study.

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