Pesticides and human diabetes: a pilot project to explore a possible link

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Abstract
An increasing number of studies show an association between environmental pollutants—especially organophosphorous pesticides—and the development of insulin resistance and hyperglycaemia. Our aim was to explore this hypothesis in farming communities around the city of Madurai, India.

Local Ethics Committee approval was obtained. In all, 260 participants more than 18 years of age from farming villages around Madurai were evaluated based on three categories of pesticide exposure.

The crude odds ratio for farmers mixing and spraying pesticides to have diabetes compared to the minimal exposure category was 2.07 (95% CI 1.01–4.24). After adjusting for sex and BMI, the odds ratio was 2.302 (95% CI 1.082–4.896).

There seems to be a moderate association between pesticide exposure and diabetes. A good study design and good control of confounding factors will testify to this association.

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Key words
pesticides; diabetes

Introduction
There has been an alarming increase in the prevalence of diabetes over the last decade. Efforts to understand the pathophysiology and prevention have largely been directed at lifestyle and genetics. However, there is a growing body of evidence for the role of environmental pollutants, especially pesticides in the aetiology of diabetes and metabolic syndrome. There seems to be an association between organophosphate pesticide exposure and hyperglycaemia with mechanistic linkages through disruption of glycogenesis, glycolysis, glycogenolysis, gluconeogenesis, hormonal disruption and oxidative stress.

Our interest in this issue was sparked by anecdotal evidence presented by an increasing number of farmers in our area with diabetes and no obvious risk factors. We also recently published the case of a 15-year-old girl with organophosphate pesticide poisoning masquerading as diabetic ketoacidosis, adding further cause for concern. The widespread use of organophosphate pesticides in rural Tamil Nadu, India, together with the above mentioned associations, stimulated the rationale for a pilot proposal to examine plausible linkages between pesticides and diabetes.

Research design and methods
Three farming villages around Madurai, India, were selected for this pilot project. Local Ethics Committee approval was obtained.

Men and women aged more than 18 years were included in the study. Participants were not pre-selected. All participants came to the village centre based on a directive issued by the village president. Pesticide exposure was categorised into three groups.

• Category 1: no or minimal exposure group (participants working in offices or people at home).
• Category 2: intermediate exposure group (participants involved in weeding, pruning, picking and harvesting).
• Category 3: high exposure group (participants involved in mixing and spraying pesticides).

Diabetes was defined as taking medications for diabetes or a random capillary glucose of ≥200mg/dl in those without a history of diabetes. Hypertension was defined as taking medications for hypertension or blood pressure recordings ≥140/90mmHg on two occasions taken 30 minutes apart in participants with no history of hypertension. Variables collected were age, gender, blood pressure, BMI, history...
of diabetes, capillary blood glucose and the degree of pesticide exposure. All data were entered on Microsoft Excel 2007 and transposed to SPSS for analysis.

**Results**

A total of 260 participants were screened in this pilot study. The key variables based on categories of pesticide exposure are summarised in Table 1. The overall prevalence of diabetes was 24.6% in this rural population with a near doubling of numbers in the high exposure group (Category 3). The odds ratio for Category 3 to have diabetes compared to Category 1 was 2.07 (95% CI 1.01–4.24). Even after adjusting for sex and BMI, the odds ratio remained the same (adjusted odds ratio 2.309 [95% CI 1.082–4.886]). For the sake of this analysis, the first two exposure categories were clubbed as one and compared with Category 3. Likewise, BMI was categorised into dichotomous groups (<25 and ≥25kg/m²). The prevalence of hypertension was 35% in the study group. The odds ratio between the minimally exposed group (Category 1) and the high exposure group (Category 3) with respect to hypertension was 1.26 (95% CI 0.64–2.4).

**Discussion**

A number of animal and human studies suggest an association between pesticide exposure and the development of insulin resistance and diabetes. In a large prospective agricultural health study of incident diabetes in licensed applicators, the odds of diabetes incidence increased with organochlorine and organophosphate pesticides. Such associations have been reproduced in different parts of the world including Africa, Europe and Australia. Our pilot study in a farming population of rural Tamil Nadu, India, raises important research questions to further explore this association.

The striking finding in our study was the high prevalence of diabetes (25%) and hypertension (35%) in a rural population of south Tamil Nadu. A population based cross-sectional study from rural Karnataka has shown a diabetes prevalence of nearly 20% with an additional 12% with impaired glucose tolerance. Intuitively, one would expect a lower prevalence of diabetes in a rural population who traditionally lead a more active lifestyle compared to an urban population. The BMI of our study group was 23.9kg/m² and this measure was much lower at 23.1kg/m² in Category 3 (the high exposure group). However, the prevalence of diabetes was highest in this category at nearly 40%. The odds ratio of having diabetes between this group and the minimal exposure group was 2.07 (95% CI 1.01–4.24), raising the possibility that risk factors other than lifestyle and genetics may have a role to play. Participants in Category 3 were involved in mixing and spraying pesticides without any personal protective equipment such as wearing masks, aprons or gloves. It is well recognised that pesticides can not only get absorbed through layers of the epidermis but can also remain in the skin itself acting as a reservoir for release in future. With studies highlighting the mechanistic linkages between pesticides and various glucose homeostatic pathways, ubiquitous use of pesticides with no protective measures seems to be an ‘attractive diabetogenic link’ to explain the high prevalence of diabetes in a category where one would expect the least number of participants to have the disease.

The above hypothesis may sound highly speculative as there are many confounding factors but, with estimates suggesting that the use of pesticides has increased 50-fold over the past 50 years, it may not be entirely unreasonable to speculate that pesticides may be a ‘cog in the wheel’, contributing in some way to the huge explosion in diabetes.

The prevalence of hypertension in our rural study population was 35%. Pesticides have been implicated in concentric left ventricular remodelling and hypertension. In animal models, sub-lethal exposure to weekly enteral organophosphate pesticides was associated with hypertrophy of cardiac myocytes, which was confirmed with morphometric studies. The authors suggested that possible explanations for this finding were persistent systemic arterial hypertension in treated animals and direct sympathetic activation. Spontaneously hypertensive rat models were found to have a more sustained rise in blood pressure following chlorpyrifos administration orally. It may be possible that individuals with a genetic predisposition to hypertension may be more susceptible from exposure to organophosphate based pesticide in the long term.

There are several limitations in our study. We were unable to test venous glucose or glycosylated haemoglobin due to financial constraints. The data were skewed with higher baseline age and more men in the high exposure group compared to the other two groups. However, this was, to some extent, taken care of by the stratified analysis. Misclassification of age was also observed, i.e. many participants had a tendency to round off their age when interviewed. However, we feel that this was non-differential misclassification as participants in all three categories exhibited this.
behaviour. The diagnosis of new hypertension was based on two recordings half an hour apart due to time constraints.

In conclusion, allowing for the above limitations, our pilot study raises valid research questions on the association between pesticide use and diabetes. A strong study design with good control of confounding factors will testify to this association.

References