Toxins and Diabetes Mellitus: An Environmental Connection?

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Abstract

Several international studies have examined the relationship between environmental influences and diabetes mellitus. The purpose of this study was to provide a comprehensive review of those findings from the scientific literature of the past 30 years. Literature relevant to the relationship between diabetes and environmental toxins was reviewed. The literature search was conducted using the National Library of Medicine, Expanded Academic, Health Reference Center, and PubMed (Medline) search mechanisms. The Internet (World Wide Web) was also used to obtain general information.

The findings suggest that two environmental toxins, arsenic and dioxin (dibenzo-p-dioxins), may have some relationship to an increased risk for diabetes. It should be noted that results only indicate a possible relationship between diabetes and environmental toxins. The authors strongly suggest that further studies be conducted to determine the true nature and extent of the relationships reported in the literature.

Diabetes is a major cause of morbidity and one of the leading causes of death in the United States. Several studies worldwide have examined the relationship between environmental influences and diabetes. This article reviews findings from the scientific literature between 1977 and 2000. The purpose of this review was to examine studies that addressed factors in the environment that could be attributed to or associated with the prevalence of diabetes. Findings have suggested that two environmental toxins, arsenic and dioxin, may have some relationship to an increased risk for diabetes.

BACKGROUND

Arsenic

Arsenic is a naturally occurring element that is widely distributed in various compounds throughout the earth's crust. Pure arsenic is a gray-colored metal, but this form is rarely found in the environment. Arsenic concentrations in the earth's crust are usually around 1.5–2 mg/kg.[1]

In the environment, arsenic is transported mainly by water. In the United States, it is present in soil at levels ranging from 0.2 to 40 μg/g, in urban air at levels of ~0.02 μg/m^3, and in water at levels averaging ~0.0001 ppm.[2]

Arsenic combined with other elements, such as oxygen, chlorine, and sulfur, is referred to as inorganic arsenic. Arsenic in plants and animals combines with carbon and hydrogen to form organic arsenic. Organic forms of arsenic are usually less toxic than inorganic forms.[3]

The main exposure to inorganic arsenic in the general population is through the ingestion of high-arsenic drinking water.[1] In the United States, the Environmental Protection Agency (EPA) standard for arsenic in drinking water is 0.05 mg/l water.[4] Of major concern today is exposure through untested well water. It has been estimated that ~350,000 people in the United States may regularly drink water containing more than the acceptable level of arsenic.[4]

In the general population, exposure to both inorganic and organic arsenic occurs through medicinal, environmental, and occupational routes. Drugs containing inorganic arsenic have been used in the treatment of leukemia, psoriasis, and chronic bronchial asthma and as a tonic, usually at a dose of several hundred micrograms per day. Wine and mineral waters can sometimes contain

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arsenic. For wine, this result is probably attributable to the use of arsenic-containing pesticides.[1] Both forms of arsenic are present in varying amounts in food. Marine foods are the main source of arsenic in the diet. They contain relatively high concentrations of organic arsenic and could supply 52% or more of the total daily intake of arsenic, depending on the food habits of the population in question.[5] Occupational exposure to arsenic occurs mainly among workers involved in the processing of copper, gold, and lead ores; the manufacturing of glass and various pharmaceutical substances; the use of arsenic pigments and dyes; and the production and use of agricultural pesticides.

Dioxin

Dioxin is a general term used to describe a family of compounds known as chlorinated dibenzo-p-dioxins. The major sources of dioxin for the general population are in our diet. Since dioxin is fat-soluble, it bioaccumulates up the food chain and is mainly found in meat and dairy products, including, in order of greatest concentration, beef, milk, chicken, pork, fish, and eggs.[6]

Dioxin is highly persistent in the environment. The most toxic form is 2,3,7,8-tetrachlorodibenzo-p-dioxins or TCDD. TCDD does not occur naturally, nor is it intentionally manufactured by industry, except in small amounts for research purposes. It may be formed during the chlorine bleaching process at pulp and paper mills and with the production of polyvinyl chloride plastics. It is also formed during chlorination by waste and drinking water treatment plants. Dioxin can occur as a contaminant in the manufacture of certain organic chemicals. The major source of TCDD in the environment, however, is incinerators that burn chlorinated wastes.[6]

Its ubiquity in food, persistence in the environment, and extreme toxicity justify the public health concern related to TCDD (or dioxin) today. Studies of exposure to TCDD in animals have shown a wide range of severe effects including carcinogenicity, immunotoxicity, developmental and reproductive toxicity, hepatoxicity, neurotoxicity, chloracne, and loss of body weight.[7,8] Effects in humans have been studied, but the picture is neither fully consistent nor complete. The most noted health effect in people exposed to large amounts of TCDD is chloracne, a severe skin disease with acne-like lesions that occur mainly on the face and upper body. Other skin effects noted in people exposed to high doses of TCDD include skin rashes, discoloration, and excessive body hair. Changes in blood and urine that could indicate liver damage have also been seen in those exposed to TCDD. Exposure to high concentrations of TCDD may induce long-term alterations in glucose metabolism and subtle changes in hormonal levels.[6]

RESEARCH DESIGN AND METHODS

We conducted a literature search using the National Library of Medicine, Expanded Academic, Health Reference Center, and PubMed (Medline) search mechanisms. The Internet (World Wide Web) was also used to obtain general information regarding environmental toxins. Keywords for the search included: diabetes, diabetes mellitus, environment, and toxins. All studies published between 1977 and 2000 relevant to the relationship between diabetes and environmental toxins were included.

RESULTS

Arsenic

Results of several studies have suggested that an association exists between

Table 1. Findings Related to Arsenic Exposure and Diabetes Mellitus

Location of Study	Source/Sample	Finding	Statistics
Bangladesh[9]	Drinking water	Arsenic exposure suggested as risk factor for diabetes	MH-PR = 5.9 (95% CI: 2.9–11.6)
Taiwan[10]	Drinking water	Increased risk factor for diabetes found among people exposed to arsenic	Exposure: 0.1–15.0 ppm OR = 6.61 (95% CI: 0.86–51.0) Exposure: ≥15.1 ppm OR = 10.05 (95% CI: 1.3–77.9)
Taiwan[11]	Drinking water	Increased risk of diabetes mortality among people exposed to arsenic	Males: SMR = 1.35 (95% CI: 1.16–1.55) Females: SMR = 1.55 (95% CI: 1.39–1.72)
Sweden[12]	Occupational: copper smelters	Weak relationship found between diabetes mellitus and arsenic exposure	MH Extension for trend: $X^2 = 4.68$; $P = 0.03$
Sweden[13]	Occupational: art glass workers	Slightly increased risk for diabetes among workers exposed to arsenic	MH-OR = 1.2 (95% CI: 0.82–1.8)

CI, confidence interval; MH, Mantel-Haenzel; MH-OR, Mantel-Haenzel Weighted Odds Ratio; MH-PR, Mantel-Haenzel Weighted Prevalence Ratio; OR, odds ratio; SMR, standardized mortality ratio

arsenic exposure and diabetes (Table 1). In particular, a somewhat increased risk for diabetes has been reported among people exposed to arsenic through drinking water.[9,10] The potential relationship between mortality from diabetes and chronic arsenic exposure via drinking water has also been evidenced.[11] Indications of a relationship between arsenic exposure and diabetes have also been reported in studies of copper smelters[12] and art glass workers.[13]

Dioxin

Results of epidemiological studies that focused on diabetes prevalence, glucose and serum levels, and exposure to dioxin are mixed (Table 2). A follow-up study of German industrial workers exposed to dioxin found diabetes less often in the exposed group than in the referent group.[14] In another study of the same cohort, mean fasting serum glucose levels in the exposed group appeared to increase with current but not back-calculated dioxin concentration.[15] A study of U.S. industrial workers exposed to dioxin revealed an increased mean dioxin level in diabetic workers as compared to non-diabetic workers and an increased fasting serum glucose level in diabetic workers versus non-diabetic workers.[16]

In the Veterans of Operation Ranch Hand Study,[17] results indicated an adverse relationship between dioxin exposure and diabetes, glucose metabolism, and insulin production. Included in the study were Air Force veterans of Operation Ranch Hand, the unit responsible for the aerial spraying of herbicides, including Agent Orange and its contaminant, dioxin, in Vietnam from 1962 to 1971. In the Vietnam Experience Study,[18] diabetes prevalence in the Vietnam cohort was similar (relative risk = 1.1) to that in the non-Vietnam veteran cohort, however.

One of the populations most heavily exposed to TCDD is that involved in the Seveso, Italy, industrial accident of 1976. The accident occurred in a chemical plant where 2,4,5 trichlorophenol was manufactured. The accident originated in one of the production kettles, causing a sudden surge in pressure and temperature that blew a safety device. Contents of the reactor, including a substantial amount of TCDD, were released into the air through an exhaust pipe and deposited as far as 6 km southeast of the plant.

Extensive monitoring of soil levels and measurements of human blood samples allowed classification of the exposed population into three categories: A (highest exposure), B (median exposure), and R (lowest exposure).[19] Long-term studies were conducted using the large population living in the non-contaminated surrounding territory as reference. An increase in diabetes in females who had median exposure (Zone B) to TCDD was reported in one study.[19] Another study of the same cohort found an excess of diabetes cases.[20] Most recently, Cranmer et al.[21] performed a study of 69 men and women from the Vertac-Hercules Superfund site, located in Jacksonville, Ariz., who had long-term exposure to past industrial pesticide contamination. Their findings are consistent with epidemiological studies and suggested that high blood TCDD levels are associated with hyperinsulinemia and insulin resistance.

Table 2. Findings Related to Dioxin Exposure and Diabetes Mellitus

Location of Study	Source/Sample	Finding	Statistics
Germany[14]	Industrial workers	Diabetes found less often in dioxin group than in referents	$P < 0.05$, Fisher's Exact test
Germany[15]	Industrial workers	Mean fasting glucose in exposed group appeared to increase with current but not back-calculated dioxin concentration	$P = 062$ regression analysis results
United States[16]	Industrial workers	Increased mean dioxin and fasting serum glucose levels in diabetic workers vs. non-diabetic workers	$P < 0.05$ logistic regression results
United States[17]	Veterans of Vietnam	Adverse relationship found between dioxin exposure and diabetes mellitus, glucose metabolism, and insulin production	RR = 1.5 (95% CI: 1.2–2.0)
United States[18]	Veterans of Vietnam	Diabetes prevalence in Vietnam cohort similar to that in non-Vietnam cohort	OR = 1.0 (95% CI: 0.4–2.2)
Italy[19]	Industrial accident	Increase in diabetes deaths among females in population exposed to dioxin	RR = 1.9 (95% CI: 1.1–3.2)
Italy[20]	Industrial accident	Excess of diabetes found among females	RR = 1.8 (95% CI: 1.0–3.0)

CI, confidence interval; RR, relative risk

Conclusions

These findings, although merely suggestive, indicate a possible relationship between arsenic exposure and diabetes. In addition, a relationship between dioxin exposure and diabetes, glucose metabolism, and insulin production has been suggested. However, the findings reported here cannot be viewed as conclusive, especially because causal relationships were not evidenced.

It is important to note that the majority of the studies were conducted in countries other than the United States. As previously mentioned, the main exposure to arsenic in the general population is through the ingestion of high-arsenic drinking water. Of major concern is untested well water. In the United States, contaminant levels in water are routinely monitored by state health and environmental control agencies. However, private well water is not routinely tested, unless requested.

In light of what has been reported here, it is still unclear to what extent environmental exposures to arsenic and dioxin contribute to the overall risk of diabetes in the United States. Hence, caution should be used when interpreting these results. Nevertheless, several of the studies are continuing in an effort to overcome existing limitations and to explore new research paths.

Acknowledgments

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