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EDITORIAL

Diabetes and evolution

Every year, 14 November is observed as World Diabetes Day. This day marks the birthday of Dr Frederick Banting, who discovered insulin along with Dr Charles Best. This is an internationally recognized World Health Organization (WHO) event coordinated by the International Diabetes Federation (IDF), with an aim to spread awareness about diabetes mellitus. This year's theme is 'Family and Diabetes'. There will be events to promote the role of family in the prevention and management of diabetes, and activities to inform society about the impact of diabetes on the family.

Globally, more than 425 million adults have this debilitating condition. This number is expected to rise to 629 million by 2045 (https://www.idf.org/). In India alone, there were an estimated 72.9 million individuals afflicted with this disorder in 2017. This number is expected to reach 134.3 million by 2045. In fact, every fifth individual living with diabetes in the world is an Indian. Moreover, these numbers are thought to be gross underestimates, as in India alone nearly 42.2 million cases go undiagnosed (https://diabetesatlas.org). These alarming statistics have earned India the title of the 'diabetes capital' of the world.

Diabetes mellitus is characterized by increased blood glucose levels due to either insulin deficiency (type 1) or insulin resistance (type 2). Diabetes is a major contributing factor for coronary heart disease, hypertension, renal failure, stroke, blindness and lower-limb amputations. In India, nearly 997,000 deaths were attributed to diabetes in 2017 alone (https://diabetesatlas.org). Considering the widespread and increasing prevalence of this condition, it is not surprising that the global economic burden of diabetes was estimated to cause a GDP loss of 1.7 trillion USD from 2011 to 2030 (https://www.who.int/diabetes). This includes both direct costs (healthcare services and medication) as well as indirect costs (loss in productivity, disability and premature death). According to the International Diabetes Federation estimates for 2017, India is thought to have spent 8,713 million USD on diabetes healthcare.

The trend of rapid rise in the incidence of type-2 diabetes over the last few decades is both alarming as well as puzzling. The global prevalence of diabetes nearly doubled from 1980 to 2014 (4.7% to 8.5%; https://www.who.int/diabetes). In the ~200,000 years history of *Homo sapiens*, something has changed in the last few decades that has made us increasingly susceptible to this hyperglycaemic condition. Sedentary lifestyle and the shift from a primarily protein-based fibre-rich diet to a refined carbohydrate-based diet are the two major changes that are attributed to the surge in the incidence of diabetes. WHO recommends at least 150 min of moderate intensity physical activity per week for the age group 18–64 years. How many of us meet this need? WHO recommends less than 10% of the total energy intake from sugars, less than 30% of the same from fat (preferably unsaturated fat) and less than 5 g of salt intake. Ironically, our streets are flooded with fast-food joints that sell 'tasty' foods rich in refined carbohydrates, saturated fat and salt at attractive prices. Sadly, such places are even more common near schools and academic institutions. The recent advent of food aggregator apps on smartphones has provided easy access to such food round the clock. Nowadays, it is not uncommon to have midnight snacks using these apps.

Although the contribution of sedentary lifestyle and altered dietary habits to the surge of diabetes incidence is known, it is not clear why these factors predispose us to insulin resistance leading to type-2 diabetes. Evolutionary medicine can provide useful insights into this problem. This emerging field of medicine uses principles of evolutionary biology to explain *why* we get a particular disease. This is different from *how* we get that disease, which is addressed by traditional branches of medicine. For example, why do we get fever? Most biology students with a basic knowledge in inflammation would answer as follows: infection causes secretion of cytokines by the immune cells in our body, and certain cytokines will reset the 'thermostat' in the hypothalamus to a higher temperature resulting in fever. This is what is taught in medical schools and it is factually correct. However, this statement does not answer the query of *why* we get fever. Instead, it answers the question, '*how* do we get fever?' The appropriate answer is that fever helps us fight infectious agents. Generally, pathogenic microbes do not thrive at higher-than-normal (37°C) human body temperature. Thus, evolutionary medicine provides an 'ultimate' explanation, while traditional branches of medicine

provide a 'proximal' explanation for human health and pathological conditions. In spite of its ability to provide novel insights into human physiology and diseases, unfortunately, evolutionary medicine is not a formal part of the curriculum in most medical schools.

Though the evolutionary reasons behind symptoms such as fever are obvious, it is not clear why modern lifestyle makes us prone to pathological conditions such as diabetes, hypertension, obesity and ischaemic heart disease. The 'evolutionary mismatch' theory proposes that certain genes were selected for conferring an evolutionary benefit to the bearer in the environment that prevailed then. Due to rapid environmental change, such genes have not been purged from the population, and are maladaptive in the current context. Diabetes and obesity are two such cases of mismatch. Humans have been hunter–gatherers during most of their evolutionary history. Therefore, they were exposed to cycles of feast and famine as food availability was unpredictable. Periods of 'feasting' were interspersed with prolonged periods of 'fasting'. In such a context, it would have been advantageous for humans to possess genes that enabled the efficient storage of excess energy as fat by developing insulin resistance. This is the basis for the 'thrifty gene' hypothesis proposed by James Neel in 1962. Such thrifty genes are maladaptive in the modern obesogenic environment and lifestyle, and could be responsible for the sudden surge in the incidence of insulin resistance (type-2 diabetes) and obesity. However, genetic studies have not provided support to this attractive hypothesis.

The thrifty phenotype hypothesis, proposed by C. N. Hales and D. J. P. Barker in 1992, suggests that the intrauterine environment experienced by the foetus is used as an indicator of the conditions it will eventually be exposed to, and is used to activate a predictive adaptive response. Poor gestational growth permanently programmes the foetus to be insulin-resistant. Such a change in metabolism ensures that there is sufficient glucose diverted for brain development rather than towards muscle and organ growth. Thus, low-birth-weight babies are at a higher risk of developing type-2 diabetes in their adult stage. This is particularly true in cases where the predicted adult environment does not match the foetal environment. In other words, low-birth-weight babies, when exposed to sedentary lifestyle and nutrient-rich food, tend to develop insulin resistance and obesity. It is important to note that the incidence of low birth weight in India varies from 25% to 30%, which is very high compared to many other countries. This explains why India has become the diabetes capital. The thrifty phenotype hypothesis has gained support from several epidemiological and animal experimental studies.

Interestingly, some animal studies have also shown strong association between insulin resistance and food habits. A recent study has shown that blind Mexican cave fish (*Astyanax mexicanus*) have higher post-prandial blood glucose levels and impaired glucose tolerance when compared to the surface-dwelling variants of the same species (Riddle, M. R. *et al*., *Nature*, 2018, **555**, 647–651). Notably, animals in the deep-cave environment face long periods of food deprivation as there is limited photosynthesis. Remarkably, these cave fish possess a mutation in the gene encoding insulin receptor that confers insulin resistance. Furthermore, the same mutation is found in a type of hereditary diabetes mellitus in humans called Rabson–Mendelhall syndrome. This condition is characterized by severe insulin resistance. Similar associations between long periods of food deprivation and insulin resistance have been reported in northern elephant seals, gerbils and humming birds. These observations also suggest that insulin resistance may have been beneficial in the nutrient-limited environment to which our hunter–gatherer ancestors were exposed. Interestingly, periodic fasting is an integral part of many cultures in the world. In fact, a diet that mimics periodic fasting has been shown to decrease obesity, diabetes, heart disease and age-related changes.

The message from these studies is clear – type-2 diabetes condition is closely related to our lifestyle and food habits. Promoting physically active lifestyle and healthy food habits is the need of the hour. Shunning sedentary lifestyle, regularly practising moderate physical activity, avoiding refined, carbohydrate-rich food and incorporating fresh fruits and vegetables in our diet are a few habits that can definitely reduce the possibility of developing diabetes. We must also spread awareness about the early warning signs of diabetes so that it is treated at an early stage. On the World Diabetes Day, 14 November, let us pledge to lead a healthier life, and encourage our families and friends to achieve the same. After all, diabetes is just a disorder due to maladaptation. We can always readapt by changing our lifestyle.

Kirtana Vasu
Sandeep M. Eswarappa*

Department of Biochemistry,
Indian Institute of Science,
Bengaluru 560 012, India
*e-mail: sandeep@iisc.ac.in