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Mini Review

Urban Air Pollution and Type 1 Diabetes: There is Still a Long Way to Go

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Abstract

Immune-mediated Type 1 diabetes is characterized by permanent insulin deficiency and absolute requirement for insulin replacement therapy. Autoimmune destruction of beta cells has been related to multiple genetic predispositions and poorly defined environmental determinants.

Exposure to air pollution (gaseous pollutants and/or particulate matter) has been associated with diabetes incidence, prevalence and mortality. Most human studies referred to diabetes mellitus, with no distinction between Type 1 and Type 2 diabetes. Few studies focused specifically on the role of air pollutants in the development of Type 1 diabetes with inconclusive results. Based on animal model studies, hypothesized mechanisms of air pollution-mediated metabolic disease included oxidative stress, adipose tissue inflammation, mitochondrial dysfunction, insulin resistance, and pancreas toxicity. Major difficulties in establishing a relationship between air pollution and Type 1 diabetes are: the retrospective design of epidemiological studies, unwatched pollution, and long-term exposure misclassification.

Keywords: Type 1 diabetes; Air pollution; Risk factors

Introduction

Immune-mediated Type 1 diabetes is characterized by permanent insulin deficiency and absolute requirement for insulin replacement therapy. Autoimmune destruction of beta cells has been related to multiple genetic predispositions and poorly defined environmental determinants [1-2]. The incidence of Type 1 diabetes is increasing in many countries and the reasons for this remain unknown: changes in environmental risk factors and/or viral infections? [3].

Exposure to air pollution (gaseous pollutants and/or particulate matter) has been associated with diabetes incidence, prevalence and mortality [1,4-7]. Most studies referred to diabetes mellitus, with no distinction between Type 1 and Type 2 diabetes. Few studies focused specifically on the role of air pollutants in the development of Type 1 diabetes with inconclusive results [4,6,8-10].

As far back as 1970, Sultz et al. evaluated the effect of continued exposure to air pollution on the incidence of chronic allergic disease in children under 15 years of age from the Erie County Study of Long-Term Childhood Diseases [11]. The average annual incidence rates for children hospitalized with diabetes mellitus by air pollution level (carbon monoxide, ozone, and particulate matter ≤2.5μm in diameter or PM2.5) and social class revealed no association. In 2006, a retrospective study of 402 children suggested that cumulative exposure to ozone and sulfate in ambient air could "predispose to the development of Type 1 diabetes in children" [6]. Insulin resistance evaluated using the homeostasis model assessment-estimated insulin resistance (HOMA-IR) index in 397 10-year-old children was associated with long-term exposure to PM10 and nitric dioxide [12]. The land use regression models were used to estimate long-term spatial variability of nitric dioxide, PM10, PM2.5, and PM2.5 absorbance; air pollution concentrations were measured at the birth address of each individual some years after the birth of the children. Thus, a notable study limitation was the potential for exposure misclassification due to changes in infrastructure or residential address over time. According to Malmqvist et al. mothers of offspring who developed Type 1 diabetes (n =324) "more often had lived in areas with elevated levels of nitrogen oxides during the third trimester or ozone during the second trimester, compared to mothers of children who had not developed the disease" (n =930). Mother's residential coordinates (yearly updated in Sweden) were linked to the air pollution databases in order to individually assess exposure [4]. In a study population of 671 children who were positive for at least 1 islet autoantibody, exposure to traffic related pollutants (PM10, nitrogen dioxide, and possibly PM2.5) accelerated "the manifestation of Type 1 diabetes but only in very young children" [9].

Several possible mechanisms whereby air pollution could contribute to the development of diabetes have been suggested: adipose inflammation and insulin resistance, mitochondrial dysfunction, impaired endothelial reactivity, oxidative stress, and pancreatic damage [13-16].

In a mouse model of diet-induced obesity, PM2.5 potentiated whole-body insulin resistance, increased visceral adiposity and inflammation, induced vascular relaxation abnormalities, and enhanced monocyte adhesion to microcirculatory beds, thus providing potential contributors to diabetes development [13]. Subsequently, in the same animal model, Xu et al. observed that PM2.5 exposure decreased mitochondrial number in white adipose tissue, reduced mitochondrial size in brown adipose tissue, lowered uncoupling protein 1 expression and induced down-regulation of brown adipose-specific gene profiles [14]. Diesel exhaust particles caused adverse effects on the pancreas of streptozotocin-induced Type

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1 diabetic mice, including a marked decrease in the size and number of islet cells with cellular vacuolation and increase of apoptotic islet cells. Elevated concentrations of 8-isoprostane along with decreased SOD activity and concentration of reduced GSH in the pancreas suggested a role of oxidative stress [15]. On the basis of findings in literature, PM2.5 exposure has been considered a modifiable cardiovascular risk factor [16]. In a streptozotocin-induced Type 1 diabetes rat model, sub-chronic exposure to continuous, real world, non-concentrated (similar to the current air quality standards) PM 2.5 affected glucose homeostasis and caused inflammation, multi-organ macro- and micro-vascular complications [17].

Conclusions

The demonstration of a significant correlation between Type 1 diabetes and pollution is an arduous endeavor due to the complexity of both diabetes pathogenesis and atmospheric chemistry. Well-designed, long-term prospective studies should be required to precisely estimate the relative risk of an outcome based on exposure, but the outcome of interest should be common (that is not the case of Type 1 diabetes). Moreover, epidemiological studies that investigate air-pollution-related health effects are facing several additional methodological problems:

1) The number of air quality indicators and the performance of air pollution sensors. There are six criteria air pollutants (ozone, carbon monoxide, sulfur dioxide, particulate matter, lead, and nitrogen dioxide) [18] but additional 187 toxic air pollutants from industrial sources [19] and the toxicity of all components is not identical. Air pollutants include gases or particle components that are directly emitted by the sources as well as secondary components that are formed by chemical and physical transformation. Thus, the performance of air pollution sensors is important in view of co-pollutants and interferences [20].

2) The selection of appropriate models for estimating individual exposure as a function of the relevant human factors and the measured pollutant concentrations [21] in order to avoid long-term exposure misclassification of modeled air pollution concentrations from several sources. Significant challenges in this respect include: characterizing place of birth or current residence as a location of long-term exposure whereas people are moving, failed geocoding of an address or mobile, lack information regarding indoor air pollution exposures, work address, exposure to air pollution at work, transportation habits, outdoor activities, incomplete dataset of annual mean pollutant concentrations, etc. [22].

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