Growing burden of diabetes in Pakistan and the possible role of arsenic and pesticides

Haji Bahadar1,2, Sara Mostafalou2 and Mohammad Abdollahi1*

Abstract

This review is undertaken to address the possible role of arsenic and pesticides in the prevalence of diabetes in Pakistan and to highlight a resourceful targeted research in this area.

A bibliographic search of scientific databases was conducted with key words of “epidemics of diabetes in Pakistan”, “diabetes in Asia”, “diabetes mellitus and environmental pollutants”, “diabetes mellitus and heavy metals”, “diabetes mellitus and pesticides”, “prevalence of pesticides in Pakistan”, and “heavy metals contamination of drinking water, vegetables and fruits in Pakistan”. More than 200 articles were examined. Studies reporting the prevalence of diabetes mellitus (DM), pesticides and heavy metal contamination of drinking water, fruits and vegetables were included in the study. According to WHO 2011 report, about 12.9 million people are suffering from DM and the number is constantly increasing. Water pollution is a major public health threat in Pakistan. Most of the people in Pakistan are exposed to arsenic and pesticides either in drinking water or through vegetables, fruits, and other edible items with various concentrations above the WHO/FAO permissible limits. Being an agricultural country, a 1169% increase has been recorded with the use of different types of pesticides since last two decades, and almost similar rise in the burden of diabetes.

There is a growing global concern of arsenic and pesticides exposure with the incidence of DM. Besides other factors, the environmental attributors in the incidence of DM in Pakistan have not been conclusively elucidated yet which in turn deserve a resourceful targeted research.

Keywords: Arsenic, Diabetes mellitus, Environmental pollutants, Heavy metals, Pakistan, Pesticides, Review

Introduction

Pollution is the addition of substances or energy to the environment, likely to produce harmful effects on human health and ecosystem. Heavy industrialization and scientific developments have led to the addition of detrimental chemicals to the environment in the form of heavy metals, agrochemicals, pesticides and hydrocarbons [1]. Environmental pollution has been a major health concern throughout the world since very long, but the risks are higher in underdeveloped countries. In low developed countries, environmental pollution contributes about 8-9% of total disease burden [2].

Pakistan, a country with a population exceeding 180 million, having four provinces along with federally administered tribal areas, is the 6th populous country of the world with a very small economy [3].

Arsenic exposure in Pakistan

The presence of arsenic (As) in drinking water has become a major public health concern around the world. Arsenic has been recognized globally as the most toxic inorganic contaminant of drinking water [4]. Water sources of Asian countries, including Pakistan are among the most affected ones for As contamination [5,6].

Regional status of arsenic exposure in Pakistan

Sindh province

Approximately 36% people in Sindh province consume drinking water or vegetables containing As above the WHO limit [7]. The ground water sources in some rural areas in Sindh province contain As up to 1.1 mg/L [8]. A study published by Arain et al. reported the contamination of vegetables with As. The vegetables grown in the south
east part of Sindh contain As in the range of 0.90-120 mg/kg, exceeding WHO/FAO limit of 0.0001 mg/kg [9]. Drinking water samples tested from districts Tharparkar, Matiari and Jamshoro have been shown to contain As in the range of 0.013-2.09 mg/L [7,10,11]. Data about the presence of As either drinking water or vegetable from other areas of Sindh are not available to completely understand the status of peoples in term of As exposure in this province.

**Punjab province**

Punjab is the most populated province of Pakistan. The drinking water sources of Punjab province have been reported to contain As level above the WHO safe limit. According to reports, approximately 20% population in Punjab is exposed to As contaminated water [12]. Drinking water sources of some regions in Punjab, such as Bahawalpur, Gujranwala, Kasur, Lahore, Multan, Muzaffargarh, Rahim Yar Khan and Sheikhupura, have been reported to contain As level in the average range of 0.0794 to 0.9 mg/L [6,8,13-15]. “Pakistan Council of Research in Water Resources” a government body responsible for water quality in Pakistan, has reported As content above the WHO permissible limits in drinking water sources of some other regions such as Attock, Multan, Sargodha and Bahawalpur. However, the values for As content in water samples of these areas have not been made public [16]. Overall, compared to other provinces of Pakistan, water samples of many areas of Punjab province have been studied for the presence of As contents. It has been reported that drinking water sources of Punjab province contain comparatively high As contents.

**Khyber Pakhtoonkhwa province**

Arsenic from the soil gets its way to ground water and ultimately enters the crops. Beside presence of As in drinking water sources, it has been reported that wheat, which is the is the main edible crop of the Pakistani population, contain As contents above safe limits. Al-Othman et al. have studied wheat crop samples from different districts of Khyber Pakhtoonkhwa for bioaccumulation of As contents. The results of this study showed that wheat crop in these areas contains As in the range of 0.005-1.113 mg/kg. The permissible limits of As in agronomic crops is 0.43 mg/kg [17]. However, WHO/FAO (Codex-1995 amended 2009) has not defined any permissible limit for As in the wheat crop Table 1.

**Balochistan province**

Studies about the presence of As prevalence in Balochistan province are limited. However, some studies have reported the presence of As within the range of permissible limits of WHO in some selected districts [13].

| References | Sample studied | Arsenic | Result |
|------------|----------------|---------|--------|
| [15]       | Drinking water | As      | 79.4 μg/L |
| [8]        | Drinking water | As      | 1.5-5 μg/L |
| [14]       | Drinking water | As      | Reported as “above WHO limit” |
| [6]        | Drinking water | As      | 10-906 μg/L |
| [5]        | Drinking water | As      | 906 μg/L |
| [11]       | Drinking water | As      | 3-106 μg/L |
| [16]       | Drinking water | As      | Reported as “above WHO limit” |
| [18]       | Drinking water | As      | 32-1900 μg/L |
| [17]       | Wheat crop     | As      | 0.005-1.113 mg/kg |
| [9]        | Vegetables     | As      | 0.00-120 mg/kg |

Maximum residue limit for As in the vegetable is 0.0001 mg/kg (WHO/FAO). Maximum residue limit of As for wheat crop is 0.43 mg/kg (Al-othman et al. 2012). The permissible limit for As in drinking water is 10 μg/L (WHO 2006).

**Pesticides exposure in Pakistan**

Pesticides presence poses a great threat to the environment and human life. The use of pesticides in agriculture is substantially increasing from the last four decades for protection of crops [19,20]. It is astonishing to note that very small quantities of applied pesticides reaches the target organism accurately and major part of “applied pesticides” is dispersed in the environment and enters the human food chain [20]. Migration of applied pesticides in drinking water and subsequent entry to food chain has remained a global concern and several cases of drinking water contamination have been reported in the developed world [21]. Pakistan being an agriculture country consumes approximately 70 thousand tons of different pesticides annually and the use of different types of pesticides in Pakistan has increased by 1169% in the last 2 decades [22-24]. Each crop in Pakistan receives at least 10 different types of pesticides, which is an alarming signal for public health [23,25]. This huge application of pesticides in agriculture sector has led to the contamination of drinking water sources, vegetables, cattle food, milk, and fish samples throughout the country [26,27]. Some water sources of Punjab province have been reported by Tariq et al. to contain different types of pesticides like bifenthrin, cyhalothrin, carbofuran, endosulfan, methyl parathion and monocrotophos exceeding the permissible limits defined by WHO/FAO. Fruits and vegetable collected from various parts of the country and tested for the presences of different types of pesticides have been reported to contain pesticides like, carbofuran, dimethoate, deltamethrin, cypermethrin, and chlorpyrifos contents exceeding the WHO/FAO maximum residue limits [27-29]. Water sources of the cotton growing areas of, both Punjab and Sindh province, and tobacco growing areas of Khyber.
PakhtoonKhwa have been found contaminated with pesticides. As Pakistan is an agricultural country, therefore a huge amount of different pesticide use for protection of crops is imminent. There are published few studies regarding the contamination of vegetables and other food items with pesticide residues from all parts of the country. Determination of pesticides in vegetables and drinking water, has remained an understudied subject in Pakistan. All available studies about the prevalence of pesticides in various areas have been accumulated in Table 2, Figure 1.

**Evidences for association of As and pesticides with incidence of diabetes**

**Arsenic**

Enough experimental and epidemiological evidences are available which suggest that As exposure add to the incidence of diabetes [33-36]. Navas-Acien et al. have published a cross sectional study of 788 individuals chronically exposed to As in the USA. The researchers found a strong correlation between chronic exposure to low level of As and non-insulin diabetes mellitus [37]. Exposure to As, either in drinking water or from

| Reference  | Sample studied | Pesticides | (WHO/FAO) permissible limit | Result     |
|------------|----------------|------------|----------------------------|------------|
| [24]       | Ground water   | Bifenthrin | ND                         | 11 μg/L    |
|            |                | Carbofuran | 7 μg/L                     | 36 μg/L    |
|            |                | Methyl parathion | 9 μg/L     | 3 μg/L     |
|            |                | Monocrotophos | 3 μg/L  epa           | 20 μg/L    |
|            |                | Carbofuran | 7 μg/L                     | 36 μg/L    |
|            |                | Endosulfan | ND                        | 6 μg/L     |
|            |                | Cyhalothrin | ND                    | 7 μg/L     |
| [30,31]    | Ground water   | Dichlorvos | ND                        | 0.03-0.45 μg/L |
|            |                | Mevinphos | ND                        | 0.06-0.21 μg/L |
|            |                | Dimethoate | 6 μg/L                    | 0.0-0.15 μg/L |
|            |                | Methylparathion | ND           | 0.0-0.06 μg/L |
|            |                | Chlorpyrifos | 30                     | 0.0-0.03 μg/L |
|            |                | Fenitrothion | ND                    | 0.0-0.2 μg/L |
|            |                | Endosulfan | ND                        | 0.0-0.2 μg/L |
|            |                | Profenphos | ND                        | 0.01-0.17 μg/L |
|            |                | Carbofuran | 7 μg/L                    | 0.0-0.26 μg/L |
|            |                | Lindane    | 2 μg/L                     | 0.11 μg/L  |
| [27]       | Fruits         | Cypermethrin | 0.1 mg/kg              | 0.94 mg/kg |
|            |                | Deltamethrin | ND                   | 0.039 mg/kg |
|            |                | Dimethoate | ND                        | 0.139 mg/kg |
|            |                | Endosulfan | ND                        | 0.774 mg/kg |
| [32]       | Vegetables     | Lindane    | 0.5 mg/kg                 | 4.21 mg/kg |
|            | Luffa          | Cypermethrin | ND                   | 1.63 mg/kg |
|            | Methylparathion | ND           | 1.71 mg/kg               |
|            | Cauliflower    | Methylparathion | 0.2 mg/kg     | 2.5 mg/kg  |
|            | Methamidopos   | 1.0 mg/kg    | 2.60 mg/kg               |
|            | P,P, DDT       | 1.0 mg/kg    | 10.3 mg/kg               |
|            | Onion          | Methylparathion | ND                   | 3.15 mg/kg |
|            | Methamidopos   | 0.5 mg/kg    | 4.61 mg/kg               |
|            | Cypermethrin   | 0.1 mg/kg    | 1.8 mg/kg                |
|            | Tomato         | Malathion   | 3.0 mg/kg                | 10 mg/kg   |
|            | Fenvvalerate   | 2.2 mg/kg    | 1.0 mg/kg                |

ND: not defined.
Figure 1 Map representing areas with high contents of arsenic, pesticides and DM prevalence in Pakistan.

Figure 2 A Schematic illustration of possible pathways by which As and pesticides may induce diabetes.
other environmental sources, and its possible link with incidence of diabetes has been reported in epidemiologic studies published from various parts of the world like Bangladesh, Taiwan, South Korea, Cyprus, Serbia, China and Mexico [35,38-43]. Recently a population based study published from Iran has suggested a relationship between even a lower exposure level of As (20–30 μg/L) and incidence of diabetes and hypertension [44]. Recently a workshop was conducted by the U.S. National Toxicology Program on environmental chemicals and the incidence of DM in which various epidemiological and experimental evidences were evaluated. It has been concluded that studies regarding As exposure with an incidence of DM are suggestive but not sufficient and further objective research in this area is highly recommended [45].

Multiple mechanisms may be involved in As induced diabetes. In experimental studies As has been reported to act on multiple targets such as, affecting insulin sensitivity, altering β cells function, alteration of β cells signaling pathways, disturbing glucose production in the liver, and the reduction of insulin secretion and initiation of oxidative stress in the pancreas [46-49] Figure 2, Table 3. Evidences from population based and experimental studies mentioned above are suggestive enough to prove that chronic As exposure may lead to the incidence of diabetes.

Pesticides
Numerous experimental studies are available about the toxic effects of pesticides and the occurrence of type 2 diabetes. Organophosphorus and organochlorine types

| Reference | Type of study | Compound          | Doses            | Duration | Outcome/result                                                                 |
|-----------|---------------|-------------------|------------------|----------|--------------------------------------------------------------------------------|
| [36]      | Experimental  | As                | 10 mg/kg         | >3 months| Islets damage                                                                  |
|           |               |                   |                  |          | Insulin secretion ↓ reactive oxygen species (ROS) ↑                               |
| [50]      | Experimental  | As                | 0.5-2 μM         | >3 months| Insulin secretion ↓                                                             |
|           | (Pancreatic β cells) |       |                  |          | Insulin mRNA levels ↓                                                           |
| [49]      | Experimental  | As                | 5.55 mg/kg       | 30 days  | Liver glycogen level ↓                                                          |
|           |               |                   |                  |          | Blood sugar level ↑                                                             |
|           |               |                   |                  |          | Glutamate pyruvate transaminase activity ↓                                      |
|           |               |                   |                  |          | Glucose 6-phosphatase activity ↓                                                |
| [48]      | Experimental  | As                | 1 mM             | –        | PI-3 kinase independent; SAPK2/p38                                             |
|           |               |                   |                  |          | IUF–Translocation from cytoplasm to nucleus ↑                                    |
| [35]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [37]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [38]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [51]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [39]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [41]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [42]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [52]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [43]      | Epidemiologic | As                | -                | >3 months| Positive association of As exposure with diabetes                               |
| [44]      | Epidemiologic | As                | -                | >3 months| Positive association of As with diabetes in population                          |
| [53]      | Experimental  | Malation          | 100-400 ppm      | 30 days  | Hepatic glycogen phosphorylase ↑                                               |
|           |               |                   |                  |          | Phosphoenol pyruvate carboxy kinase ↑                                           |
| [54]      | Experimental  | Malation          | 25-100 mg/kg/day | 32 days  | Phosphoenol pyruvate carboxy kinase                                              |
|           |               |                   |                  |          | Glucose 6-phosphatase ↑                                                         |
| [55]      | Epidemiologic | Organo -chlorine Pesticides | - | >3 months | Positive association of pesticides with diabetes Insulin resistance observed |
| [56]      | Epidemiologic | Organo -chlorine Pesticides | - | >3 months | Positive association of pesticides with diabetes Insulin resistance observed |
| [57]      | Epidemiologic | Malation          | -                | >3 months| Positive association of pesticides with diabetes Insulin resistance observed |
of pesticides in particular have been mentioned to possess deleterious effect on glucose metabolism and insulin secretion [53,55,57]. However, few epidemiologic studies exist in the literature about the role of pesticides in the occurrence of diabetes [58,59]. A prospective study published by Montgomery et al. have reported a high prevalence of diabetes in the 33457 licensed pesticide applicators in the US, and the ratio of diabetes incidence was noted more in organochlorine and organophosphorus type of pesticide applicators [56]. Pesticides may cause diabetes by affecting multiple pathways involved in glucose regulation. The involved mechanisms include oxidative stress, nitrosative stress, pancreatitis, inhibition of choline esterase, altered mitochondrial functions, and alteration of adrenal gland functions [54,60-62] (Figure 2, Table 3).

Overview of DM prevalence in Pakistan

DM is the leading chronic diseases and has emerged a big socioeconomic burden in Pakistan. Various populations-based studies and national surveys have shown that DM is a highly prevalent disease in almost all regions of Pakistan, with an overall ratio of 22.04% in urban and 17.15% in rural areas [63-65]. According to various surveys, the pattern of DM prevalence in Pakistan is as Punjab; male, 16.6%, female, 19.3%, Khyber PakhtoonKhwa; 11.1% both sexes, Balochistan; 10.8% both sexes, Sindh; male 16.2% female 11.7% [66-68]. According to the latest data provided by the International Diabetes Federation, (www.Idf.Org/Diabetesatlas/Data-Visualisations) Pakistan is among the leading countries with high prevalence of DM. As per WHO 2011 report total prevalence of diabetes is 12.9 million among them 9.4 million are diagnosed, while 38 million population is pre-diabetic and the number of diabetic patients would increase to 14 million by 2030 [69] Figures 3 and 4.

Discussion and conclusion

Like other poor countries, polluted water is also one of the major public health threats in Pakistan with special emphasis to drinking water. Pakistan stands at position 80 in the world community in term of drinking water quality. Water used for drinking purposes is contaminated with heavy metals and pesticides [22]. About 89% of drinking water sources have poor quality and are not according to the parameters set by WHO for human consumption [14,18]. Pakistan is an agricultural country, and for the sake of high crop yield, there has been recorded about 1169% increase in the use of different types of pesticides for the last two decades, and almost similar rise in the burden of diabetes, and according to various studies the number of diabetic patients in Pakistan would become two fold by 2030. According to World Bank Report 2010, Pakistan is facing health crises with high incidence of diabetes, affecting poor families which increase the burden of poverty (Figure 3).

Experimental and some epidemiologic studies gathered above suggest that environmental pollutants such as pesticides, As, Cd and Hg are risk factors in the incidence of DM. Excessive As presence has been reported in water sources of many other countries of the World like Argentina (1–9900 μg/L), China (0.05-850 μg/L), India (10–3200 μg/L), Brazil (0.5-350 μg/L), Mexico (8–620 μg/L), USA (1–100,000 μg/L), Taiwan (10–1820 μg/L), and particularly Bangladesh having 1–2500 μg/L [70-72]. And according published data As exposure has been considered as one of the risk factors in the incidence of DM in these countries and some countries like China, India, Brazil and USA are at the forefront of this epidemic (http://www.idf.org/diabetesatlas/data-visualisations).
We are of the opinion that there might be a correlation of heavy metals like As and pesticide exposure with the prevalence of DM in Pakistan. Even though, there are many regions, where the drinking water sources are grossly contaminated with heavy metals and pesticides, but to correlate the prevalence of DM in exposed population and exposure to these pollutants; there is a complete lack of targeted epidemiologic research in the affected areas. We are of the view that along with other confounding factors, the role of As and pesticides in the epidemic of DM in Pakistan cannot be overlooked. Furthermore, there is a need of an urgent attention of concerned quarters like environmental researchers/toxicologists, governmental and non-governmental organizations to objectively evaluate the epidemics of DM in Pakistan from various dimensions including identifying the role of environmental pollutants and to take practical steps in this regard. No doubt, comprehensive and objective data derived from a resourceful targeted research on environmental pollutants and the prevalence of DM in Pakistan would be extremely laudable among environmental scientists. Data obtained from such targeted research will significantly add to the growing body of evidences about the role of environmental pollutants in the occurrence of chronic diseases.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
HB wrote the initial draft of the article and completed intensive literature review. SM edited the article. MA gave the idea, read, and edited the manuscript. All authors read and approved the final manuscript.

Funding sources
This paper is the outcome of a financially non supported in-house study.

Author details
1Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, International Campus, Tehran University of Medical Sciences, Tehran, Iran. 2Department of Pharmacology and Toxicology, School of Pharmacy, Ardebil University of Medical Sciences, Ardebil, Iran.

Received: 5 September 2014 Accepted: 27 November 2014
Published online: 14 December 2014

References
1. Madaku H: Water pollution and man’s health. Internet J Gastroenterol 2006, 4(1):1–11.
2. Briggs D: Environmental pollution and the global burden of disease. Brit Med Bull 2003, 68(1):1–24.
3. Wahedee Y, Tahir S, Ahmad T, Qadri I: Sequence comparison and phylogenetic analysis of core gene of hepatitis C virus from Pakistani population. Afr J Biotechnol 2010, 9(29):4561–4567.
4. Chowhan S, Flora SJ: Arsenic and fluoride: two major ground water pollutants. Indian J Exp Biol 2010, 48(7):666–678.
5. Rahman MM, Naidu R, Bhattacharya P: Arsenic contamination in groundwater in the Southeast Asia region. Environ Geochem Health 2009, 31(Suppl 1):19–29.
6. Mukherjee A, Sengupta MK, Hossain MA, Ahamed S, Das B, Nayak B, Lodh D, Rahman MM, Chakrabarti D: Arsenic contamination in groundwater: a global perspective with emphasis on the Asian scenario. J Health Popul Nutr 2006, 24(2):142–163.
7. U DIG A, Mughal A, Maheshwari B: Arsenic contamination in ground water sources of district Miani, Sindh. Int J Chem Environ Eng 2012, 3(4):259–266.
8. Haque N, Nabi D, Baig M, Hayat W, Treffy M: Groundwater arsenic contamination: A multi-directional emerging threat to water scarce areas of Pakistan. JAHS publication 2008, 324:24.
9. Arain MB, Kazi TG, Baig JA, Jamali MK, Afzali HI, Shah AQ, Jallabani N, Sarfraz RA: Determination of arsenic levels in lake water, sediment, and foodstuff from selected area of Sindh, Pakistan: Estimation of daily dietary intake. Food Chem Toxicol 2009, 47(1):242–248.
10. Brahman KD, Kazi TG, Afzali HI, Naseem S, Arain SS, Ullah N: Evaluation of high levels of fluoride, arsenic species and other physicochemical parameters in underground water of two sub districts of Tharparkar, Pakistan: A multivariate study. Water Res 2013, 47(3):1005–1020.
11. Baig JA, Kazi TG, Arain MB, Afzali HI, Kandhoor GA, Sarfraz RA, Jamali MK, Shah AQ: Evaluation of arsenic and other physico-chemical parameters of surface and ground water of Jamshoro. Pakistan J Hazard Mater 2009, 166(2–3):662–669.
12. Ahmad T, Khiallown M, Tahir A, Rashid H: Arsenic an emerging issue: Experiences from Pakistan. Paper presented at: 30th WEDC international conference, Viaentiane, Lao 2004. Water, Engineering and Developing Center, Loughborough University Leicester LE11 3TU UK. http://wedd.lboro.ac.uk/resources/conference/30/Ahmad.pdf.
13. Soomro M, Khokhar M, Hussain W, Hussain M: Drinking water quality challenges in Pakistan. Pakistan: Council of Research in Water Resources, 2011:1–28.
14. PCWR. National Water Quality Monitoring programme 5th Monitoring report 2005-2006: Pakistan Council for Research in Water Resources, Islamabad, Pakistan. http://www.pcwr.gov.pk/parkpublication%20pcwr.aspx.
15. Ahmad SA, Gulzar A, Rehman HU, Soomro Z, Hussain M, Rehman M, Qadir M: Study of Arsenic in drinking water of district Kasur Pakistan. World Appl Sci J 2013, 24(5):634–640.
16. Tahir MA, Rasheed MH, Imran MS: Water quality status in rural areas of Pakistan. Pakistan Council of Research in Water Resources 2010, (143):1–66. www.pcwr.gov.pk/Btl_wr…/Rural%20areas%20Report/WQReport.pdf.
17. Al-Othman ZA, Ali R, Al-Othman AM, Ali J A: Hability: Assessment of toxic metals in wheat crops grown on selected soils of Kyber Pakhtun Khaw, Pakistan, irrigated by different water sources. Arab J Chem 2012. doi:10.1016/j.arabjc.2012.04.006.
18. Farooqi A, Masuda H, Siddiqui R, Naseem M: Sources of arsenic and fluoride in highly contaminated soils causing groundwater contamination in Punjab, Pakistan. Arch Environ Contam Toxicol 2009, 56(4):693–706.
19. Van der Werf HMG: Assessing the impact of pesticides on the environment. Agric Ecosyst Environ 1996, 60(2):381–96.
20. Pimentel D: Amounts of pesticides reaching target pests: environmental impacts and ethics. J Agricul Environ Ethics 1995, 8(1):17–29.
21. Gaughey, M. E: Pesticides in surface waters: Distribution, trends, and governing factors. Environmen Progress 1999, (18)(1):58–69 doi:10.1002/ ep.6701801170.
22. Azizullah A, Khattak MNK, Richter P, Hæder DP: Water pollution in Pakistan and its impact on public health A review. Environ Int 2011, 37(2):479–497.
23. Tarig MI, Afzal S, Hussain I, Sultana N: Pesticides exposure in Pakistan: a review. Environ Int 2007, 33(3):1107–1122.
24. Tarig MI, Afzal S, Hussain I: Pesticides in shallow groundwater of Bahawalnagar, Muzaffargarh, D.G. Khan and Rajan Pur districts of Punjab, Pakistan. Environ Int 2004, 30(4):471–479.
25. Khan M, Zia MS, Qasim M: Use of pesticides and their role in environmental pollution. World Acad Sci Eng Technol 2010, 72:122–128.
26. Hussain S, Masud T, Afzal K: Determination of pesticides residues in selected varieties of mango. Pakistan J Nutr 2002, 1(1):41–42.
27. Anwar T, Ahmad I, Tahir S: Determination of pesticide residues in fruits of Nawabshah district, Sindh, Pakistan. Pak J Bot 2011, 43(2):1133–1139.
28. Latif Y, Sherazi STH, Bhanger MI: Assessment of pesticide residues in commonly used vegetables in Hyderabad, Pakistan. Ecotoxicol Environ Safety 2011, 74(2):2299–2303.
29. Tahir S, Anwar T, Ahmad I, Aziz S, Mohammad A, Afzal K: Determination of pesticide residues in fruits and vegetables in Islamabad market. J Environ Biol / Acad Environ Biol India 2001, 22(1):71–74.
30. Afzal K, Anwar T, Ahmad I, Mohammad A, Tahir S, Aziz S, Baloch U: Determination of insecticide residues in groundwater of Mardan Division, NWFP, Pakistan: A case study. Water SA 2000, 26(3):409–412.
31. Ahad K, Mohammad A, Khan H, Ahmad J, Hayat Y: Monitoring results for organochlorine pesticides in soil and water from selected obsolete pesticide stores in Pakistan. Environ Monit Assess 2010, 166(1-4):191–199.

32. Masud SZ, Hasan N: Pesticide Residues in Foodstuffs in Pakistan: Organochlorine, Organophosphorus and pyrethroid insecticides in Fruits and Vegetables. In Environ Toxicol Assess. Edited by Richardson M; London: Taylor and Francis Ltd; 2004:270–280.

33. Huang CF, Chen YW, Yang CY, Tsai KS, Yang RS, Liu SH: Arsenic and diabetes: current perspectives. Kaohsiung J Med Sci 2007, 23(7):402–410.

34. Smith AH: Arsenic and diabetes. Environ Health Perspect 2013, 121(3):A70–A71.

35. Rahman M, Tondel M, Ahmad SA, Axelsson O: Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol 1998, 148(2):198–203.

36. Yen CC, Lu FJ, Huang CF, Chen WK, Liu SH, Lin-Shiau SY: The diabetogenic effects of the combination of humic acid and arsenic in vitro and in vivo studies. Toxicol Lett 2007, 172(3):91–105.

37. Navas-Acien A, Silbergeld EK, Escobedo-de la Peña J: Inorganic arsenic exposure and type 2 diabetes mellitus in Mexico. Environ Res 2007, 104(3):383–389.

38. Wang SL, Chang FH, Liou SH, Wang HJ, Li WF, Hsieh DP: Inorganic arsenic exposure and its relation to metabolic syndrome in an industrial area of Taiwan. Environ Int 2007, 33(6):805–811.

39. Pan WC, Sewo WJ, Kle ME, Hoffman EB, Quamruzzaman Q, Rahman M, Mahliuddin G, Mostafa G, Lu Q, Christians DC: Association of low to moderate levels of arsenic exposure with risk of type 2 diabetes in Bangladesh. Am J Epidemiol 2013, 178(10):1563–1570.

40. Rhee SY, Huang YC, Woo JT, Chin SO, Chon S, Kim YS: Arsenic exposure and prevalence of diabetes mellitus in Korean adults. J Korean Med Sci 2013, 28(6):861–868.

41. Makris KC, Christofi CA, Palii M, Ettinger AS: A preliminary assessment of low level arsenic exposure and diabetes mellitus in Cyprus. BMC Public Health 2012, 12(3):134.

42. Wang W, Xie Z, Lin Y, Zhang D: Arsenic-induced alteration in the expression of genes related to type 2 diabetes mellitus. Toxicol Appl Pharmacol 2013, 280(1):101–116.

43. Kuo C-C, Moon K, Thayer KA, Navas-Acien A: Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. Curr Diab Rep 2013, 13(6):831–849.

44. Díaz-Villaseñor A, Burns AL, Sarafian M, Cebrián ME, Ostrosky-Wegman P: Arsenic-induced alteration in the expression of genes related to type 2 diabetes mellitus. Toxicol Appl Pharmacol 2007, 225(2):123–133.

45. Tseng CH: The potential biological mechanisms of arsenic-induced diabetes mellitus. Toxicol Appl Pharmacol 2004, 197(2):67–83.

46. Macfabe NM, McKinnon CM, Felton-Edkins ZA, Gragg H, James RF, Docherty K: Glucose stimulates translocation of the homeodomain transcription factor PDX1 from the cytoplasm to the nucleus in pancreatic beta-cells. J Biol Chem 1999, 274(22):1011–1016.

47. Pai S, Chatterjee AK: Prospective protective role of melatonin against arsenic-induced metabolic toxicity in Wistar rats. Toxicology 2005, 208(1):25–33.

48. Díaz-Villaseñor A, Burns AL, Salazar AM, Sordo M, Hiriart M, Cebrián ME, Ostrosky-Wegman P: Arsenic reduces insulin secretion in rat pancreatic β-cells by decreasing the calcium-dependent calpain-10 proteolysis of SNAP-25. Toxicol Appl Pharmacol 2008, 231(2):291–299.

49. Lai MS, Hsieh YM, Chen CJ, Shyu MP, Chen SY, Kuo TL, Wu MM, Tai TY: Ingested inorganic arsenic and prevalence of diabetes mellitus. Am J Epidemiol 1994, 139(5):484–492.

50. Jovanovic D, Raic-Milutinovic Z, Paunovic K, Jakovljevic B, Pavisic S, Milojevic J: Low levels of arsenic in drinking water and type 2 diabetes in Middle Banat region, Serbia. Int J Hyg Environ Health 2013, 216(1):50–55.

51. Abdollahi M, Faraji M, Pourmournahmed M, Saadat M: Hyperglycemia associated with increased hepatic glycogen phosphorylase and phosphoenolpyruvate carboxykinase in rats following subchronic exposure to malathion. Comp Biochem Physiol C Toxicol Pharmacol 2004, 137(4):343–347.

52. Mostafaloo S, Eghbal MA, Nili-Ahmadabadi A, Baeri M, Abdollahi M: Biochemical evidence on the potential role of organophosphates in hepatic glucose metabolism toward insulin resistance through inflammatory signaling and free radical pathways. Toxicol Ind Health 2012, 28(9):840–851.

53. Lee D-H, Lind PM, Jacobs DR, Salihovic S, van Bavel B, Lind L: Polychlorinated Biphenyls and Organophosphate Pesticides in Plasma Predict Development of Type 2 Diabetes in the Elderly The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Diab Care 2011, 34(1):1778–1784.

54. Montgomery M, Kamel F, Saldana T, Alavanja M, Sandler D: Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural health study, 1993–2003. Am J Epidemiol 2008, 167(10):1235–1246.

55. Saadat M, Al Bass MA, Saleem HM: Malathion exposure and insulin resistance among a group of farmers in Al-Sharkia governorate. Clin Biochem 2012, 45(18):1591–1595.

56. Saldana TM, Basso O, Hoppin JA, Baird DD, Knott C, Blair A, Alavanja MC, Sandler D P: Pesticide exposure and self-reported gestational diabetes mellitus in the Agricultural Health Study. Diab Care 2007, 30(3):629–534.

57. Everett CJ, Matheron EM: Biomarkers of pesticide exposure and diabetes in the 1999–2004 National Health and Nutrition Examination Survey. Environ Int 2010, 36(4):398–401.

58. Rahimi R, Abdollahi M: A review on the mechanisms involved in hyperglycemia induced by organophosphorus pesticides. Pest Biochem Physiol 2007, 88(2):115–121.

59. Mostafaloo S, Abdollahi M: Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. Toxicol Appl Pharmacol 2013, 286(2):175–177.

60. Saeidnia S, Abdollahi M: Toxicological and pharmacological concerns on oxidative stress and related diseases. Toxicol Appl Pharmacol 2013, 273(3):442–455.

61. Shera KS, Jawad F, Maqbool A: Prevalence of diabetes in Pakistan. Diab Res Clin Practice 2007, 76(2):219–222.

62. Akhter J: The burden of diabetes in Pakistan: the national diabetes survey. J Pak Med Assoc 1999, 49(9):205–205.

63. Zahid N, Claussen B, Hussain A: Diabetes and impaired glucose tolerance in a rural area in Pakistan and associated risk factors. Diabetes Metab Syndr. Clin Res Reviews 2008, 2(1):125–130.

64. Shera A, Rafique G, Ahmed K, Baqai S, Khan I, King H: Pakistan national diabetes survey prevalence of glucose intolerance and associated factors in North West Frontier Province (NWFP) of Pakistan. J Pak Med Assoc 1999, 49(9):206–210.

65. Shera KS, Basit A, Fawwad A, Hakeem R, Ahmedani M, Hydie MZI, Khwaja IA: Pakistan National Diabetes Survey: Prevalence of glucose intolerance and associated factors in the Punjab Province in Pakistan. Pmcr Diab 2010, 4(2):297–83.

66. Shera A, Rafique G, Khwaja I, Ara J, Baqai S, King H: Pakistan national diabetes survey: prevalence of glucose intolerance and associated factors in Shikarpur, Sindh Province. Diab Med 1995, 12(11):116–1121.

67. Shaw J, Sicaire R, Zimmert P: Global estimates of the prevalence of diabetes for 2010 and 2030. Diab Res Clin Practice 2010, 87(1):14–14.

68. Nordstrom DK: Worldwide occurrences of arsenic in ground water. Science 2002, 296:2143–2145.

69. Mandal BK, Suzuki KT: Arsenic round the world: a review. Talanta 2002, 58(1):201–235.

70. Chowdhury UK, Binwas BK, Chowdhury TR, Samanta G, Mandal BK, Basu GC, Chandra CR, Lodh D, Saha KC, Mukherjee SK: Groundwater arsenic contamination in Bangladesh and West Bengal, India. Environ Health Perspect 2000, 108(5):393.

Cite this article as: Bahadar et al.: Growing burden of diabetes in Pakistan and the possible role of arsenic and pesticides. Journal of Diabetes & Metabolic Disorders 2014;13:117.

doi:10.1186/s40200-014-0117-y