Diabetes Epidemic and the Thrifty Gene

Mogher Khamaisi PhD and Itamar Raz MD

Diabetes Center and Department of Internal Medicine, Hadassah University Hospital, Jerusalem, Israel
Affiliated to Hebrew University Medical School, Jerusalem, Israel

Key words: Bedouin, lifestyle, nomads, obesity, urbanization

IMAJ 2002;4:720–721

Diabetes mellitus, long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the twenty-first century. The past two decades have seen an explosive increase in the number of people diagnosed with diabetes worldwide. Pronounced changes in the human environment, behavior and lifestyle have accompanied globalization and have resulted in escalating rates of both obesity and diabetes.

The diabetes epidemic, both in developed and developing nations, refers particularly to type 2 diabetes. Paradoxically, part of the problem relates to the achievements in public health during the twentieth century such as the elimination of many of the communicable diseases, which have resulted in people living longer. Non-communicable diseases such as diabetes and cardiovascular disease have now become the main public health challenge for the present century due to their impact on personal and national health and their associated premature morbidity and mortality [1].

In this issue of *IMAJ*, Drs. Abou-Rabiah and Weitzman describe the diabetes epidemic among the Bedouin population in the Negev desert and show an enormous increase in the rate of this disease [2]. Forty years ago the prevalence of diabetes in this population was about 0.5%, while today it exceeds that of the neighboring Jewish population and is approaching 10%. Moreover, obesity, previously rare in this population, has become a major public health problem and, according to the authors' findings, may be a very prevalent condition among Bedouins. Once a population of nomads with a deficient food supply and a non-sedentary lifestyle, the Bedouin have shifted from nomadic to settled living that has resulted in an epidemic of diabetes. Similarly, investigations in the Arab world indicate an increase in diabetes. The prevalence in Tunisia in 1988 was 4.7% and 5.2% in urban men and women aged 40–50 years, respectively. Nine years later, in 1997, the rates of self-reported diabetes in a corresponding population were 7% and 13% respectively. Age-adjusted rates indicate that in Egypt today, 9.3% of the population over the age of 20 have diabetes compared to 6.5% in 1987. In Oman, 10% of people aged >20 have diabetes, and in Saudi Arabia, the figure is 12% in people aged >15 years [3]. Different age-adjusted rates are associated with various degrees of urbanization, and urban life is associated with a higher occurrence of diabetes. Among nomadic Bedouins in Egypt, the prevalence of diabetes is 1.8%. The prevalence in the same age group in the rural agricultural villages is 6.5%, and in the urban areas 11.8%. Similarly, in Tanzania, shifting from rural to urban surroundings increased the prevalence of diabetes from zero to nearly 8% [3].

The prevalence of diabetes in Israel among various Jewish ethnic groups of immigrants, and changes in the prevalence of diabetes within the same groups as a result of changes in environmental conditions, emphasize the influence of the environment on the manifestation of this disease. The transition from a rural to an urban lifestyle and the increased westernization in both Yemenite and Ethiopian societies provide an opportunity to study the process of change and its effect on eating habits and the development of health risk factors [4]. Most regions in Ethiopia and Yemen are rural. The incidence of cardiovascular disease, hypertension, diabetes and obesity is very low in both countries. The traditional diet is low in calories, fat and sugar, and high in complex carbohydrates. The high level of physical activity is seasonal, as is food availability. However, prolonged studies are required to shed more light on the role of the environment in the development of diabetes and other non-communicable diseases in these populations. The change from cyclical seasonality of food shortages to stabilized availability of food probably has the most significant effect on the metabolic processes involved in glucose-insulin interdependence.

Long-term adaptation mechanisms, such as a reduction in resting metabolic rate and the thrifty genotype, have been identified for a number of populations, among them rural Ethiopians. In response to urbanization following immigration and stabilized food availability, there is an increase in energy density, fat and carbohydrate intake and a decrease in physical activity; and the thrifty genotype promotes rapid weight gain, abdominal fat accumulation, insulin resistance and possible development of diabetes.

In 1962, under the title "Diabetes Mellitus: A 'thrifty' genotype rendered detrimental by 'progress'," Dr. James Neel [5] proposed the idea that the basic defect in diabetes mellitus was a quick insulin trigger. He suggested that this trigger was an asset to our tribal hunter-gatherer ancestors with their intermittent, sometimes feast-or-famine alimentation, since it should have minimized renal loss of precious glucose.

Although type 2 diabetes obviously blossomed with inactivity and over-alimentation, the striking prevalence in various American Indian groups created the suspicion that there might be a particular predisposition to the disease in some tribal groups, a predisposition that surfaced with reservation-style living. In other words, the thrifty genotype hypothesis was of limited ethnic applicability. An interesting observation on the role of lifestyle in the emergence of

type 2 diabetes in American Indians involves the Pima Indians of southern Arizona and a closely related group, the Pima Indians of the Sierra Madre Mountains of northern Mexico, two groups estimated to have separated some 700–1,000 years ago. The findings of the studies performed in those groups [3] give no support to the notion that the high frequency of type 2 diabetes in reservation American Indians might be due simply to an ethnic predisposition; rather, the high rate predominantly reflects lifestyle changes.

Several groups of investigators have presented evidence for the action of alleles at a single major locus in the etiology of type 2 diabetes. Bogardus et al. [6] reported that in Pima Indians, fasting insulin levels have a trimodal distribution, suggesting a major role for a bi-allelic system, and segregation analysis of the familial distribution of type 2 diabetes in the same group also yielded evidence for the action of a single major gene. Mitchell et al. [7] recently reported evidence for a major (dominant) allele, affecting post-challenge insulin levels in Mexican Americans. Employing the sibpair approach, a more recent genome-wide search for susceptibility genes in Mexican Americans with type 2 diabetes produced evidence for a major susceptibility locus on chromosome 2, with the allele accounting for 30% of the familial clustering [8], as in the study of Mitchell et al. [7].

It is now clear that the original thrifty genotype hypothesis, with its emphasis on feast or famine, presented an overly simplistic view of the physiologic adjustments involved in the transition from the lifestyle of our ancestors to life in the high-tech fast lane. Eaton and Eaton [9] have emphasized how different in composition was the Stone Age body that received intermittent alimentation compared with our bodies of today. Whereas the total daily energy expenditure in adult members of hunter-gatherer and traditional agricultural societies was approximately 3,000 kcal/day, in today's industrialized societies it is in the order of 2,000 or less.

Despite all these advances in our understanding of type 2 diabetes, the nature of the environmentally precipitated genetic maladjustments that result in the disease remain obscure. Given the intensity of the current efforts to localize and characterize the genes, the functioning of which seems to be compromised in type 2 diabetes, speculation concerning their nature seems of little value at this time. However, the concept of a "thrifty genotype" remains as viable as when first advanced, and it now seems desirable, in view of the direction this essay is taking, to begin to put the concept of a "compromised" thrifty or adaptive genotype into a broader context that will include two other diseases presenting similar epidemiologic characteristics.

Increased rates of non-communicable disease risk factors, such as obesity, diabetes, hypertension and overweight, have been documented in numerous populations in transition. The prevalence and incidence of these risk factors vary in different populations. Currently nutrition has become a significant factor in elucidating human adaptability to immigration. Changes in economic status, eating habits, food selection and physical activity of populations in transition suggest a strong interaction between the environment, nutrition and metabolism in compromising health.

Although directing funds to treating diabetes and its complications is important, the rapid escalation in the number of people with diabetes demands urgent action in the field of prevention. Recent studies have highlighted the potential for intervention in subjects with impaired glucose tolerance to reduce progression to type 2 diabetes. One such study is the recently completed Diabetes Prevention Program in the United States [10]. This study showed that during a 3 year period, lifestyle intervention (targeting diet and exercise) reduced the risk of progressing from impaired glucose tolerance to diabetes by 58%, whereas the oral hypoglycemic drug, metformin, reduced the risk by 31% [11]. Two other large-scale studies, in Finland and Da Qing (China), have also demonstrated the efficacy of lifestyle interventions in the prevention of diabetes.

Development of the 'thrifty' genotype, which confers a selective advantage during periods of food scarcity, may be the survival mechanism that jeopardizes weight maintenance during the course of immigration and westernization. Insulin resistance, the underlying factor in obesity and diabetes, may be the phenotypic expression of the thrifty genotype.

In conclusion, diabetes prevalence rates in Israeli Bedouin, as in the Arab world, are high. Urban residence, personal income and economic growth are interrelated, and, together with an affluent diet and a sedentary lifestyle, are associated with diabetes and obesity. Most Bedouin have experienced varying degrees of economic growth and urbanization. However, none of these factors are sufficient to explain the increased rates of diabetes. It appears that cultural factors and perceptions are no less significant than a receptive genotype.

References

1. Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414:782–7.
2. Abou-Rbiah Y, Weitzman S. Diabetes among Bedouins in the Negev: the transition from a rare to a highly prevalent condition. *IMAJ* 2002;4:687–9.
3. Nielsen JV. Diabetes in the Arab world: prevalence and risk factors. *Pract Diabetes Int* 1999;16:82–6.
4. Trostler N. Health risk in immigration: the Yemenite and Ethiopian cases in Israel. *Biomed Pharmacother* 1997;51:352–9.
5. Neel JV. The "Thrifty genotype" in 1998. *Nutr Rev* 1999;57:S2–9.
6. Bogardus C, Lillioja S, Nyomba BL, et al. Distribution of in vivo insulin action in Pima Indians as mixture of three normal distributions. *Diabetes* 1989;38:1423–32.
7. Mitchell BD, Kammerer CM, Hixson JE, et al. Evidence for a major gene affecting postchallenge insulin levels in Mexican-Americans. *Diabetes* 1995;44:284–9.
8. Hanis CL, Boerwinkle E, Chakraborty R, et al. A genome-wide search for human non-insulin-dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2. *Nat Genet* 1996;13:161–6.
9. Eaton SB, Eaton SB 3rd. Paleolithic vs. modern diets – selected pathophysiological implications. *Eur J Nutr* 2000;39:67–70.
10. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care* 1999;22:623–34.
11. Larkin M. Diet and exercise delay onset of type 2 diabetes, say US experts. *Lancet* 2001;358:565.

Correspondence: Dr. M. Khamaisi, Diabetes Center and Dept. of Internal Medicine, Hadassah University Hospital, P.O. Box 12000, Jerusalem 91120, Israel.
Fax: (972-2) 642-4514
email: murir@hadassah.org.il