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Adverse Effects on Risk of Ischaemic Heart Disease of Adding Sugar to Hot Beverages in Hypertensives Using Diuretics

A Six Year Follow-up in the Copenhagen Male Study

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Non insulin dependent diabetes mellitus (NIDDM) and essential hypertension (EH) are two of several manifestations of the insulin resistance syndrome. Although subjects with NIDDM and subjects with EH share a common defect in carbohydrate metabolism, only diabetics are advised to avoid sugar. We tested the theory that an adverse effect of diuretics treatment in men with EH with respect to risk of ischaemic heart disease (IHD) would depend on the intake of dietary sugar using sugar in hot beverages as a marker. The cohort consisted of 2,899 men from the Copenhagen Male Study aged 53-74 years (mean 63) who were without overt cardiovascular disease. Potential confounders were: age, alcohol, smoking, physical activity, body mass index, blood pressure, fasting lipids, cotinine, NIDDM, and social class. A total of 340 men took antihypertensives; 211 took diuretics (95% thiazides and related agents), and 129 used other antihypertensives. During 6 years, 179 men (6.2%) had a first IHD event. Among the 340 men taking antihypertensives, the incidence rate was 11%. Diuretics use was associated with a high risk of IHD in hypertensive men with a relatively high intake of dietary sugar; the cumulative incidence rate was 22%; in diuretics treated men with a low intake of sugar, the rate was 7%. After controlling for potential confounders, relative risk (95% c.i.) was 3.1 (1.3-7.6), $p = 0.01$. Among the 129 men who took other forms of antihypertensive drugs, the IHD incidence rate was 8%, and independent of the intake of sugar. The results indicate that the risk of IHD in hypertensives using diuretics is associated with intake of dietary sugar, which may explain at least some of the discouraging effects of antihypertensive agents on the reduction of risk of IHD. *Key words: diuretics, epidemiology, hypertension, insulin resistance syndrome, ischaemic heart disease, risk, sugar.*

INTRODUCTION

Non insulin dependent diabetes mellitus (NIDDM) and essential hypertension are two of several manifestations of Syndrome X [1], also known as Reaven's Syndrome, the Athero-Thrombogenic Syndrome, or the Plurimetabolic Syndrome. Other major manifestations are: raised concentration of serum triglycerides (TG), lowered concentration of serum high density lipoprotein cholesterol (HDL), obesity, and atherosclerotic disease including ischaemic heart disease (IHD). These pathophysiological signs and diseases have insulin resistance as a common characteristic. The syndrome indicates that a disorder in carbohydrate metabolism is associated with an increased risk of IHD.

It is well known that diabetics have an increased risk of cardiovascular disease and that they should avoid dietary sugar. A study by Warram [2] of hypertensive diabetics showed that those treated with diuretics had an approximately fourfold increased risk of cardiovascular mortality compared with untreated hypertensives. Diuretics are *in themselves* diabetogenic [3] and the results of the study of Warram suggested that when the inherent carbohydrate metabolism disorder in diabetics is further compromised, the adverse effects on the cardiovascular system are increased.

Antihypertensive agents in the reduction of risk of ischaemic heart disease (IHD) have been discouraging, i.e. the benefits of reducing blood pressure have been less than expected. It has been hypothesized that adverse metabolic effects of treatment might account for this [4]. Although they share a disorder in carbohydrate metabolism, in contrast to diabetics, patients with essential hypertension are not generally told to give up their intake of dietary sugar. However, the joint effect of essential hypertension, diuretics intake, and use of sugar might have negative effects on the cardiovascular system. We tested this hypothesis in a prospective study of middle-aged and elderly men.

MATERIALS AND METHODS

The Copenhagen Male Study was set up in 1970 as a prospective cardiovascular cohort study of 5,249 men from 14 randomly selected private or public companies [5,6] (mean age of 48 years) (range 40–59).

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Fifteen years later, in 1985-86, a new baseline was established which was used for the present study. All survivors from the 1970 study were traced by means of the Danish Central Population Register. Between June, 1985, and June, 1986, all survivors (except 34 emigrants) from the original cohort were invited to take part in this study. A total of 3,387 (75%) men gave their informed consent; their mean age was 63 years (range 53–74).

The 1985-86 study took place at Glostrup Hospital, University of Copenhagen. Each subject was interviewed about a previously completed questionnaire and examined, with measurements of height, weight and blood pressure; a venous blood sample was taken after the subject had fasted for at least 12 h for measurements of serum selenium, lipid and cotinine concentrations, and a urine sample was used for the determination of glucose. According to a system by Svalastoga [7], later adjusted, the men were classified into 5 social classes, based on level of education and job profile [8].

The men reported if they used sugar in their tea or coffee. Men who reported use of sugar in their tea or coffee are referred to as 'sugar users'. During the interview the men were queried about their use of antihypertensive medication, and use of other forms of medicine. When they reported use of diuretics it almost invariably (95%) meant use of thiazides and related agents. They reported when treatment due to hypertension had been initiated, and whether they had ever changed from one form of antihypertensive medication to another. They reported whether they had diabetes and which treatment they were given. Total weekly alcohol consumption was calculated from questionnaire items about average alcohol consumption on weekdays and at weekends. Intakes of beer, wine and spirits were reported separately. Most of the alcohol consumed was in beer, and one drink corresponded to 10–12 g ethanol. The men classified themselves as never smokers, previous smokers, or current smokers. Current tobacco smoking was calculated from information about the number of cigarettes, cheroots, cigars, or the weight of pipe tobacco smoked daily. One cigarette was taken as equivalent to 1 g tobacco, 1 cheroot as 3 g, and 1 cigar as 4 g tobacco. As previously estimated by means of measurements of serum cotinine, the validity of tobacco smoking was high[9]. As regards leisure time physical activity, the men classified themselves as either physically active less than 4 h/week, or physically more active.

Blood pressure was measured on the right arm with the subject seated using a manometer developed by London School of Hygiene [9]. Hypertension was defined as receiving antihypertensive treatment or having a systolic blood pressure $\geq$ 150 mmHg and a diastolic blood pressure $\geq$ 100 mmHg. Body mass index (BMI) was calculated as weight in kg/height in sqm. Serum cholesterol, triglycerides (TG) and HDL cholesterol were analyzed using standardized methods [10]. LDL was calculated according to the Fridewald formula [11]. Urine content of glucose was investigated by stix.

Excluded from the prospective study were men who at baseline had a history of acute myocardial infarction, angina pectoris, or stroke or who had intermittent claudication. For all who reported admission to hospital because of acute myocardial infarction before the start of the study, we checked hospital records. The diagnosis was accepted if at least two of the following symptoms/signs were recorded: retrosternal pain lasting more than 20 min, typical, serial electrocardiographic changes in more than two electrocardiograms, acute increase of relevant serum enzymes (alanine aminotransferase, lactate dehydrogenase or creatinine phosphokinase MB). Information on angina pectoris, stroke and intermittent claudication was established from the questionnaire. A total of 342 men (10.1%) were excluded due to cardiovascular diseases or symptoms, 2,923 men, corresponding to 96% of men without overt cardiovascular disease, had reported whether they received treatment due to hypertension or not. Among these, 340 reported that they received antihypertensive medicine, and which kind of medication they were given. Some 211 men took diuretics, either alone, $n = 103$, or in combination with other drugs, predominantly beta-blockers, $n = 108$, 129 men took other forms of antihypertensive medicine, predominantly beta-blockers. The control group, referred to as 'normotensives', consisted of men who reported that they did not take antihypertensive medication and who were not hypertensive according to the blood pressure criteria applied in this study. Twenty men with untreated hypertension were excluded from the incidence study. A total of 2,899 men were regarded as eligible for the incidence study.

In 1993, a register follow-up was carried out on morbidity and mortality between 1985–1986 and December 31, 1991. All men who had taken part in the 1985-1986 study were traced by means of the Danish Central Person Register. Information on hospital admissions for non-fatal acute myocardial infarction and death certificate diagnoses within the follow-up period were obtained from the National Health Service register and from the Danish Institute of Clinical Epidemiology. We used the diagnoses from registers. IHD diagnoses accepted were codes 410-414, International Classification of Diseases, 8th revision.

To estimate which cardiovascular risk factors separated IHD-cases from non-cases, and those who died from all causes from survivors, stepwise logistic regression analyses were applied using the maximum likehood ratio method. Logistic regression analyses were performed with interaction terms for the intake of sugar in hot beverages (coded 1 = yes, 0 = no) and hypertension treatment with diuretics (coded 1 = yes, 0 = no) to examine if interactive effects significantly improved the model fit provided by main effects of the single variables [12]. For transparency, logistic regression analyses were performed including a four group variable containing 1) normotensives not taking sugar in hot beverages, 2) normotensives taking sugar, 3) hypertensives treated with diuretics not taking sugar, and 4) hypertensives treated with diuretics and also taking sugar in their hot beverages. In these analyses men receiving hypertension treatment with drugs other than diuretics were excluded.

All basic analyses, Student's *t*-tests and Chi-squared analyses, and the logistic regression analyses, were performed using the SPSSPC+ statistical software, version 3.1 [13,14]. For all analyses a probability-value of less than or equal to 0.05 was taken as significant.

The study has been approved by The Ethics Committee for Medical Research in the County of Copenhagen.

RESULTS

During the follow-up period 271 men (9.3%) died from all causes, 179 men (6.2%) had a first IHD event, 25% being fatal.

Table I presents characteristics of treated hypertensives and normotensives not taking diuretics. A number of cardiovascular risk factors significantly separated hypertensives from normotensives. Levels of HDL were lower, levels of TG higher. The proportion of men who took sugar in hot beverages was smaller, and also the proportion of smokers was smaller. Hypertensives were also less physically active in their leisure time and weighed 2.4 BMI values more than normotensives, corresponding to 7-8 kg. Both systolic BP and diastolic BP were higher, the proportion of NIDDM was higher, and hypertensives were a little older.

Table II presents characteristics of hypertensives treated with diuretics and hypertensives treated with other drugs. Only blood pressure levels were significantly different between groups with 3 mmHg lower systolic BP and also 3 mm lower diastolic BP in diuretics users.

Table III shows which factors were most strongly associated with risk of IHD during the 6-year follow-up period after multivariate adjustment for the interrelationship of variables in a forward stepwise logistic model. The strongest predictive factor was the interaction of adding sugar to hot beverages and being a hypertensive taking diuretics, alone or in combination with other drugs. Also getting older, a high LDL, a high TG, use of tobacco, and a relatively low consumption of alcohol, were significantly associated with IHD risk.

Table IV shows absolute and relative risk of IHD and ACM, referencing the group of hypertensives treated with diuretics but not using sugar. In the analyses, hypertensives given drugs other than diuretics were excluded. It appears that normotensive, whether they used sugar or not, had a slightly and not significantly lower risk of IHD as compared with the group of hypertensives taking diuretics but no sugar. Among hypertensives taking diuretics and using sugar, the risk of IHD was statistically significantly, more than threefold, increased, compared with those not using sugar. With respect to ACM, the risk was slightly but not significantly higher in hypertensives taking diuretics and sugar compared with those not taking sugar.

Table V shows which factors were most strongly associated with risk of ACM during the 6-year follow-up period after multivariate adjustment for the interrelationship of variables in a forward stepwise logistic model. Including the same potentially predictive factors as in Table III, significant predictors were: getting older, a high HDL, use of tobacco, low social class, and TG. Univariately, TG was not different between those who died and others, but multivariately significant due to its relationship with HDL.

Among the 129 men receiving antihypertensive medication but no diuretics, the IHD incidence rate of IHD was 8%, and there was no difference between those who used sugar and those who did not (not shown).

DISCUSSION

The original observation of this study was that the combined use of diuretics and dietary sugar was a strong risk factor for ischaemic heart disease among middle-aged and elderly hypertensive men.

We are well aware that our exposure data with respect to use of dietary sugar are indeed less than optimal, and that using a question on use of sugar in hot beverages as a marker of dietary sugar might be problematic. In a recent study on refined-sugar intake and risk of colorectal cancer, La Vecchia et al. [15] also used a question on sugar intake in hot beverages. They stated that 'It is difficult to obtain precise estimates of

Table I. *Serum lipid, lifestyle, clinical/paraclinical, and sociodemographic characteristics of treated hypertensives and normotensives not using thiazide diuretics*
Values presented are mean (SD) or frequency in percent.

	Hypertensives ($n = 3400$)	Normotensives ($n = 2559$)
Serum lipids		
LDL, mmol/l	4.36(1.02)	4.47(1.01)
HDL, mmol/l	1.27(0.34)	1.37(0.35)***
Triglycerides, mmol/l	2.02(1.45)	1.50(1.02)***
Lifestyle factors		
Uses sugar in hot beverages, %	28.5	36.8**
Alcohol, beverage/week	19.5(16.0)	17.6(13.8)*
Smokers, %	38.5	54.1***
Tobacco, grs/d by smokers	17.0(8.7)	17.6(13.8)
Physical activity < 4 h/week, %	55	46**
Clinical/paraclinical parameters		
BMI. kg/m^2	27.8(4.3)	25.4(3.1)***
Systolic BP, mm Hg	132(16)	120(16)***
Diastolic BP, mm Hg	81(11)	71(11)***
Lewis phenotype Le(a-b-), %	12.7	8.9*
NIDDM, %	3.9	1.6**
Other characteristics		
Low social class, %	54	50
Age, years	63.7(5.2)	62.7(5.1)***

p-value of Student's *t*-test or Chi-squared analysis.

Table II *Serum lipid, lifestyle, clinical/paraclinical, and sociodemographic characteristics of hypertensives treated with diuretics (alone or in combination) and hypertensives treated with other drugs*
Values presented are mean (SD) or frequency in percent.

	Diuretics ($n = 211$)	Other drugs ($n = 129$)
Serum lipids		
LDL, mmol/l	4.37(1.02)	4.33(1.02)
HDL, mmol/l	1.28(0.34)	1.27(0.33)
Triglycerides, mmol/l	2.04(1.47)	1.98(1.41)
Lifestyle factors		
Uses sugar in hot beverages, %	29	27
Alcohol, beverage/week	19.6(15.8)	19.3(16.4)
Smokers, %	36.1	42.5
Tobacco, grs/d by smokers	17.5(8.3)	16.3(9.2)
Physical activity < 4 H/week, %	52	62
Clinical/paraclinical parameters		
BMI, kg/m^2	28.0(3.8)	27.4(5.0)
Systolic BP, mm Hg	131(15)	134(17)*
Diastolic BP, mm Hg	79(10)	82(13)*
Lewis phenotype Le(a-b-), %	11.9	14.0
NIDDM, %		
Other characteristics		
Low social class, %	53	55
Age, years	64.1(5.2)	63.1(5.3)

p-value of Student's *t*-test or Chi-squared analysis.
*: $p < 0.05$

Table III. *Characteristics of men who had a first IHD event during the 6-year follow-up and in others*
Values presented are mean (SD) or frequency in percent. Variables not significant after multivariable adjustment: HDL, use of sugar in hot beverages, hypertension treatment with diuretics, hypertension treatment with drugs other than diuretics, leisure time physical activity, BMI, systolic BP, diastolic BP, Lewis phenotypes (Le(a-b-) vs. rest), NIDDM, and social class.

	IHD event ($n = 179$)	No IHD event ($n = 2720$)	p
(Sugar diuretics)[a]	0.12	< 0.001	
Age, years	64.1(5.5)	62.7(5.1)	< 0.01
LDL, mmol/l	4.68(1.01)	4.44(1.02)	< 0.01
TG, mmol/l	1.71(0.81)	1.53(0.97)	< 0.05
Tobacco, g/d	10.7(16.7)	8.8(10.9)	< 0.05
Alcohol, beverages/ week	15.5(14.3)	17.9(14.1)	< 0.05

[a]Interaction term between use of sugar in hot beverages and hypertension treatment with diuretics. The value presented is the partial regression coefficient.
The *P*-value shows the probability outcome after a forward stepwise multiple logistic regression analysis with the maximum likelihood ratio method. Variables are presented by order of entry into the model. A priori probability to enter the model was $p < 0.05$.

taste for sugar and the pattern of sugar intake, and our information on sugar added to hot beverages is only a crude approximation of overall sugar intake and its time pattern'. We agree with this. Nonetheless, La Vecchia et al. found strong and consistent associations between sugar intake and risk of colorectal cancer. If the associations found in our study are causal, that a high dietary sugar consumption in combination with use of thiazide diuretics is a highly dangerous interaction associated with an excess risk of IHD, due to the widespread use of diuretics as well as dietary sugar, public health implications may be substantial. More studies are evidently needed and the results of the present study should therefore be regarded as hypothesis generating. Furthermore, from the National Food Agency of Denmark we have received the information that, based on data on dietary habits collected in a contemporary study (1985) among a random sample of the adult Danish population ($n = 2,242$), the correlation between sugar use in hot beverages and total daily intake of refined sugars was quite high, Pearson's $r = 0.56$. Accordingly, sugar intake in hot beverages seems to be at least a reasonable marker of dietary sugar intake.

Our data did not allow a conventional analysis of dose-effect. However, it is unlikely that lack of precision in these respects could explain the interplay of diuretics use, intake of sugar, and risk of IHD, rather the genuine interplay of these factors may have been stronger than it was possible to demonstrate in this study.

The finding is interesting in the light of the observations of Warram, that diuretics treatment in diabetics was associated with an almost fourfold increased risk in cardiovascular mortality [2]. The findings of the present study and that of Warram indicate that, if diuretics are given to patients with disturbed carbohydrate metabolism, the risk of premature IHD may be substantially increased. Carlsen has shown [16] in a short-term trial that treatment with low doses of bendrofluazide, < 2.5 mg/d, in mild to moderate hypertension have minimal influence on various biochemical variables associated with the insulin resistance syndrome: blood glucose and triglyceride concentration. Doses of 1.25 mg/d had no influence on these variables. It can be speculated that if the insulin sensitivity is not affected by the diuretics use, perhaps sugar intake would not increase the risk of IHD in low-dose diuretics treated patients. In the present study, sugar users

Table IV. *Absolute and relative risk of IHD and all causes of mortality (ACM) according to hypertension, use of diuretics and sugar*
Relative risk estimates were adjusted for relevant potential confounders (see Table I).

	Normotensives, no sugar ($n = 1617$)	Normotensives, sugar ($n = 942$)	Hypertensives diuretics, no sugar[a] ($n = 149$)	Hypertensives diuretics, sugar ($n = 62$)
Absolute risk				
IHD, % (n)	5.0(81)	6.7(63)	7.4(11)	22.6(14)
ACM, % (n)	8.1(131)	10.3(97)	12.1(18)	22.6(14)
Relative risk 95% c.i.				
IHD	0.7(0.4–1.3)	0.9(0.4–1.7)	1	3.1(1.3–7.6)**
ACM	0.7(0.4–1.3)	0.8(0.5–1.6)	1	1.7(0.7–3.9)

[a] reference category in relative risk analysis.
** $p = 0.01$.

Table V. *Characteristics of men who died from all causes of mortality (ACM) during the 6-year follow-up and in others*
Values presented are mean (SD) or frequency in percent. Variables not significant after multivariable adjustment: LDL, interaction term between use of sugar in hot beverages and hypertension treatment with diuretics, use of sugar in hot beverages, hypertension treatment with diuretics, hypertension treatment with drugs other than diuretics, leisure time physical activity, BMI, systolic BP, diastolic BP, Lewis phenotypes (Le(a-b-) vs. rest), NIDDM, and social class.

	ACM $n = 271$	Others $n = 2628$	p
Age, years	65.7(5.5)	62.5(5.0)	< 0.0001
Low social class, %	60	49	< 0.001
Tobacco, g/d	10.8(13.1)	8.7(11.2)	< 0.01
HDL, mmol/l	1.41(0.41)	1.36(0.34)	< 0.05
TG, mmol/l	1.59(1.07)	1.56(1.10)	0.01

The p-value shows the probability outcome after a forward stepwise multiple logistic regression analysis with the maximum likelihood ratio method. Variables are presented by order of entry into the model. A priori probability to enter the model was $p < 0.05$.

had the highest risk both in low-dose monotherapy treated patients and in patient on higher doses (not shown). However, we cannot exclude the possibility that some of the patients in our study on low-dose therapy had previously been treated with higher doses of thiazides.

Was sugar use more common among men with pronounced hypertension, and did sugar use therefore simply reflect severity? The answer is no. Among those treated with diuretics only, 29.1% used sugar; among those treated with diuretics and other antihypertensive drugs, the proportion was 29.6%.

In the late 1960s and at the beginning of the 1970s, Yudkin and co-workers focused on the biochemical and nutritional effects of dietary intake of sugar [17]. They showed that the intake of dietary sugar had a number of effects likely to increase the risk of myocardial infarction [18]. Blood lipids were affected, and also such variables as blood platelet adhesiveness and electrophoretic mobility of platelets; a study on pigs showed that animals fed with sucrose had a rise in insulin. Despite these associations, as reviewed by Shrapnel [19], no prospective studies were performed supporting the hypothesis of a relationship between sugar intake and risk of IHD. Interest was lost in the potential impact of sugar intake for the risk of IHD, and sugar intake subsequently disappeared from the scene of cardiovascular epidemiology in the mid-1970's.

Dietary sugar, suchrose, is composed of two monosaccharide molecules, glucose and fructose. In recent years, a number of experimental studies have demonstrated that insulin resistance may be increased following the intake of fructose [19]. The findings of the present study and the observation of the phenomena of the Reaven's Syndrome [1,20] lend support to the original observations of Yudkin and coworkers that disorders in sugar metabolism may play an important role in the aetiology and pathogenesis of cardiovascular disease. However, for sugar intake to increase the risk of IHD, it seems that insulin sensitivity must be affected.

Both the intake of sugar and diuretics stimulate the insulin production which may be the biological mechanism responsible for the increased risk among men using sugar as well as diuretics. As reviewed by Lithell [21], a high level of blood insulin may accelerate the atherosclerotic process. Insulin enhances cholesterol transport into arteriolar smooth muscle cells, increases endogenous lipid synthesis in these cells, stimulates the proliferation of arteriolar smooth muscle cells, augments collagen synthesis in the vascular wall, increases the formation of and decreases the regression of lipid plaques, and stimulates the production of various growth factors. It has also been shown that an association exists between carbohydrate metabolism and the coagulation system [22].

The observations of the present study support the views presented in a recent paper by Tobian [23] that diuretics should not be regarded as a first choice drug for the treatment of hypertension, at least not without due consideration to the glucose tolerance status of the patient.

In conclusion, the results indicate that the risk of IHD in hypertensives using diuretics is associated with the intake of dietary sugar. This may explain at least some of the discouraging effects of antihypertensive agents on the reduction of risk of IHD.

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