Impact of Environmental Factors as an Etiology for Diabetes Mellitus

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Abstract

The prevalence of diabetes has increased to a greater extend over the past few decades and is estimated to increase over few years. According to the World Health Organization, India has the unique distinction of being the country with the largest number of diabetic patients in the world. In 1995, prevalence of diabetes was 19.4 million and is projected to increase to nearly 80 million in 2030. Impact of nitrates, nitrites, nitrosamines, polychlorinated biphenyls, coffee, childhood diet, dietary supplements, metals, alcohol, air pollution, maternal environment, for the development of type 1 and type 2 diabetes are discussed in this review. It is clear that some environmental pollutants affect pancreatic beta cell function, as both epidemiological and experimental research is accumulating. It is very important to explore the role of environmental factors in etiology of diabetes to elucidate the heterogeneity of diabetes and expand our understanding of how best to prevent the disease.

Keywords: Environmental factors, Prevalence, Type 1 diabetes, Type 2 diabetes.

INTRODUCTION

Type 1 and type 2 diabetes mellitus have shown increasing incidence worldwide, making them a key concern to public health. The occurrence of diabetes mellitus has increased remarkably as a consequence of changes in human lifestyle and behavior.[1] Understanding the impact of environmental factor as an etiological factor is an emerging issue. This review is to identify the impact of environmental factors as an etiology for type 1 and type 2 diabetes. Scientists at the International Joint Commission suggested that the relevance of corresponding distribution of toxic substances might account for the variation in diabetes rates.[2]

Type 1 diabetes occurs when production of insulin is reduced by the pancreatic β cells. Environmental factors are thought to trigger the autoimmune process against β cells. The Monozygotic twins have 20–35% concordance of type 1 diabetes,[3,4] signifying the role of environment in diabetes etiology. Communicable agents or nutritional factors are usually considered etiologically relevant ecological factors that arouse an immune response.[5]

Type 2 diabetes occurs when there is relative deficiency of insulin and insulin resistance. The Monozygotic twins have 30% concordance of type 2 diabetes[5]

Environmental triggers to diabetes is mentioned in figure 1

ARGUMENTS SUPPORTING ENVIRONMENTAL FACTORS IN THE PROGRESSION OF TYPE 1 DIABETES

Role of exogenous elements in the pathophysiology of type 1 diabetes is being supported by a few data. The occurrences of type 1 diabetes is lowest rate in Europe and the highest rate is observed in Finland.[7] Precedent decades have revealed a substantial rise in the occurance of type 1 diabetes in Europe and Finland[8] which can be due to lifestyle and environmental changes. Patients with high risk HLA genotype reduced over last decades with recently diagnosed type 1 diabetes, while people with low risk HLA genotype has increased[9,10]These data are well-matched with an elevated environmental pressure that results in development to clinical diabetes of less genetic susceptibility. The Potential risk factors to Type 1 Diabetes is shown in Table 1

ASSOCIATION OF GENETIC SUSCEPTIBILITY WITH ENVIRONMENTAL FACTORS IN TYPE 1 DIABETES

Study conducted by Forbes et. al.,[21] shown that AGER gene polymorphisms which is inherited may confer vulnerability to environmental insults. Clinical disease in children with high to medium risk HLA II backgrounds may be analyzed if the level of circulation of soluble RAGE (receptor for advanced glycation end products) is reduced before the emerging of overt diabetes. A population based twin cohort study conducted by Nistico et al showed Genetic contribution to type 1 diabetes has vulnerability of 40%, and the shared and individual-specific environmental components were 51% and 9% respectively.[22] This study suggested that in addition to genetic effects, the environmental effects increase the risk of type 1 diabetes.

ARGUMENTS SUPPORTING ENVIRONMENTAL FACTORS IN THE PROGRESSION OF TYPE 2 DIABETES

Rapid increase has been seen in the prevalence and incidence of type 2 diabetes in population undergoing westernization. This is a key epidemiologic arguments in association with the impact of environment.[23,24,25] The changeover to westernization is habitually accompanied by increasing in risk of obesity; decreases in physical activity; dietary intake of more calories, fat, and less complex carbohydrates.

Study conducted on Qatari population showed a higher prevalence of diabetes in association with diabetic population in Japan making type 2 diabetes a life –style related disease.[26] The Potential risk factors to Type 2 Diabetes is shown in Table 2.

ASSOCIATION OF GENETIC SUSCEPTIBILITY WITH ENVIRONMENTAL FACTORS IN TYPE 2 DIABETES

Evidence that environmental elements alter phenotypic expression emerged from the Diabetes Prevention Program (DP) [41] shows a remarkable prevention of type 2 diabetes on every 6.9 or 13.9 persons who done lifestyle modification. Risk of developing diabetes was dissipated in people who were on lifestyle intervention according to a post hoc analysis conducted genotyping 3500 participants for transcription factor 7 like 2 polymorphism [42]

The figure explains about the environmental factors that are contributing to the pathophysiological effects leading to Diabetes Mellitus
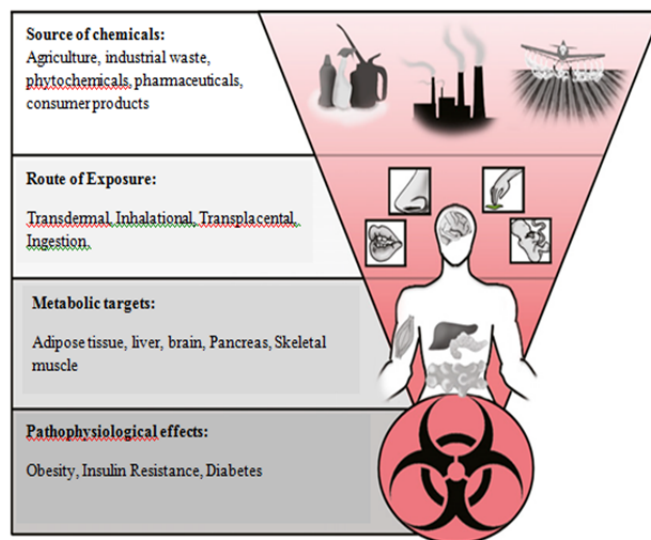

Fig 1: Environmental triggers to diabetes[6]

Table 1: Potential Risk Factors for Type 1 Diabetes

Sl.no	Etiology	Potential risk factors	Reference
1	Nitrates, Nitrites, and Nitrosoamines	Helgason et. al., in his study showed the occurance of type 1 diabetes in male offspring if cured mutton, a source of N-nitroso compounds, when taken in pregnancy. The study proposed that dietary nitrosamine activity was repressed by estrogen and promoted by testosterone, thus accounting for the male specificity.	[11]
2	Polychlorinated Biphenyls	A cross sectional study conducted on pregnant women showed an increase in polychlorinated biphenyls to 30% in type 1 diabetes compared to non-diabetes.	[12]
3	Coffee	A correlation coefficient of 0.74 was found when national coffee consumption per Person during 1978-1982 was compared in children (0-14 years) with annual incidence of type 1 diabetes.	[13]
4	Childhood diet	Consumption of food rich in protein or carbohydrates can increase the risk of type 1 diabetes as in a case control study by Dahlquist *et al*.	[14]
5	Latitude, Temperature	Preceding studies propose that there is a link between type 1 diabetes and the physical environment including prevalence of certain viruses, diet, lifestyle patterns and the ethnicity of inhabitants. This incidence increases during cold climate as well as with the equatorial distance.	[15]
6	Dietary supplement Vitamin D	Higher intake of nutritional supplements of vitamin D can trigger type 1 diabetes mellitus. A prospective, longitudinal cohort study was conducted by Aronsson et al in four countries (USA, Sweden, Finland, Germany) showed a higher intake of vitamin D by pregnant women through diet which add up to the development of type 1 Diabetes	[16]
7	Enterovirus	Previously hidden self-components will be exposed when infected by enterovirus as the pancreatic islet cells may exhibit cytolysis. Dotta et. al., conducted a study where enterovirus was detected in three of six pancreatic tissue samples from patients with T1DM. Additionally, pancreatic injury was caused by Coxsackie viruses. Elshebani et. al., verified that enteroviruses that were secluded from patients who were recently diagnosed with T1DM, induced the damage of human pancreatic islets *in vitro*.	[17,18,19,20]

Table 2: Potential Risk Factors for Type 2 Diabetes

Sl.no	Etiology	Potential risk	Reference
1	**Metals**	Several metals, such as cadmium, mercury and the metalloid arsenic, have been associated with the development of type 2 diabetes epidemiologically. In 1970s there was a report bringing forth the capability of metals to interrupt insulin secretion.	
	➤ **Cadmium**	Secretory activities of pancreatic beta cells are inhibited by cadmium which is mediated by calcium uptake interference. A diminished insulin release rate was found with high level of cadmium whereas low concentration of cadmium is suggested to stimulate insulin release. Moreover, in the Third National Health and Nutrition Examination Survey, cadmium was related with both impairing fasting glucose and diabetes.	[27,28]
	➤ **Arsenic**	Arsenic causes the initiation of oxidative stress and the drop of insulin transcription and secretion in the pancreatic beta cell. The available epidemiological data on arsenic and diabetes suggest a higher incidence of diabetes on exposure to arsenic. Arsenic is metabolized *in vivo* to trivalent arsenic. A trivalent arsenical, phenylarsine oxide, has adverse effects on the insulin receptor and glucose transport in *in vitro* experiments.	[29,30,31]
	➤ **Mercury**	The subsistence of mercury-induced beta cell damage underlined the relation between type 2 diabetes and methyl mercury poisoning in Japan. Mercury, as mercuric chloride ($HgCl_2$), target the pancreas by varying intracellular Ca^{2+} homeostasis in beta cells and declining insulin secretion from toadfish islets.	[32,33]
2	**Alcohol**	There was a higher rate of weight gain in people drinking alcohol when compare to non drinkers which contribute to non-insulin dependent diabetes mellitus. Study conducted by Balkau et al among diabetics in France have found a 7- to 13-fold excess mortality owing to alcohol and cirrhosis, much higher than for coronary heart disease or diabetes.	[34]
3	**Air Pollution**	Endothelial function is altered by the exp osure to air pollution which often precede Insulin Resistance changes and have been caught up in reduction in peripheral glucose uptake. Studies related to diabetes prevalence or incidence, Ontario, Canada on 7,634 patients attending two respiratory clinics with chronic exposure to NO2 (traffic-related pollution) showed 1 ppb NO2 increased DM prevalence in women but there is no significant association in men. Another study conducted on 1,776 non diabetic women in Ruhr, Germany showed an increase in diabetes incidence over a mean of 16 years upon exposure to particulate matter or in relation to traffic exposure or NO2	[35,36,37,38, 39]
4	**Maternal environment**	Risk of obesity and type 2 diabetes development at younger ages can be increased to the children who were open to the elements of maternal diabetes and/or obesity during pregnancy. By the time these female off spring attain their childbearing years they might have already developed obesity, diabetes and abnormal glucose tolerance, thereby perpetuating the cycle. Across generations, this cycle is likely developing the risk and/or progress to the onset of obesity and type 2 diabetes.	[40]

CONCLUSION

Several studies of environmental factors have been published recently which indicate an important role for physical immobility and augmented dietary fat in the etiology of Diabetes. It is very important to explore the role of environmental factors in etiology of diabetes to elucidate the heterogeneity of diabetes and expand our knowledge of best option in preventing the disease. In the future, new avenues need to be developed to reveal the intricate role of environmental factors. The current data reflect decades of functional work to decode the underlying pathology. It is hoped that this review will ultimately translate into new therapeutic modalities.

REFERENCE:

1. Zimmet, P., Alberti, K.G., Shaw, J., *Nature*. 2001,*414,*782–787.
2. Elliot, S., Eyles, J., DeLuca, P., *Environ Health Perspect*.2001,*109*,817–826.
3. Barnett, A.H., Eff, C., Leslie, R.D., Pyke, D.A., *Diabetologia*.1981,*20*,87–93.
4. Kaprio, J., Tuomilehto, J., Koskenvuo ,M., et al. *Diabetologia*.1992;*35*:1060–1067.
5. Dahlquist, G., *Diabetes Metab Rev*.1995,*11*,37–46.
6. Neel, B.A., Sargis, RM., *Diabetes*.2011,*60*,1838-1848.
7. Patterson, C.C., Dahlquist, G., Green, A., *Lancet*.2000,*355*,873–876.
8. Gale, E.A.,. *Diabetes*.2002,*51*,3353–3361.
9. Hermann, R., Knip, M., Veijola, R., et. al., *Diabetologia*.2003,*46*,420–425.

10. Gillespie, K.M., Bain, S.C., Barnett, A.H., et al.. *Lancet*.2004,*364*,1645–1647.
11. Helgason, T., Ewen, S.W., Ross, I.S., Stowers, J.M., *Lancet* 1982,2,1017–1022.
12. Longnecker,M.P., Klebanoff, M.A., Brock,J.W., Zhou, H., *Diabetes Care*.2001,*24*,1099–1101.
13. Tuomilehto, J., Tuomilehto-Wolf, E., Virtala, E., LaPorte, R., *Br Med J*.1990,*300*,642–643.
14. Dahlquist, G.G., Blom, L., Persson, L.Å., Sandstro¨m, A.I.M., Wall, S.G.I., *Br Med J*.1990,*300*,1302–1306.
15. Diabetes Epidemiology Research International Group: *Diabetes*.1988,*37*,1113–1119.
16. Androsson, C.A., Vehik, K., Yang, J., et al. *Public Health Nutrition.*.2012,*16*,1390-1402.
17. Dotta, F., Galleri, L., Sebastiani, G., Vendrame,F., *Curr Diab Rep*.2010,*10*,357-361.
18. Coppieters, K.T., von Herrath, M.,. *J Pathol*.2013,*230*,1-3.
19. Dotta, F., Censini, S., van Halteren, A.G., et.al.. *Proc Natl Acad Sci*.2007,*104*,5115-5120.
20. Elshebani, A., Olsson, A., Westman, J., Tuvemo, T., Korsgren, O., Frisk, G., *Virus Res*.2007,*124*,193-203.
21. Forbes, J.M., Sodurlund, J., Yap, F.Y., et al. *Diabetologia*.2011,*54*,1032-1042.
22. Nistico, L., Lafusco, D., Galderisi, A., *J Clin Endocrinol Metab*.2012,*97*,1483-1491.
23. Weiss, K.M., Ferrell, R.E., Hanis, C.L., *Yearbook Phys Anthropol*.1984,27,153-178.
24. Bennett PH: Diabetes in developing countries and unusual populations. In *Diabetes in Epidemiologic Perspective,* Mann JI, Pyorala K, and Teuscher A, Eds. Churchill-Livingstone, Edinburgh, 1983;43-57.
25. Zimmet, P.Z., *Diabetes Care* .1992,*15*,232-252.
26. Matsuoka, K.,. *Diabetes Res Clin Pract*.2000,*50*,17-22.
27. Nilsson, T., Rorsman, F., Berggren, P.O., Hellman, B., *Biochim Biophys Acta*.1986,*888*,270–277.
28. Schwartz, G.G,, Il'yasova, D., Ivanova, A., *Diab Care*.2003,*26*,468–470.
29. Izquierdo-Vega, J.A., Soto, C.A., Sanchez-Peña, L.C., De Vizcaya-Ruiz, A., Del Razo, L.M., *Toxicol Lett*.2006,*160*,135–142.
30. Díaz-Villaseñor, A., Burns, A.L., Hiriart, M., Cebrián, M.E,, Ostrosky- Wegman, P., *Toxicol Appl Pharmacol*.2007,*225*,123–133.
31. Douen ,A.G., Jones, M.N., *Biofactors*.1990,*2*,153–161.
32. Chen, Y.W., Huang, C.F., Tsai, K.S., et al. *Diabetes*.2006,*55*,1614–1624.
33. Chen, Y.W., Huang, C.F., Tsai KS., et al. *Chem Res Toxicol*.2006,*19*,1080–1085.
34. Balkau, B., Eschwege, E., Ducimetiere, P., Richard, J.L., Warnet, J.M., *Clin Epidemiol*.1991,*44*,465-474.
35. Mills, N.L., Törnqvist, H., Robinson, S.D., et al. *Circulation*.2005,*112*,3930–3936.
36. Sun, Q., Wang, A., Jin, X., et al.. *JAMA*.2005,*294*,3003–3010.
37. Baron, A.D., Steinberg, H.O., Chaker, H., Leaming, R., Johnson, A., Brechtel, G., *J Clin Invest*.1995,*96*,786–792.
38. Brook, R.D., Jerrett, M., Brook, J.R., Bard, R.L., Finkelstein, M.M., *J Occup Environ Med*.2008,*50*,32–38.
39. Krämer, U., Herder, C., Sugiri, D., et al. *Environ Health Perspect*.2010,*118*,1273–1279.
40. Dabelea, D., Crume, T., *Diabetes*.2011,*60*,1849-1855.
41. Knowler, W.C., Barrett-Connor, E., Fowler, S.E., et al. *N Engl J Med*.2002,*346*,393-403.
42. Florez, J.C., Jablonski, K.A., Bayley, N., et al. *N Engl J Med*.2006,*355*,241-250.