

SHORT COMMUNICATION

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THE EFFECTS OF DIPHENYLHYDANTOIN ON THE RELATIONSHIP BETWEEN HIGH-DENSITY LIPOPROTEIN CHOLESTEROL AND SEVERAL BIOCHEMICAL ASSAYS

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Summary

Correlations have been calculated between high-density lipoprotein cholesterol and total plasma cholesterol, albumin, γ -glutamyl transpeptidase, aspartate aminotransferase, alkaline phosphatase, triglyceride, urea, creatinine and uric acid for diphenylhydantoin (DPH) users and for subjects attending a multiphasic health screening centre. For women DPH users, high-density lipoprotein levels correlated significantly with gamma glutamyl transpeptidase, cholesterol and alkaline phosphatase. These correlations were significantly different from those found for male DPH users and from subjects attending the health screening centre. In male DPH users, high-density lipoprotein cholesterol correlates negatively with urea and uric acid levels, a relationship which is found neither in women DPH users nor in the health screening centre population.

Introduction

The best single biochemical assessment of cardiovascular risk is high-density lipoprotein [1,2,3], frequently measured as high-density lipoprotein cholesterol (HDL-C). The mechanism which regulates levels of HDL-C is not understood. However, agents which increase the production of liver microsomal enzymes often increase levels of high-density lipoprotein. High-density lipoprotein levels increase with ethanol consumption [4,5,6] and with exposure to chlorinated hydrocarbon pesticides [7]. Markers of liver microsomal enzyme activity which might be expected to correlate with HDL-C include drug half-lives and also the biochemical liver function tests such as gamma glutamyl transpeptidase (GGT)

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[8,9,10], and possibly alkaline phosphatase which probably is affected by liver function only indirectly. Ethanol consumption increases levels of GGT and aspartate aminotransferase [11]. However, Danielsson et al. [5], who studied alcoholic men, did not find a relationship between HDL-C and GGT, aspartate aminotransferase or alanine aminotransferase.

We thought it worthwhile to investigate the relationship between HDL-C and other biochemical tests in both men and women taking an antiepileptic drug 5,5-diphenylhydantoin (DPH), which is known to stimulate the production of liver microsomal enzymes [12] and also to increase plasma levels of high-density lipoprotein [13]. HDL-C and GGT, aspartate aminotransferase, alanine aminotransferase, urea, uric acid, albumin, triglycerides, creatinine and cholesterol have been measured. Considerable differences between male and female DPH users and between DPH users and our reference population, subjects attending a health screening centre in Sydney, Australia, were found.

Methods

Aliquots of plasma from epileptic patients were assayed. Samples were used only, if DPH was the only drug the patient was using and if at least 10 $\mu\text{mol/l}$ was present in the plasma. Eighteen men, 17–78 years with an average age of 52.7 years and 12 women, 19–76 years, average age 48.1 years, have been studied.

These patients were compared with men and women attending the Medichk Referral Centre, a multiphasic health screening centre in Sydney. Fasting blood specimens were collected and analysed from 509 men, 19–70 years with an average age of 43.5 years and from 420 women, 17–78 years with an average age of 42.0 years.

HDL-C was measured using the method of Allen et al. [14]. The other biochemical assessments were measured with a Technicon SMAC. Calculations have been performed using the Statistical Packages for the Social Sciences, SPSS [15]. Differences between correlation coefficients were assessed by z-transformations [16]. In order to avoid comparing total cholesterol and HDL-C, as HDL-C is contained in the total cholesterol, the variable corrected cholesterol has been constructed. Corrected cholesterol is total cholesterol less HDL-C. The major component of corrected cholesterol would be low-density lipoprotein cholesterol as in these fasted subjects chylomicra would be absent and the quantity of cholesterol in very low-density lipoprotein is considerably less than that in low-density lipoprotein.

Results

Male DPH users had an average of 1.02 ± 0.40 mmol/l of HDL-C and women DPH users had 1.30 ± 0.38 mmol/l. They had elevated GGT (207 I.U./l for men and 117 I.U./l for women) and alkaline phosphatase (150 I.U./l for men and 115 I.U./l for women).

For the correlations see the Table. Values in parentheses in the Table are the correlations for subjects attending the Medichk Referral Centre and provide reference values for this population.

TABLE

CORRELATION BETWEEN HDL-C AND SEVERAL BIOCHEMICAL TESTS FOR MEN AND WOMEN USING DIPHENYLHYDANTOIN

	Men <i>n</i> = 18	Women <i>n</i> = 12
Total cholesterol	+0.206	+0.706 ** (+0.125 **)
Corrected cholesterol	-0.062	+0.490 * (-0.160 **)
Gamma glutamyl transpeptidase	+0.239	+0.733 ** (-0.095)
Aspartate aminotransferase	-0.240	+0.175
Uric acid	-0.590 ** (-0.016)	+0.005
Urea	-0.526 * (+0.048)	-0.069
Albumin	+0.047	-0.110
Triglycerides	-0.051	+0.148
Alkaline phosphatase	-0.023	+0.499 *
Creatinine	-0.092	+0.282

* $p \leq 0.05$.** $p \leq 0.01$.

± Figures in brackets are correlation coefficients for the 420 women and 509 men attending a multiphasic health screening centre.

Discussion

As can be seen from the Table, HDL-C correlates significantly with GGT in female ($p \leq 0.01$), but not in male DPH users. For women also, the correlations of HDL-C with cholesterol and alkaline phosphatase are significant, but in men these relationships are unaffected. However, for male DPH users, there are significant negative correlations between HDL-C and urea and uric acid ($p \leq 0.01$) and these correlations are significantly different from the men in the Medi-check population ($p \leq 0.02$ and $p \leq 0.05$). HDL-C was not significantly correlated with alanine aminotransferase and aspartate aminotransferase for either male or female DPH users.

The results for men using DPH are consistent with those of Danielsson et al. [5] for male alcoholics. Neither agent increases the correlation between HDL-C and GGT in men, although both agents independently increase levels of liver microsomal enzymes and HDL-C. For women DPH users, there is a very strong correlation between HDL-C and the enzymes gamma glutamyl transpeptidase and alkaline phosphatase and also with total cholesterol. Although the mechanism responsible for this relationship is not understood clearly, Nikkilä et al. [11] note that DPH increases the amount of smooth endoplasmic reticulum in the liver and that lipoprotein lipids are synthesized and organized into particles in the smooth endoplasmic reticulum.

The correlations with HDL-C of urea and uric acid could be of renal or nutritional origin; the absence of correlation between HDL-C and creatinine would seem to make renal factors unlikely, so it seems likely that protein and purine intake have some influence on plasma HDL-C and on HDL metabolism in men using DPH.

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