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Diabetes, cardiovascular disorders, proteomics and 2,3,7,8-TCDD body burden in Czech patients 50 years after the intoxication

Daniela Pelclova, Tomas Pelcl, Zdenka Fenclova, Stepanka Vlckova, Tomas Navratil, Sergey Zakharov
First Medical Faculty, Charles University

Objective: Cardiovascular and metabolic diseases attributable to 2,3,7,8-tetrachlorodibenzo-p- dioxin (TCDD) are associated with aryl hydrocarbon receptor (AhR) activation and subsequent induction of metabolic changes and inflammation in blood vessels and/or with premature cell senescence mediated by produced reactive oxygen species. No antidote is available to increase TCDD elimination and only symptomatic treatment is used. First TCDD analysis was available in 1996 and now we back-calculated the zero-time level, using the physiologically based pharmacokinetic model by Emond.

Methods: Examination of eight men (72.4±1.3 years) included TCDD in blood serum using HRGC/HRMS, internal examination, densitometry of the body fat, Duplex Doppler ultrasonography and eye fundus examination. Hypertension was defined as systolic blood pressure 140 mmHg and/or diastolic blood pressure 90 mmHg or use of antihypertensive medication. Hyperlipidemia was defined according to cholesterol levels (limit of 5.2 mmol/l), triglycerides levels (limit 1.7 mmol/l) or use of lipid-lowering drugs. Diabetes was defined as based on glycohemoglobin (limit of 42 mmol/mol) or use of oral antidiabetics. The prevalence of disorders was compared with the general male population. Skin microvascular reactivity was measured by laser Doppler perfusion monitoring in the fingers and forearm during post-occlusive reactive and thermal hyperemia and compared with findings in 2003. Proteomics of the exhaled breath condensate was performed by mass spectrometry.

Results: Mean TCDD level was 180±110 pg/g blood lipids; median 112 pg/g (12 pg/g was found in 8 the controls, including 4 wives). Mean TCDD body deposit is 4.95±3.7 mcg. The back-calculated TCDD plasma level may have reached 35,000-350,000 pg/g fat. All patients had residues after chloracne and plaques in the carotid arteries, 87.5% hyperlipidemia, 62.5% had diabetes, ischemic heart disease with myocardial infarction and/or ictus, and increased intima-media thickness. The prevalence of diabetes, hypertension, hyperlipidemia and cardiovascular disorders in this group of patients is 1.5-2.0 fold higher, comparing with the general population. Proteomics found 15 proteins significantly different from a control comparable group by t-test ($p<0.5$).

Conclusion: These results in eight last survivors of severe TCDD exposure and 50 years persistence in plasma suggest that TCDD promoted long-term metabolic impairments. From the last examination in 2010, cholesterol and triglycerides levels of the subjects decreased and no further progression of microvascular impairments from 2003 was seen. The patients need permanent complex pharmacological treatment that may mitigate the progression of all their metabolic and vascular disorders.