

Persistent organic pollutants and epidemic of diabetes and metabolic syndrome

Dear fellow diabetes investigators, you, myself and our Editor-in-Chief, Dr Hotta, have the same goal; to do something about the epidemic of diabetes in Asia. I will not show the numbers again, as you have seen enough; simply there are too many people around us with diabetes.

Why there are so many? Professor Eung-Jin Kim, Honorary President of Korean Diabetes Association, told me that diabetes was a rare disease in early 1960s. He saw only five cases of diabetes the whole year in 1957 at Seoul National University Hospital, which had 450 beds back then. It is clear that the diabetes epidemic in Korea (and elsewhere) is due to a change of the environment. Huge changes have occurred over the last half century in South Korea. She has industrialized, westernized and became wealthier. I do not believe industrialization is bad for South Koreans, as they live much longer now.

Was the diabetes epidemic an inevitable consequence of these changes associated with industrialization? If it was, it might have been avoided. Something bad was introduced during the industrialization process; so-called persistent organic pollutants (POP). Recently, evidence supporting this conclusion has been forthcoming and is getting stronger. Persistent organic pollutants are defined as 'chemical substances that persist in the environment, bio-accumulate through the food web, and pose a risk of causing adverse effects to human health and the environment'. The Stockholm Convention on POP, an organization formed by international treaty, identified 12 POP initially and then added nine POP later. Here is the list: pesticides (aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, toxaphene, chlordecone, alpha hexachlorocyclohexane, beta hexachlorocyclohexane, lindane and pentachlorobenzene), industrial chemicals (hexachlorobenzene, polychlorinated biphenyls [PCB]; hexabromobiphenyl; hexabromodiphenyl ether and heptabromodiphenyl ether; pentachlorobenzene; perfluorooctane sulfonic acid, its salts and perfluorooctane sulfonyl fluoride; tetrabromodiphenyl ether and pentabromodiphenyl ether) and by-products (hexachlorobenzene; polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans [PCDD/PCDF], PCB, alpha hexachlorocyclohexane, beta hexachlorocyclohexane and pentachlorobenzene). (Source: <http://chm.pops.int/Convention/tabid/54/language/en-US/Default.aspx>).

An epidemiologist at Kyung-pook National University College of Medicine, Korea, Duk-Hee Lee, found some years ago that serum levels of gamma glutaryl transferase (GGT) within its reference range strongly predicted the future risk of diabetes in a cohort study in Korea¹. After confirming this association in other well-established cohort studies, she asked herself why this

relationship should exist. She hypothesized that this association might be a result of exposure to some environmental pollutants, as GGT is an enzyme that is involved in the metabolism of glutathione, and glutathione is known as a detoxification agent. After a review of literature on environmental pollutants, she became convinced that POP might be responsible.

To prove the association between POP and diabetes/metabolic syndrome in humans, POP should be measured. However, measuring POP levels is very difficult, prohibitively expensive and needs a devoted machine (usually GC/MS), facilities and people. Luckily for her, she found that the US Center for Disease Control and Prevention, already had measured the 50 most frequently detected POP in blood samples taken during the US 1999–2002 National Health and Nutrition Examination Survey (NHANES) for biomonitoring POP in the USA general population. NHANES is designed to be nationally representative of the non-institutionalized USA civilian population on the basis of a complex multistage probability sample. The majority of participants were found to have serum concentrations under the limit of detection (LOD) of many kinds of POP. Therefore, they selected six POP (2,2,4,4,5,5-hexachlorobiphenyl [PCB153], 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin [HpCDD], 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin [OCDD], oxychlordane, p,p-dichlorodiphenyltrichloroethane [DDE], and trans-nonachlor) for which at least 80% of the study subjects had concentrations more than the LOD.

The results were striking. A body load of persistent organic pollutants (as a matter of fact, a sum of six POP) was associated with the prevalence of diabetes in a strong dose-dependent manner (Figure 1)². The association was stronger among obese subjects than non-obese patients. Furthermore, it was striking to see when POP concentrations were very low, the prevalence of diabetes was very rare among the obese subjects with BMI ≥ 30 kg/m². Further analysis of NHANES data showed POP levels were also associated with several other conditions, including metabolic syndrome.

Observations showing the association between POP and diabetes soon followed from Denmark (Greenland Inuit), Taiwan, Japan, and very recently from the Slovak Republic³. These data appear too strong to deny a causal association. However, the mere presence of a statistical association between two variables, POP and diabetes/metabolic syndrome in our case, does not establish a cause-effect relationship. Does exposure to POP induce insulin resistance? Soo Lim *et al.*⁴ at Seoul National University Medical College, Korea, reported that rats treated with low doses of atrazine develop insulin resistance along with

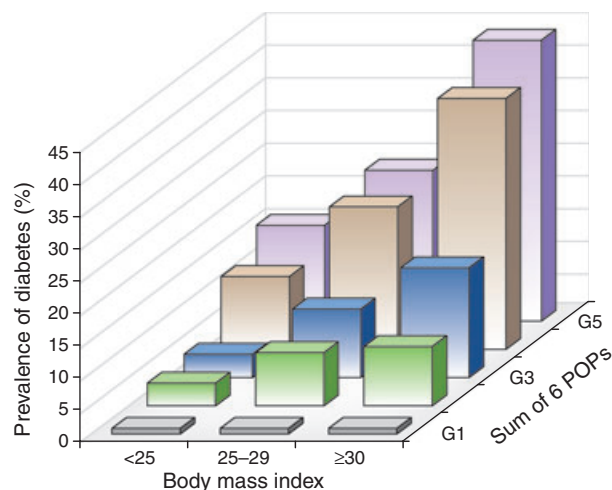


Figure 1 | Relationship between sum of six POPs detected in US populations, body mass index and prevalence of diabetes, 1999–2002 NHANES study. Obesity does not increase prevalence of diabetes as far as POPs level is low, but interacts with POPs to increase the risk of diabetes. (Courtesy of Lee DH).

abdominal obesity. Even though atrazine is not listed as a POP, it is the most heavily used pesticide in the USA and persists a fairly long time in the environment. Jerome Ruzzin at National Institute of Nutrition and Seafood Research, Norway, and his colleagues in Europe⁵ reported this year that Wistar rats exposed for 28 days to lipophilic POP through the consumption of a high-fat diet containing crude fish oil obtained from farmed Atlantic salmon developed insulin resistance and again abdominal obesity.

To prove unequivocally that POP exposure causes diabetes/metabolic syndrome, we need a human study. Due to ethical reasons, it cannot be done. Duk-Hee Lee informed me that people are looking for stored samples in their refrigerators, if their diabetes/metabolic syndrome cases had higher serum POP levels long before they develop evidence of metabolic abnormalities. Results of those nested case-control studies are heartily expected.

Dear fellow diabetes investigators, I think we have a very good answer to the question of ‘why is there a diabetes epidemic in my country?’ It is due to the contamination of our environment by POP during industrialization. Ruzzin *et al.*⁵ give a good description of biochemical mechanisms in their paper and I have provided a slightly different explanation in a recent review, emphasizing biophysical aspects⁶. In short, POP act similar to pesticide atrazine and damage mitochondria. In fact, pesticides are designed to inhibit photosynthesis of plants, and generally

inhibit mitochondrial function as they share similar structural motifs.

To prevent a worsening of the diabetes epidemic in society and to treat individual patients who have already developed diabetes, we need to understand more about POP. We need to control POP use. How many POP are there? From where do they come into our body? I am worried about my Chinese and Indian friends because DDT use is still permitted there. It is banned everywhere except in these two countries and Mexico. As a clinician, I am wondering what might be the best way to treat POP overload. What would happen if they are eliminated? To answer these questions and more, we need to develop less expensive POP monitoring method(s), as chemical measurement of POPs level in serum is prohibitively expensive.

I hope you can submit an article to this Journal proudly claiming that you solved one of the questions posed here in the near future.

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