ORIGINAL ARTICLE

Novel Approaches for the Management of Diabetes

Gundu H. R. Rao

Emeritus Professor, Laboratory Medicine and Pathology, Director, Thrombosis Research, Lillehei Heart Institute, University of Minnesota, Minneapolis, Minnesota, USA

ABSTRACT

Metabolic diseases such as hypertension, excess weight, obesity, type-2 diabetes, and vascular diseases, have increased rapidly during the last four decades, to epidemic proportions worldwide. The number of individuals with type-2 diabetes, rose from 108 million (1980) to 462 million (2017) in the last four decades. In 2019, according to the World Health Organization, estimated 1.5 million deaths were due to diabetes, and another 2.5 million deaths were due to high blood glucose levels. There are more prediabetics, than diabetics worldwide and these individuals are 'at risk', to develop full-blown diabetes in less than a decade. This large group of individuals,who are at risk of developing diabetes, are in need of immediate interventions to postpone, reduce, reverse, or prevent diabetes. In addition to this large 'at risk' population, in China, India, and Africa many low-birth-weight children are born, who also are at risk for developing metabolic diseases in their later years. David Barker, a British epidemiologist developed a hypothesis to explain fetal programming, which leads to metabolic disease in later life. Researchers at the Children's National Hospital, Washington DC have reported a study, which may lead to the development of an alternate hypothesis, that suggests a possible role for maternal exosomal miRNA in fetal programming of adipose tissue biology. We have established a professional society as well as a global consortium, to develop robust educational programs, and appropriate intervention strategies, for the prevention of cardiometabolic diseases.

Key words: Metabolic diseases, hypertension, obesity, type-2 diabetes, Novel approaches

INTRODUCTION

There are many kinds of endocrine disorders. Diabetes mellitus is the most common, and one of the oldest, endocrine disorder, that occurs when the pancreas either does not produce sufficient insulin, or the body cannot use the available insulin. November is the Diabetes awareness month. American Diabetes Association writes, "one in five people with prediabetes in America, do not know they, have it?" Experts also say. "By taking actions such as healthy eating, moving more, taking medication, and not smoking, it is possible to reduce the risk of further damage to the system, and to prevent or delay organs from getting dysfunctional." The theme for World Diabetes Day 2021-23 is "Access Diabetes Care- if not now when?" World Diabetes Day is celebrated every year on November 14th to mark the birthday of Sir Frederick Banting, who discovered insulin hormone, with Charles Herbert Best in 1922. According to experts, an estimated 463 million people worldwide suffer from diabetes, that needs to be treated with insulin sensitizers, making up about 90 percent of the cases. With the call to action "of not now when?", World Diabetes Day on Nov 14 marks, the start of a 3-year "Access to Diabetes Care" campaign. Diabetes care accounted for US$760 billion in health expenditure,- a staggering 10% of the global health care spend. Moreover, 4.2 million deaths were attributed to diabetes in 2019, a figure of unfathomable magnitude (1).

I drove from my hometown, Bengaluru, to Chennai (India) in November of 2018, to participate in the World Diabetes Day, as well as to sign a book contract with Jaypee Brothers Medical Publishers, on "Current Trends in Diabetes: Focus on South Asians." The book was published early this year in

Address for correspondence:
Gundu H. R. Rao, Emeritus Professor, Laboratory Medicine and Pathology, Director, Thrombosis Research, Lillehei Heart Institute, University of Minnesota, Minneapolis, Minnesota, USA.

DOI: 10.33309/2639-832X.040101

India, with 34 chapters covering all aspects of epidemiology, early diagnostics, clinical complications, and management (2). I was hoping that experts in these fields of research, will have some suggestions, novel approaches, great strategies for reduction, reversal, or prevention of this rapidly increasing metabolic disease (3-13). However, I was disappointed to see, that the experts limited their reviews, to the known areas of epidemiology, management of hyperglycemia, and clinical complications. Currently, I am working as a co-editor for a special issue on , "Insights in Diabetes: Molecular Mechanisms" to be published by Frontiers in Endocrinology. In addition, to develop an 'out of the box' monograph on this very important topic, I am also negotiating a book contract with the Elsevier Publishers. In this invited review, I will discuss some aspects of novel approaches to reduction, reversal, and prevention of diabetes.

Reduction of Type-2 Diabetes

Incidence and prevalence of type-2 diabetes has increased rapidly in the last four decades. According to a recent report by the International Diabetes Federation, - Diabetes Atlas Committee, in 2019, global diabetes prevalence was estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030. One in two (50.1%) people, living with diabetes do not know that they have diabetes. The global prevalence of impaired glucose tolerance is estimated to be 7.5% (274 million) and projected to reach 454 million by 2030 (14).In addition to overt diabetes, an estimated 352 million people worldwide are at risk of developing diabetes. Having said that, I must remind readers, that data on the number of prediabetics, is just an estimate and not real. We are of the opinion, that there are more prediabetics than diabetics worldwide. In the USA, more men (37.4 % of adults) than women (29.2%), have prediabetes. The window of opportunity to prevent or slow the progression of prediabetes to type-2 diabetes, is about three to six years. Prediabetes, the common precursor to diabetes, affects more than 86 million Americans. An estimated 90 percent of the people with prediabetes, do not even realize that they have this condition, which is reversible. There are plenty of preventive measures to stop the onset of full diabetes. The USPSTF concludes,-with moderate certainty, screening of prediabetes and type-2 diabetes, and referring patients with prediabetes to effective preventive interventions has a moderate net benefit(15). Since the prediabetic population is bigger than the diabetic population, it is very important to consider early interventions for prediabetes. It has been shown that lifestyle interventions were more effective than medical interventions (metformin), as they have beneficial effect of weight, blood pressure and lipid levels. The National Institutes of Health has several resources related to screening, diagnosis, prevention, and management of prediabetes.

Reversal of Type-2 Diabetes

A Newcastle University research team has discovered that type-2 diabetes can be reversed by an extreme low-calorie diet alone. A Newcastle news bulletin claims, that University's findings could benefit millions of people across the globe. 'These findings are very exciting. They are revolutionizing the way Type-2 diabetes is treated.' The trial, DIRECT (Diabetes Remission Clinical Trial), found that almost nine out of 10 people taking part, who lost 15Kg or more put type-2 diabetes into remission. A new study from Newcastle University, has shown that people who reverse their diabetes and then keep their weight down remain free of diabetes (17). The research is an on going part of a growing evidence, showing that people with type-2 diabetes, who successfully lose weight can reverse their condition, because fat is removed from their pancreas, returning insulin production to normal. The same research team from the Newcastle University, also demonstrated the reversal of type-2 diabetes after bariatric surgery. They concluded, "The study showed, that the degree of achieved weight loss, is the major determinant of return to normal blood glucose levels after bariatric surgery. Normoglycemia can be achieved in long-duration type-2 diabetes, but a greater degree of weight loss is required, than for short duration diabetes (18).

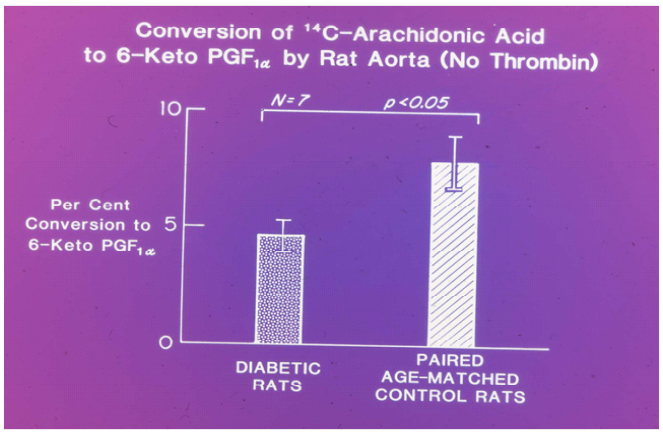

Figure 1. Conversion of arachidonic acid to Prostacyclin by rat aorta.

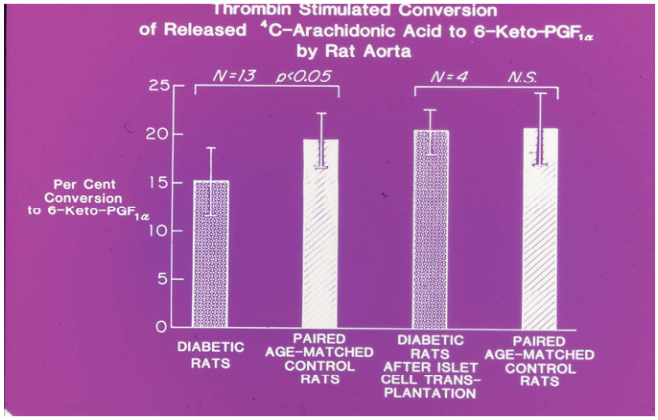

Figure 2. Conversion of arachidonic acid by rat aorta in diabetic and control animals

Figure Legend: Fig. 1; Conversion of radiolabeled arachidonic acid to prostacyclin (PGI_2) by diabetic and control rat aorta. Stable metabolite of prostacyclin,6- Keto-PGF1α is quantitated for PGI_2. Fig. 2; Conversion of radiolabeled arachidonic acid to PGI_2 as measured by 6-Keto- PGF1α in thrombin stimulated rat aorta.

Discovery of prostaglandins, and biologically active metabolites of arachidonic acid, opened new arena of medical research. We at the University of Minnesota, in early 80s, were interested in the role of arachidonic acid metabolites, in platelet activation mechanisms and thrombosis. Since we knew that diabetics had hyperactive platelets, we wanted to explore arachidonic acid metabolism in platelets and aorta of rats using a drug induced diabetes model. Animal models can be developed using Streptozotocin, a glucosamine-nitrosourea compound. Following its uptake into the beta cells, streptozotocin is split into glucose and methylnitrosurea moiety. Owing to its alkaline properties, this metabolite destroys the beta cells, and induces a state of insulin-dependent diabetes. We used this method to induce insulin-dependent diabetes in rats and followed arachidonic acid metabolism in rat aorta and blood platelets. (19). Drug induced diabetes rats showed altered arachidonic acid metabolism in both aorta and blood platelets. They produced less of vasoactive prostacyclin and more of thromboxanes, compared to the control rats. Upon islet cell transplantation, and normalization of pancreatic functions, arachidonic acid metabolism was also normalized (Figures 1,2). We have included just partial data of this study in this presentation.

The development of appropriate materials, for the microencapsulation of xenogeneic tissues, is a limitation to their current application of xenogeneic islet cell transplantation, for the treatment of type-1 diabetes. We demonstrated that optimization of alginate/chitosan PEG with a mild crosslinking, provides microcapsules with appropriate functionalities,to encapsulate mammalian tissues, including pancreatic islet cells (20). For diabetic treatment, adult stem cells have taken a lead over islet transplantation, due to limitations associated with allogenic transplantation and shortage of donors (21). Four decades after we demonstrated the beneficial effects of islet cell transplantation, Vertex Pharmaceuticalsof Boston, MA, have reported the results of a trial, which infused cells, grown from stem cells similar to the insulin-producing pancreatic islet cells,in the first ever human studies of this kind. Mr. Shelton was the first recipient, who received the cell infusion on June 29th of this year. The New York Times (Nov 27, 2021) published an article titled, "A Cure for Type-1 Diabetes? For One Man, It Seems to Have Worked." The challenge these researchers faced was, to find out what sequence of chemical messages, would turn stem cells into insulin-secreting islet like cells. The only concern that clinicians have is, 'the trade-off between the burdens of diabetes, and complications from immuno suppressive medications."

Prevention of Type-2 Diabetes

The experts are of the opinion, that early detection and treatment of diabetes, can postpone or even prevent, the serious clinical complications associated with diabetes, such as retinopathy, neuropathy, nephropathy, and vascular diseases (22). In a news bulletin titled, "Tackling diabetes from every angle", Calley Jones writes, "Physicians, geneticists, chemists, and other researchers in Broad's Diabetes Research Group are working together and taking multiple approaches to improve treatment for patients with diabetes." They analyzed DNA from nearly 9,000 people from Latin America with diabetes, as a part of the Slim Initiative for Genomic Medicine in the Americas (SIGMA), identified several variants in the gene *SLC16A11,*that dramatically increases the risk for type-2 diabetes. When we consider the global population, China, India, and Africa have about half of the total 7.6 billion people. People from these regions have an additional genetic or epigenetic factor that contributes to the development of cardio metabolic diseases. Large number of children born in Asia, Africa and, India are of low birth weight(LBW). Several studies have demonstrated that the so called, 'thin-fat' low birth weight babies, develop metabolic diseases early on, during later years of life (23-28).

In the early 1990s, small size at birth was shown to be associated with an increased risk for developing metabolic diseases such as hypertension, obesity, diabetes, and coronary artery disease in UK, European and the US populations (29-32). According to the seminal epidemiological work done at the Mission Hospital, Mysore, India, thirty percent of the children born in India, are of low birth weight. They have maintained birth record of all the children born in this hospital from 1934. In view of the availability of such a large data base, the Medical Research Council(MRC) of UK has set up an epidemiology wing at this hospital campus. Based on the studies done at this hospital and by the Pune Maternal Nutrition Study Group at KEM hospital Pune, Dr David Barker a British Epidemiologist proposed his famous hypotheses,-that adverse nutrition in early life, including prenatally as measured by birth weight, increase the susceptibility to the metabolic syndrome, diabetes, hypertension, and hyperlipidemia and complications including heart disease (33). We the members of the South Asian Society on Atherosclerosis and Thrombosis (SASAT), established a chapter of our professional society at the Mission Hospital, Mysore, and are following the progress in research in this area in the UK as well as the USA. We also have facilitated a bilateral collaborative research between the researchers at the Children's National Hospital, Washington DC, and the Pune Maternal Nutrition Study Group.

Fetal origins of adult disease, a concept first popularized by Dr. David Barker, has subsequently led to many studies, which have provided evidence, that certain diseases do have links pointing to fetal origins. The concept of fetal origin of adult disease have been extended well-beyond CVD, and now includes investigations of the development of central nervous system, early origins of adult mental health and cognitive function. In view of the fact, that the epigenetic alterations during the fetal development may cause several adult metabolic diseases, as well as diseases of the nervous system, we would like to see that, the future research focus on possible intervention strategies that may halt, reverse, or prevent, these epigenetic modulations of the fetal metabolism.

Since 1990, we are continuing our efforts in India, to develop collaborative research programs. Since malnutrition, as well as micronutrient deficiency, plays an important role in the development of metabolic risks, we would like to develop micronutrient supplements for maternal consumption, as well as for newborn children. The micronutrient deficiency in pregnancy, seems to be a worldwide problem.

A news release from the Children's Hospital, Washington DC, says, "The work that children's National Health System physician-scientist Robert Freishtat and colleagues are doing, could soon be a 'game changer', when it comes to early intervention and prevention of obesity related illness (34). We already know that there's a direct relationship between the amount of visceral adipose, or belly fat a person has, and development of some of the most common and life-threatening complications of obesity, including cardiovascular disease, and the insulin resistance, that leads to diabetes. What remained unclear until recently, were the precise mechanism of how the increase in belly fat, triggers the onset of cardiometabolic diseases."These findings prompted us, to contact Dr. Robert Freishtat and explore possibilities for developing a bilateral US-India research project, on the role of maternal exosome (miRNA) in reprogramming the fetal genetic material and gene expression. Since the Diabetes group at the King Edwards Memorial (KEM) hospital Pune, had established a large biobank of fetal and maternal tissues, we negotiated with Professor C.S Yajnik, a working arrangement for preliminary studies. We were also able to find a third partner, Genotypic Technology at Bengaluru, India, who could perform the needed miRNA assays at a short notice. Encouraging results from these preliminary studies helped the team secure, funding's for further studies, from the prestigious National Institutes of Health (NIH) , USA (35).

According to Dr. Robert Freishtat, the lead investigator of this project, " A novel possibility of this research is, that an adiposity-related maternal factor crosses the placenta, to reprogram fetal cardiometabolic development pathways. Preliminary studies by this team have identified adipocyte-derived exosomes as maternal factor, capable of driving abnormal fetal cardiometabolic development, and known to be interorgan mediator of cardiometabolic disease in obese children and adults. As nanoparticle-sized endocytic vesicles,- 'these exosomes' can cross the placenta and their microRNA contents are predicted, to alter developmental pathways and gene expression."In view of these observations from researchers of the Children's National Hospital, Washington DC, we are considering the 'New Hypothesis' for the fetal origin of adult diseases, which hypothesizes that maternal cord blood adipocyte derived exosomal miRNAs, target adipogenesis and modulate adiposity of the infant, as well as promote developmental origins of health and diseases (DOHaD).

Several miRNAs have recently been found to regulate adipose tissue biology, insulin secretion, and action. Their imbalance may play a role in the development of obesity and metabolic complications (36-39). We are interested in exploring the role or miRNAs in the development of metabolic risks, such as oxidative stress (miR34a, miR638, miR150-3p), inflammation (miR27a, miR146a, miR155), endothelial dysfunction (miR29, miR126a-3p), subclinical atherosclerosis (miR121) and diabetes-related clinical complications such as peripheral neuropathy (miR146a), retinopathy (miR21, miR124, miR200), nephropathy (miR29c), and various vasculopathies (miR200b, miR200c, miR503), as well as fetal reprogramming of adipose tissue biology.

When I started our professional society, SASAT (www.sasat.org) in 1993 at the University of Minnesota, I just had one objective in mind. To develop a robust educational program and to explore novel strategies to reduce, reverse, or prevent cardiometabolic diseases in South Asians. Over the last three decades, we have organized international conferences in India and abroad every other year. We have published several monographs on this topic under the aegis of SASAT in India (41-49). We also started a chapter of SASAT at the Mission Hospital, Mysore, in 1995, to follow the progress of research on DOHaD on 'Mysore Cohort', as well as at the KEM Pune, with 'Pune Maternal Nutrition Study Group. We successfully completed an exploratory bilateral study on the 'Maternal Adipocyte-derived Exosomes in the Thin-Fat Baby Paradox' with the NIH support. We have established a consortium, 'Scientific Consortium for Non-Communicable Disease Reduction Across Generations (SCNRG)', at the Children's National Hospital, Washington DC, to continue our national and international activities, on these topics of great public health interest. The mission of this group is to provide a global DOHaD leadership and a catalytic platform, for collaborative surveillance, prevention, and treatment of NCDs, especially among children and vulnerable groups. SASAT and SCNRG, together would like to explore various novel approaches for the reduction, reversal, and prevention of cardiometabolic

diseases. As described briefly in this article these approaches include, recommendation of lifestyle changes, increased physical activity, development of better maternal and neonatal nutrition supplements, stem cell, molecular, genetic, and epigenetic approaches(36-40).

CONCLUSION

Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputations. It is one of the oldest endocrine disorder known, and it is still elusive as far as prevention is concerned. Instead, it is growing rapidly to epidemic proportions worldwide. Every World Diabetes Day, we come up with new themes, to address this growing public health menace. A brief review of literature demonstrates that there is very little emphasis on reduction, reversal, or prevention of diabetes. Therefore, in this invited review, we have discussed some novel approaches aimed at various prevention strategies. Because there is a greater number of prediabetics than diabetics, we have called for action, to concentrate on this group for developing and implementing prevention strategies. Of course, it would be great if adolescent healthy subjects are encouraged, to undergo impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) for the early diagnosis of prediabetic state. The transition from early metabolic abnormalities to these measurable states of metabolic risks, as well as diabetes takes many years. It gives a great opportunity for the health givers, to diagnose early metabolic risks and initiate robust lifestyle change, encourage physical activity, and introduce them to healthy diet.

Apart from these 'at risk' population, we also have been following the metabolic changes that lead to fetal programming and put low birth children for the development of cardiometabolic risks. It is estimated that close to 150 million babies are born worldwide every year. A large percent age of these babies in countries like, China, India and Africa are born with low birth weight, and as such are at risk of developing cardiometabolic diseases at later stage in their life. Better maternal and neonatal nutrition can indeed reduce the developmental origins of health and disease. We also have discussed some cutting-edge technologies, such as islet cell and stem cell transplantation. Recent success in mRNA therapeutics has prompted us to suggest some novel approaches using gene expression, gene manipulation, synthetic biology, mRNA studies, role of miRNA in cell and tissue programming, genetic and epigenetic control of metabolic health. Finally, we the members of SASAT have joined hands with the researchers working on problems related DOHaD in India, UK, and the USA to develop a common task force for developing educational and preventive strategies for the prevention of cardiometabolic diseases.

ACKNOWLEDGEMENT

The author acknowledges his sincere thanks to Dr. Robert Freishtat, Associate Director, Research Center for Genetic Medicine, Children's National Hospital, Washington DC;Dr. Chittaranjan Yajnik, Director, Pune Maternal Nutrition Study Group, India, Dr. Krishnaveni, Senior Scientist, CSI Holds worth Memorial Hospital, Mysore, India, and Dr. Caroline Fall, Professor of Pediatric Epidemiology, University of Southampton, UK, for sharing their research findings, and for their continued support of his national and international activities as the founder, CEO of South Asian Society on Atherosclerosis and Thrombosis (www.sasat.org).

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How to cite this article: Rao G H R. Novel Approaches for the Management of Diabetes. Clin Res Diabetes Endocrinol 2022;4(1):1-7.
DOI: 10.33309/2639-832X.040101