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Alcohol Intake, Serum β_2-microglobulin and Ventricular Extrasystoles

Factors related to death in five-year follow up of middle-aged men

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ABSTRACT

Common causes of death in middle-aged men in Sweden are ischemic heart disease and malignant tumours. In this work the authors relate some findings in a healthy survey of sixty-year old men to mortality in the ensuing five-year follow-up period. Of the original population of 331, 60-year old men 15 subjects (4.5%) died in the follow-up period. The factors tested for relation to death in the follow-up period were: indices of alcohol abuse, serum concentration of β_2-microglobulin and occurrence of ventricular extrasystoles in a long term (6 hrs) ambulatory electrocardiogram. It was found that in seven of the fifteen deceased subjects at least episodical heavy abuse of alcohol had prevailed. This was not evident at the health examination by use of serum gammaglutamyltransferase analysis, nor through the death certificates, but through hospital records and registration at the Temperance Board. Four subjects died (1.2%) of malignant tumours, and three of these subjects had serum-β_2-microglobulin values above the 95th percentile in the study population. An increased risk of death, though statistically not significant, was noted in men with ventricular extrasystoles compared to those without ventricular extrasystoles in long term electrocardiogram. However, all men with ventricular extrasystoles $\geq$ 30/hour and those with ventricular tachycardia were alive five years later. Among the men who died due to ischemic heart disease, ventricular extrasystoles in the long-term electrocardiogram prevailed only in subjects with indices of alcohol intake. Alcohol induced fatal arrhythmias might thus be the terminating event in middle-aged men with traditional risk-factors for ischemic heart disease.

MATERIAL AND METHODS

All men born in 1915, living in Uppsala were invited to a health examination at their age of sixty years in 1975. The procedures of this health investigation have been described in detail elsewhere (15). A total of 331 60-year old men took part, which corresponded to a participation rate of 78.4%.

Laboratory investigations

The serum samples were taken in the fasting state in the morning and included analysis of S-β_2-microglobulin (6) and S-Gammaglutamyltransferase (S-GT) (11). Furthermore each subject was instructed to collect all urine during the 24 hours following the health examination. Analysis for any contents of ethyl alcohol in urine was carried out according to the method by Bonnichsen et al (1).

Medical history

Each participant was asked by means of a self-administered questionnaire modified after Collen (2) if he had ingested any alcoholic beverages the day prior to the health screening. The registers of hospital records for in-hospital stay at the University Hospital of Uppsala were searched. Furthermore the register of the Temperance Board was evaluated, for subjects belonging to the actual study population, registered, due to alcohol abuse.

Death Certificates

The death certificates for all subjects in the study group who died in the five year period (1975-1980) following the health examination, were obtained in copies from the National Bureau of Statistics in Stockholm.

Long-term ECG

A 6-hour ambulatory ECG recording was carried out during unrestricted daily activities. A portable one-channel tape-recorder (HRB2 SRA-Hellige, Sweden) was used. The electrodes were attached in bipolar lead vertically over sternum. Analysis was carried out through a scanner with 20-fold time compression (Memoport Hellige, Sweden).

The electrocardiograms were fully printed out on standard electrocardiographic paper with paper-speed 125 mm/sec for subsequent manual evaluation of arrhythmias.

Arrhythmia classification in the long-term ECG

A ventricular extrasystole (VES) was defined as a premature wide QRS complex (> 0.12 sec), without a preceding P-wave. Frequent VES were defined as a mean hourly count $\geq$30. Complex VES comprised bigeminy, couplets, multiformity, ventricular tachycardia (VT) ($\geq$ 3 VES consecutively with rate >100 per min), and the R on T phenomenon ($RR'/QT \leq 0.85$).

RESULTS

Tables 1-3 show all 15 subjects (4.5 %) who died in the five years following the health examination. All subjects underwent autopsy. Seven

subjects died outside hospital. The subjects who died are grouped in the three tables according to causes of death, nemely ischemic heart disease (IHD), malignant tumours and other causes respectively. Eight subjects died due to IHD, four subjects due to a malignant tumour and the remaining three of other causes.

Table 1. Subjects (no 1-8) who died due to Ischemic heart disease (IHD).

Subject No	S-GT ukat/l	Age at death years	Indices of alcohol intake	Risk factors for IHD (abbreviations se below)	VES in long-term ECG
1	0.70	61	Registered at Temperance board	S	+
2	0.50	62		S	0
3	0.17	62		HL,HT	0
4	0.22	61			0
5	0.68	61	Alcoholism (Dept of Psychiatry). Acute alcohol pancreatitis	S	+
6	0.38	61	Alcoholism (Dept of Psychiatry). Pos questionnary reply	HL, S	+
7	0.18	60	Alcohol in urine	HL, S	+
8	0.51	61	Pos questionnary reply		-

Abbreviations: HL = Hyperlipidemia, HT = Hypertension, S = Tobacco Smoking, + = occurrence of VES, 0 = no occurrence of VES, - = no long term ECG performed

Indices of alcohol intake

As can be seen from Table 1-3 indices of alcohol intake were found in 9 of the 15 deceased subjects. However, in two of the cases (no 8 and no 11) the index registered was a positive reply of the questionnaire. These cases certainly represented occasional intake. In the remaining 7 subjects however, there were signs of at least episodical heavy alcohol abuse. Four of the fifteen subjects were registered at the Temperance Board (27%) which should be compared to 7% in the remaining population alive.

Serum β_2-microglobulin

Table 2 shows the subjects who died due to a malignant tumour. In one subject (no 11) the tumour was known at time of the health examination. The values of β_2-microglobulin should be judged against the mean value in the remaining population alive which was 2.05 ± 0.48 mg/l.

Table 2. Subjects (no 9-12) who died due to a malignant tumor.

Subject No	S-β_2 mg/l	S-GT ukat/l	Age at death years	Origin of mal.tumor	Indices of alcohol intake
9	2.40	2.34	61	Kidney	
10	3.82	0.23	63	Lungs	Registered at Temperance Board Alcoholism (Dept of Psychiatry)
11	2.92	0.20	61	Prostata	Pos questionnary reply
12	4.28	0.70	64	Gallbladder	

Table 3. Subjects (no 13-15) who died of other causes than IHD and malignant tumor.

Subjects No	S-GT ukat/l	Age at death years	Cause of death	Indices of alcohol intake
13	0.24	62	Amyotrofic lateral sclerosis	
14	0.64	62	Perforating ulcus ventriculi	Acute alcohol pancreatitis Reg at Temperance Board Pos questionnary reply
15	0.33	64	Ruptured aortic aneurysm	Reg at Temperance Board Alcoholism (Dept of Psychiatry)

Long-term ECG

Technically satisfactory long-term ECG recording were obtained in 292 subjects in the entire screened population. VES were noted in 121 of these recordings (41.4%). Among the eight subjects who died due to IHD seven underwent long-term ECG, four of these had VES on the long-term ECG, but none however had VT, frequent VES or R/T as defined above. The risk of death due to IHD was 3 times higher in men with VES compared to those without VES. This difference was however not statistically significant ($p = 0.2$, Fischers exact test).

DISCUSSION

Increased alcohol intake has been shown by several authors (3, 8, 10) to be related to higher mortality and morbidity, of all causes compared to that among low consumers and abstainers. In our study nearly half of the deceased men had indicators of at least epidosical alcohol abuse. This was not disclosed by the S-GT values which previously (13, 14, 16, 17) has been related

to increased alcohol intake, and in only one of the subjects alcoholismus chronicus was mentioned in the death certificate as contributory cause of death. Increased alcohol intake as contributory, or main cause of death, is certainly underreported in the National Statistics on mortality. Further one might speculate if those subjects whose findings suggested at least episodical heavy abuse of alcohol, voluntarily had abstained from alcohol intake the weeks preceding the health examination. The reported rapid decrease of S-GT activity ($T_{\frac{1}{2}}$ 7-10 days) at alcohol abstention might thus explain the unforeseen low S-GT values.

Serum microglobulin is a small protein (m.w. 11.800), reported by some authors (9, 12, 13) to show elevated serum concentrations in patients suffering from malignant tumours.

In our study only four (1.2%) of the originally investigated population had died due to a malignant tumour in the five-year follow-up period. However, in three of these four subjects the serum β_2-microglobulin values were found above the 95^{th} percentile in the entire population. The erytrocyte sedimentation rate (ESR) was not elevated in any of these cases, nor were there any other signs of inflammatory disorders or decreased renal function, the latters (5, 12) have been reported as important causes of elevated serum β_2-microglobulin.

Further studies are needed to clarify the possible role of serum β_2-microglobulin as a possible early circulating marker of a malignant tumour.

Some studies (4,7) performed, have not found a correlation between occurrence of VES and fatal outcome of IHD. Hinkle et al (7) investigated 283 actively employed men with a median age of 55 years, with continous 6 hours ambulatory ECG. They found that frequently occuring VES (>10/1000) was associated with a ten fold increase in the risk of developing death due to IHD, in comparison to men without VES. As in our study deaths due to IHD, was not predicted by occurrence of VT or coupled VES.

In our follow-up study during five years the risk of death due to IHD was increased 3 times if VES were noted, during a 6 hour continous recording. However, all men with VES > 29/hour and those with VT were alive five years after the initial investigation. The findings of VES in the group who died due to IHD was confined to men with indices of alcohol intake. The wellknown arrhytmogenic action of ethyl alcohol and it's metabolites certainly worsens the long-time prognosis concerning IHD in subjects with traditional risk factors for IHD.

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