INCREASED D-GLUCARIC ACID EXCRETION IN SUBJECTS HIGHLY EXPOSED TO TCDD

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Introduction

D-glucaric acid is produced mainly in the liver as a byproduct of the glucuronic acid pathway; some studies in animals and in humans showed an increased urinary excretion of D-glucaric acid after hepatic microsomal enzymes induction[1]. The measurement of this metabolite in urine samples is a sensitive and quantitative test for an indirect measure of enzyme induction[2].
2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin) is known to induce hepatic microsomal enzymes both in animals and in humans[3].
We previously reported D-glucaric acid levels higher than controls[2] in urine samples of subjects exposed to TCDD in 1976 at Seveso. After 1988 we have been able to measure TCDD in serum samples collected in 1976-77 from these people[4].
Here we present a study of correlation of D-glucaric acid excretion in exposed people[2] and their serum level of TCDD in 1976 with the aim to verify if this test can be used as a biomarker of dioxin exposure.

Materials and methods

D-glucaric acid excretion in 16 children (age range 6.1-8.3 yrs , median 7.4 yrs) exposed to TCDD (1976 serum levels on lipid base, range 42.6-26,400 ppt, median 297 ppt) has been evaluated. A group of 26 control subjects matched for age and sex were chosen from children living in Cannero (a non industrialized village on lake Maggiore). All subjects were free of apparent diseases but chloracne in exposed and their laboratory tests were within reference limits.
Urine samples were collected, upon informed consent, in 1976 (August-October) from exposed subjects and in 1979 (February-March) from controls and kept frozen at –20°C after collection.
D-glucaric acid was determined late in 1979 by the method of Simmons[5], as already described[2].
In 1989-1994 we measured TCDD levels in serum samples collected in 1976-77 and kept frozen at –20°C until determination. All these measurements were performed[4] at Centers for DiseaseControl and Prevention (CDC),GA, Atlanta.

Results and Discussion

Exposed subjects have D-glucaric acid median levels (median = 26.2 μmol/g creatinine) higher than controls (median=22.8 μmol/g creatinine).

If we consider TCDD exposure it is interesting to note that D-glucaric acid values are definitely higher (median=59.2 μmol/g creatinine) in subjects with TCDD serum levels higher than 1000 ppt, as shown in Table 1.

	Controls	Exposed people		
		All subjects	<1000 ppt	>1000 ppt
N	26	16	11	5
25th percentile	11.9	17.6	14.6	45.6
Median	**22.8**	**26.1**	**21.6**	**59.2**
75th percentile	25.6	39.6	26.5	77.1

Table 1. D-glucaric acid levels distribution in urine (μmol/g creatinine) by TCDD serum levels on lipid base in 1976 (ppt)

All the subjects with the highest D-glucaric acid values (>40 μmol/g creatinine) had chloracne type 3 or 4, the most severe grade of it (Figure 1). Subjects with chloracne type 1 or 2 have D-glucaric acid levels as non chloracneic ones with the same TCDD serum levels.
Due to the small set of data, it is not possible to know if subjects with chloracne type 3 or 4 have higher urinary excretion of D-glucaric acid than non chloracneic ones with the same exposure levels.
Our results suggest that urinary excretion of D-glucaric acid could be an useful biomarker of TCDD exposure. A simple method to screen large populations has been recently developed by some of us[6] . The metabolic change due to TCDD induction, even in absence of clinical disease, can modify xenobiotic metabolism causing a possible threat to human health[7].

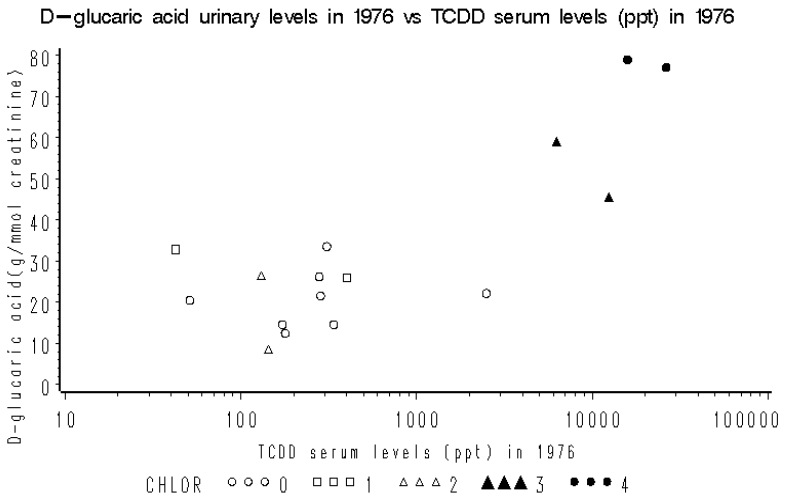

Figure 1. D-glucaric acid excretion and TCDD serum levels (ppt) in 1976 in people with different types of chloracne

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