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Editorial

Diabetes in 2007 - What are the promises & challenges?

When the IDF *Diabetes Atlas* was released at the 19th World Diabetes Congress, alarm bells went off among Indian delegates as India now has 40.9 million people with diabetes and the projected estimate for the year 2025 was 69.9 million[1].

Diabetes can now be controlled through improved medical care, monitoring, and lifestyle changes. The burgeoning epidemic of type 2 diabetes mellitus is now receiving increasing attention because of its human and fiscal costs and the disability and death associated with the disease. The major cause of mortality in diabetic patients is cardiovascular disease. Indeed, non-communicable chronic diseases including diabetes now cause a substantial health burden in the developing world[2].

These are exciting times for scientific discoveries since the basic mechanisms of molecular pathogenesis of diabetes are rapidly being unraveled. This, together with the increasing sophistication of technologies and animal models, should now permit researchers to find newer and better therapeutic options for diabetes. This special issue of IJMR focuses on diabetes and has a collection of excellent articles which address the molecular pathogenesis, genetics, biomarkers, epidemiology and disease management, as well as utility of model systems in diabetes research.

Hart and colleagues[3] discuss the uses of health related quality-of-life (HRQOL) assessment in diabetes care with special reference to Type 1 diabetes and the interpretation of treatment effects on quality of life.

The reasons for ethnic differences in the risk of type 2 diabetes are not entirely understood. For example, South Asians (people from India, Pakistan, Bangladesh, Nepal and Sri Lanka) have remarkably high prevalence of type 2 diabetes compared to Caucasians. One important factor contributing to increased type 2 diabetes in Asian Indians is excessive insulin resistance (IR) compared to Europeans[4] which could be due to an environmental or a genetic factor or by combination of both. Abate and Chandalia[5] review the status in migrant Asian Indians and discuss how the understanding of the etiology and mechanisms causing increased insulin resistance in Asian Indians is expected to provide clues to more effective prevention and treatment of diabetes in this ethnic group.

Over the past 20 yr, extensive efforts have been made to identify the insulin receptor signaling pathways leading to the plasma membrane translocation of GLUT4. McCarthy and Elmendorf[6] update our current state of knowledge on the intricate insulin signaling network responsible for glucose transport in peripheral adipose and skeletal muscle tissues with special reference to delineating signaling connections spanning the insulin receptor and GLUT4.

When ER functions are severely impaired, the cell is eliminated by apoptosis via several apoptotic executioners[7]. Explaining the protein folding machinery and downstream signaling events, Sundar Rajan and colleagues[8] delineate how ER stress could result in β cell dysfunction and insulin

resistance. The concept that 'the sustained ER stress of obesity (or chronic overnutrition in the absence of obesity) can get transduced into increased insulin resistance' is significantly important for Indians, as we experience a total epidemiological diet transition.

While insulin resistance and pancreatic β cell dysfunction are the two prominent causes of type 2 diabetes, it has been proposed that both of these complications have roots in mitochondiral defects[9]. Recent findings have suggested that inherited defects in mitochondrial oxidative phosphorylation activity might play a key role in the development of IR. Sreekumar and Nair[10] cover this topic by providing an integrated view on the interrelation between skeletal muscle mitochondrial changes resulting in reduced oxidative phosphorylation and insulin resistance that could have potential in developing treatments for many diseases.

Recent evidence has shown that AMPK activity can also be regulated by physiological stimuli, independent of the energy charge of the cell, including hormones and nutrients. Understanding of how to activate AMPK in skeletal muscle would offer significant pharmacologic benefits in the treatment of type 2 diabetes. In this context, Misra and Chakrabarti[11] explore how future targets for type 2 diabetes treatments will likely be those that can cause beneficial changes in the activity of AMPK.

Many factors influence the rate of cellular damage accumulation (and hence biological ageing) and that the pathogenesis of some important diseases is related to biological ageing. Do we have a biomarker to monitor the accelerated biological ageing? Recent studies propose that telomere shortening is a marker of biological ageing and atherosclerosis[12]. Balasubramanyam and colleagues[13] review this exciting area of research with their recent observation that telomere shortening in the prediabetes state, could be an interface for predisposition to cardiovascular disease and diabetes. Although many of these studies were of cross-sectional nature, a recent prospective study (West of Scotland Primary Prevention Study) showed that the mean leukocyte telomere length could be a predictor of future coronary heart disease events[14].

Working with cultured cell lines and an animal model of obesity, it has been recently shown that reactive oxygen species (ROS) have a causal role in multiple forms of insulin resistance[15]. The relation of ROS to insulin sensitivity may have evolved because increased accumulation of ROS could be interpreted by the cell as an imbalance between substrate availability and oxidative capacity to which decreased insulin signaling (and thus decreased glucose uptake) would be an appropriate response. Evans[16] discusses the scientific rationale for proposing the evaluation of antioxidants for insulin resistance, and provide an update of intervention studies, with an emphasis on clinical trials, in which antioxidants have been tested.

Radha and Mohan[17] provide an overview of the genetic predisposition of type 2 diabetes with special reference to Asian Indians. The opportunities are great for future diabetes genetic epidemiology research to provide clinically useful information, which is the primary goal of the Human Genome Project.

The cause of β cell destruction has remained an enigma for years, but two discoveries in the 1970s have provided the basis for our current thinking about the disease[18,19]. The first was a strong linkage of type 1 diabetes to the highly polymorphic HLA class II immune recognition molecules - DR and, later, DQ - located on chromosome 6. Biomarkers that are able to identify people at risk prior to autoantibody appearance could be used to identify a window of opportunity during which immunomodulation could be more effective in preventing disease. Mehra and colleagues[20] cover this topic by reviewing the use of genetic, immunologic, and metabolic markers to predict type 1 diabetes.

The review by Dejkhamron and colleagues[21] provide an overview of the major advances in our understanding of the etiology, pathogenesis, and clinical management of Type 1 diabetes.

With the help of large-scale epidemiological population-based studies done in India, Mohan and colleagues[22] give a first-hand information on diabetes and its natural history starting from prediabetes stage. The next generation of diabetes-epidemiologists need to break away from existing models and begin to think about ways of understanding what drives the evolution of diabetes and other diseases in a population. This means we need to break away from our orientation towards single diseases and begin to focus on the big picture.

The modern era of the "metabolic syndrome" began with the seminal work of Reaven in his Banting Lecture in 1988. He described the association of glucose intolerance, hypertension, dyslipidaemia and obesity and termed it Syndrome X with insulin resistance suggested as the unifying underlying aetiological factor. Misra and colleagues[23] give an account on metabolic syndrome in Asian Indians. It is important to note that the criteria for defining MS are subjected to constant revision. Inclusion of modified cut-offs of waist circumference and BMI and measures of truncal subcutaneous fat in the NCEP ATPIII definition requires further validation.

The exact mechanism(s) by which diabetes causes retinopathy is an intense area of research and several theories have been postulated to explain the typical course and history of the disease. Rema and Pradeepa[24] discuss the epidemiology, pathogenesis, current and future treatments of diabetic retinopathy with special reference to the CURES Eye Study which has identified several systemic risk factors for the onset and progression of diabetic retinopathy.

Mudaliar[25] provides an update of newer agents now available and in development for the treatment of diabetes and presents an overview of diabetes prevention strategies. These newer agents could change the way diabetes and its complications are treated in the next decade.

Based on the CODI (Cost of Diabetes in India) study, which is the most extensive and comprehensive study done in India on cost of treatment, Kapur[26] gives a detailed cost analysis status of diabetes care in India. It is likely that these estimates are conservative and underestimate the true cost of the disease.

Sridhar[27] makes an attempt to explain the interface of the diabetes and psychiatric disorders and discuss the potential influences these disorders and the drugs used to treat them have on each other. An association between these disorders becomes an extremely important area for scientific research with therapeutic and preventive implications.

Bhonde and colleagues[28] describe potential applications of isolated islets in biological and biomedical research. Cataloging and exploring the function of newly identified proteins specific for the beta cell, determining their subcellular localization, their interaction partners, and identifying their role in beta cell function would be a translational 'bioengineering' enterprise.

Srinivasan and Ramarao[29] give an elaborate overview of animal models and their applications in diabetes research. One criticism is that animal models of diabetes research may not have direct translational applications in humans. However, it is important to realize that this criticism vanishes if animal models are used "to ask precise questions based on the observations made in clinical practice and to research the answers".

We believe that this special issue provides an efficient platform for fostering research on a range of scientific topics and challenges and open-up avenues for building newer and better collaborative

partnerships between physicians, scientists and pharmaceutical industry and health policy makers.

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