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Review Article

Fetal Origin of Adult Cardiometabolic Diseases: Micronutrient and microRNA Interventions

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Abstract

President Barack Obama in his State of the Union Address on January 30, 2015, launched a program called "Personal Medicine". In his lecture to the nation, he said, "Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type, - that was an important discovery. What if matching a cancer cure to our genetic code was as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?" These are very important questions, begging for appropriate answers. With such thoughts in mind, Scientists in Bengaluru, India, organized a conference recently, called Genomics-2019, aimed at discussing the role of this emerging science and technology, transforming the lives with Genomics. I was invited to present a key note lecture, and I selected the topic of "Fetal Origin of Adult Diseases: From Micronutrients to Micro RNAs", a topic that is very dear to my heart. CSI Holdsworth Mission Hospital (HMH), Mysore, India, has kept meticulous records of newborn babies, in this institution since 1934. Collective studies from this institution and other centers in India, as well as by the UK epidemiology group, have demonstrated, that children born with low birth-weight are 'at risk', for the development of cardiometabolic diseases in their later life. Based on these and other similar studies Professor David Barker, a British Epidemiologist suggested a hypothesis,- 'Barker Hypothesis' to explain, Fetal Origin of Adult Diseases (FOAD)". This hypothesis states, that intrauterine growth retardation, low birth weight, and premature birth, have a causal relationship to the origins of hypertension, coronary artery disease, and non-insulin dependent diabetes, in middle age. After almost three decades, studies from Children's National Hospital (CNH), Washington DC, has demonstrated, that adipocyte-derived exosomal RNAs (miRNAs), may serve as 'biological tweets' and thus may be a game changer for detecting adiposity/obesity-related disorders. Thus, a new hypothesis may be in the offing, to explain the fetal origins of adult cardiometabolic diseases. In this overview, we discuss both the old hypothesis, and the new hypothesis for the FOAD, and present our view points on possible intervention strategies for using micronutrient supplements, as well as micro RNAs as therapeutics.

Keywords: *Cardiometabolic Diseases; Micronutrient; microRNA*

Introduction

President Barack Obama, in January of 2015, during his State of the Union address, announced the launch of a new Initiative called "Precision Medicine". He announced, "Tonight I'm launching a new Precision Medicine Initiative, to bring us closer to curing diseases like cancer and diabetes- and to give all of us access to the personalized information we need to keep ourselves and our families healthier" [1]. The proposed initiative has two main components: a near-term focus on cancers, and a longer-term aim to generate knowledge applicable, to the whole range of health and disease. According to Francis Collins, Director of the prestigious National Institutes of Health

(NIH), USA, both components are now within reach, because of advances in basic research, including molecular biology, genomics, and bioinformatics. He further elaborates his vision by saying, "Ultimately, we will need to evaluate the most promising approaches, in much larger numbers of people over long periods. Towards this end, we envisage assembling over time, a longitudinal "cohort" of 1 million or more Americans, who have volunteered to participate in research. Participants will be asked to give consent for extensive characterization of biologic specimens (cell populations, proteins, metabolites, RNA, DNA-including whole -genome sequencing) and behavior data, all linked to their electronic health record".

In view of such announcements, reports, and write-ups, there is a great interest in the application of emerging technologies for transforming lives and in designing better personalized, precision medicine. There is an equal enthusiasm, for the development of P4 health delivery, -meaning preventive, predictive, personalized, and participatory [2]. In order to create awareness, develop an interactive platform for all the stakeholders, a conference on Genomics-2019 was held in Bengaluru (24^{th}, 25^{th} January 2019) India. As a part of this effort, I reviewed the work on the Fetal Origins of Cardiometabolic Diseases (CMDs). Metabolic diseases like hypertension, excess weight, obesity, type-2 diabetes, and vascular diseases have increased to epidemic proportions worldwide [3-16]. Excess weight and obesity, have increased in the last three decades by two-fold, and diabetes (type-2) by four-fold worldwide. In the same period in China, diabetes has increased by 17-fold [16]. Both in India and China, one of earliest contributing factor for the development of metabolic diseases is, the birth of low-weight children. In these countries, more than 30% of the children born are of low-birth weight. Several studies have demonstrated, that these low birth-weight children are 'at risk' for developing metabolic diseases, such as hypertension, obesity, type-2 diabetes, and cardiovascular diseases (CVDs).

From 1934 onwards, the birth weight, length, and head circumference of all babies born in CSI Holdsworth Memorial Hospital (HMH), Mysore, India, were recorded in obstetric notes [17-26]. The studies with the 'Mysore Cohort', were among the first in a low-and middle-income country, to test developmental origins of health disease (DOHaD) concepts, with predicted association between small size at birth and adult coronary heart disease, insulin resistance, and low lung function [19]. The Mysore Parthenon study findings suggest, that exposure to maternal nutritional deficiencies, as well as over nutrition, may contribute to an increasing burden of cardiovascular disease in India, and that these two conditions, may co-exist in the same mother, leading to dual insults to the offspring [18]. During 1993 - 2001, in a collaborative study with Barker's group at the Medical Research Council (MRC) Life course Epidemiology Unit, University of Southampton, UK, the records were used to trace people born in HMH, Mysore, India, between 1934 - 1966 [17]. 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 [27-32]. 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.

Discussions

Old hypothesis on fetal origin of adult diseases

Barker's hypothesis states, that intrauterine growth retardation, low birth weight, and premature birth, have a causal relationship to the origins of hypertension, coronary artery disease, and non-insulin dependent diabetes, in middle age. According to Malhotra and associates, there are two prongs to this hypothesis [27]. The first is that, a fetus faced with limited amount of nutrients, has to choose how to use what is available, and best of all, protect the growth of the brain. The second prong is, that a fetus takes cue about what it will consume, after it is weaned from its mother's physiology, and adapts accordingly. Barker's idea was that a fetus faced with a lack of adequate nutrients, develops thrifty habits. At the time the hypothesis was developed, what changes in genetic regulation are involved in programming of 'thrift' were unclear. But according to Dr Barker, the fetus's tissue become more resistant to insulin- a molecule, that opens the

door for glucose to enter the cells, so that they can be burned easily, to get the needed energy. Secondly, the fetus becomes better able to lay down fat deposits in later life. According to Professor Yajnik, a leading investigator on FOAD at the King Edward's Memorial (KEM) Hospital, Pune, India, the body composition of the child is influenced by maternal adiposity, before pregnancy and by aspects of maternal nutritional intake, and circulating nutrient concentrations during pregnancy [33-36]. His group at KEM have demonstrated, that thin Indian newborns, have poor muscle and visceral mass, but higher adiposity for a given weight, compared with white Caucasian babies. They have proposed this composition as 'thrifty phenotype' of Indian babies. Thus, the small Indian babies are programmed to deposit fat from their intrauterine life. They further note, that poor intrauterine growth, also predicts higher central adiposity at 8 years of age. He concludes, "Further research is necessary to define the role of specific nutrients and metabolites in the intrauterine processes promoting adiposity, before maternal interventions to curtail the epidemic of obesity are planned". Since the time these studies were published, there are several other studies, which have demonstrated the benefits of maternal micronutrient supplementation on pregnancy outcome [37]. The authors of this study from Harvard School of Public Health, found that multiple micronutrient supplementation was more effective than iron and folic acid supplementation at reducing the risk of low birth weight and of small size for gestational age.

Excess weight and adiposity, seem to play a very important role in the adiposity-related disorders, as well as the development of metabolic risks, such as oxidative stress, low grade chronic inflammation, hypertension, endothelial dysfunction, hardening of the arteries, and subclinical atherosclerosis. Dr. Bela Shah of the Indian Council of Medical Research (ICMR), working with Dr Paul McKeigue, Professor of Genetic Epidemiology and Statistical Genetics, Institute of Population Health Science and Informatics, London, reported for the first-time, relation between the central abdominal adiposity, with the risk of developing type-2 diabetes and CVD [38]. Extending these ideas, Bajaj and associates, based on the results of a bilateral study between the University of Minnesota and Madras Diabetes Research Foundation, (MDRF), Chennai, India, showed that compared to the US, the waist-weight ratio is significantly higher in men and women from India. These results support the hypothesis, that South Asians are particularly predisposed toward central adiposity [39]. In view of these observations, Word Health Organization (WHO), suggested a new guidelines and guidance recommendation for appropriate body-mass index for Asian population. When considered collectively, these studies suggest that the visceral fat (central abdominal adiposity or waist circumference not BMI), plays a very important role in the development of metabolic diseases in the South Asian Populations.

Visceral adiposity and development of metabolic diseases

Several epidemiological and physiological studies have demonstrated, a strong association between the excess abdominal adipose tissue, and the presence of metabolic risk factors for coronary artery disease, including insulin resistance, impaired glucose tolerance, type-2 diabetes, dyslipidemia, and increased inflammatory proteins [41-44]. There seems to be variable role for the fat in signaling events, depending upon where these tissues are located. Some studies suggest, that deep subcutaneous abdominal fat, may have adverse properties. Pericardial and perivascular fat relate to atheromatous disease. There has been recent interest in recognizable brown adipose tissue, which is metabolically active, oxidizes fatty acids, and generates heat. The exact role of these active tissues, in promotion of metabolic risks are not clear. In Asian Indian population, visceral but not subcutaneous fat, seems to be associated with insulin resistance, and glucose intolerance, as well as increasing levels of C-reactive protein (CRP) and TNF alpha, whereas, in diabetic subjects, visceral fat has been associated with both insulin resistance and poor glycemic control [43-45]. Studies on Australian adults, have shown stronger association of cardiovascular disease, with increased Waist-Hip Ratio (WHP) than by the BMI [45]. A new study, published in the journal of Cell Metabolism, challenges the current understanding of what causes diabetes, writes, Ana Sandoiu in Medical News Today (16th October 2018).

According to this report, more than two decades ago, researchers suggested, that the action of an enzyme called Protein Kinase C-epsilon (PKC ε) in the liver may cause diabetes, by acting on insulin receptors. Using knock out mice model, researchers have demonstrated, that these rodents are protected from glucose intolerance and insulin resistance [44]. Schmitz-Peiffer and associates conclude, "What we found is, that if we removed PKCε production solely from the tissue, the mice were protected from becoming glucose intolerant, similar to when we removed PKCε from the entire animal (knockout model). "If PKCε is changing the nature of fat, and affecting the overall health of fat cells, it is changing the types of messages it sends, and factors it releases, - which could be acting on the liver and possibly other organs, to interfere with glucose metabolism". The new study just recently (October 2018) reported by the Australian researchers, is challenging what we know about the causes of diabetes. The new study points to fat tissue, as a source of the disease, and widens our understanding beyond the traditional focus on liver, pancreas, and elevated level of blood glucose. According to these researchers, "In high-fat-diet

(HFD)-fed mice with PKCε removed from the fat tissue, they saw mostly small, healthy fat cells. In HFD-fed mice with intact PKCε, which were the glucose intolerant, they saw more of unhealthy, engorged fat cells, that tend to have less access to oxygen and inflamed".

New hypothesis on fetal origin of adult diseases

Obesity is a known risk for developing type-2 diabetes. The above-mentioned study, adds to the growing evidence, demonstrating connection between body fat and the risk for developing the metabolic diseases. One such seminal finding is, the revelation from the Children's National Hospital Washington DC, which has been reported as the game changer for detecting obesity-related complications. 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. 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 clear, until recently, were the precise mechanism for how the increase in belly fat, triggers the onset of additional disease".

According to Dr Robert Freishtat, the leader of this research, "as the visceral fat grows, somewhere on the path of obesity the fat cell changes, and begins to release different exosomes than lean adipose cells do. These new messages disrupt some important processes, that eventually prevent body from effectively dealing with sugar and cholesterol". Dr. Freishtat describes exosomes, as "biological tweets"- short messages, shed by all cells that allow for intercellular communication and altered gene expression. In their exploratory studies, the researchers collected fat tissue from lean and obese female patients, used modified bead-based flow cytometry to separate, identify, and compare the exosomal miRNA shed by the fat cells of both lean and obese individuals. They feel strongly, that successfully identifying and isolating these exosomes, has opened the door for developing a test to detect them, an idea that may permit even intervention to delay or prevent the onset of obesity-related illness [46,47]. Exosome/microvesicle-mediated epigenetic reprogramming of cancer cells, have been reported by oncology researchers [47]. Microvesicles (MVs) released by different cell types, remain in the extracellular space in the proximity of the cell of origin, and mediate cell-to-cell communication, similar to what Dr Freishtat has described as 'biological tweets.' MV's similar to the exosomes contain, genetic material under the form of mRNA and miRNA that play an important role in epigenetic reprogramming of host cell metabolism. 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 bio-bank 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 [48].

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 mediators 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". He further states, "Because we developed techniques to isolate these exosomes from body fluids, our overall objective for these studies are, to test this association between maternal adipocyte-derived exosomes and infant adiposity, while building upon existing research capacity for a prospective multicenter study in India". In view of these observations, the 'New Hypothesis' for the fetal origins of adult diseases is that maternal and cord blood adipocyte-derived exosomal miRNAs that target adipogenesis, are associated with high infant adiposity. As the body's fat grows, somewhere on the path to obesity, the fat cells change and begin to release different exosomes, than the lean

adipose cells do. These new messages disrupt important processes, that eventually prevent the body from effectively dealing with sugar and cholesterol.

Future Goals

Coming back to the theme of my key note lecture, "Fetal Origin of Adult Diseases: From Micronutrients to Micro RNAs", we would like to continue our efforts for developing interventions, as they relate to both the old hypothesis and the new one. In 1990, we applied for a small grant called, "Reach out the World" offered by the International Society on Thrombosis and Hemostasis (ISTH), USA. With that seed funds,- to create awareness, develop educational and prevention strategies, we started a professional society, South Asian Society on Atherosclerosis and Thrombosis (USA), at the University of Minnesota. In the last three decades, we have organized fifteen International Conferences in India, and published eight books on this topic [49,50]. Since 1990, we are continuing our efforts in India, to develop collaborative research programs. In view of the fact that 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 [51-54]. Studies by the British researchers showed, that compared with iron-folic acid supplementation alone, maternal supplementation with multiple micronutrients during pregnancy in low-income countries, resulted in a small increase in birth weight and reduction in the prevalence of low birth weight of about 10%. Studies by Harvard researchers as well as UK researchers, have demonstrated a limited role of micronutrient supplementation on pregnancy outcome [37,52]. These observations suggest, that the story of current epigenetic interventions, are preliminary in nature, and further extensive studies are needed, to reap the benefits of these early observations.

Currently, complete commercially available methodical procedures for miRNA investigations are available. There are techniques allowing the identification of new miRNAs and new miRNA targets, validation of predicted targets, measurement of miRNAs and other precursor levels, and validation of physiological role of miRNAs under *in vitro* and *in vivo* conditions.

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). It is evident from several studies, that obesity alters microRNA expression in metabolically important organs, and miRNAs are involved in changes to normal physiology acting as mediators of disease processes.

MicroRNAs regulate multiple pathways including insulin signaling, immune mediated inflammation, adipose expression, adipogenesis, lipid metabolism, and food intake regulation. Thus, miRNA therapeutics represents an innovative and attractive modality [55]. Understanding the molecular basis of adipogenesis and fat cell development in obesity seems to be essential, to identify new biomarkers and therapeutic targets, for the development of anti-obesity drugs. MicroRNAs appear to play regulatory roles in many biological processes associated with obesity [56-60]. Metabolic diseases are characterized by the failure of regulatory genes or enzymes, to effectively modulate specific regulatory pathways, in the control of biological and physiological processes [61]. Specific extracellular RNAs regulate key processes central to the pathogenesis of CVDs. We hypothesize that the expression of plasma RNAs change over time, is influenced by the duration and intensity of exposure, to diabetes or CVD risk factors, such as prolonged hyperglycemia, endothelial dysfunction, hardening of the arteries, and subclinical atherosclerosis phenotypes, and therefore be useful as predictors of incidence of acute CVD events.

Excess weight, obesity, and type-2 diabetes, seem to be the driving force, behind the global mortality and morbidity. In the literature on these topics, experts have described the increase incidence of these metabolic diseases as Epidemics, Tsunami's and now, as Global Syndemic. The 'Global Syndemic' of metabolic diseases, is the greatest threat to human health in every part of the world, says the new report by the Lancet Commission on Obesity [62]. It notes that malnutrition in all its forms, including undernutrition and obesity, is by far

the biggest cause of ill health and premature death globally. For instance, excess weight is estimated to affect 2 billion people worldwide, causing 4 million deaths annually. Stopping this trend urgently requires a new social movement for change and radical rethink of the relationship between policymakers, business governance and civil society, adds the report. Among the report's key findings: One in three members of the global population is malnourished, and the problem exists in every country on the planet- yet, the strategies available to resolve it are not being implemented due to lack of money, skills, or political indifference/ political pressure.

Conclusions

Cardiometabolic diseases, such as hypertension, excess weight, obesity, prediabetes, type-2 diabetes, and various vascular diseases, have rapidly increased in their incidence worldwide. Various metabolic risks, like oxidative stress, low-grade chronic inflammation, altered circulatory physiology, endothelial dysfunction, hardening of the arteries, subclinical atherosclerosis, and conditions that promote thrombotic state of the circulating blood, seem to be the driving force behind acute vascular events. In view of the fact, all the metabolic diseases, seem to be prevalent 'in excess' in Asians, we started a professional society to address this ethnic specific 'Syndemic' of metabolic diseases. Early on, we recognized the contributions of the UK-India collaborative studies, on the fetal origin of adult diseases. Although, it seems to be a unique problem associated with Asian phenotype, careful examination of published reports, suggest that alterations and developments of metabolic risks, occur early on in the life. What is still not clear, is how a 'trigger or tweet' in the early stages of life (Intrauterine alterations), can have a prolonged memory of these 'commands' and initiate the development of cardiometabolic risks later in the life of an individual. This is not just in the case of metabolic diseases, but is true for cancers as well as neurological diseases. In view of these observations, we feel strongly, that there is an immediate need to develop various intervention strategies for preventing epigenetic -related fetal reprogramming of adult metabolism. The other area of great interest is, to research the reasons for the prolonged incubation time for the development of adult diseases, knowing that the reprogramming occurs during fetal growth. What mechanism keeps these biological signals suppressed for several decades. In other words, what other epigenetic signals reactivate the suppressed messages? Extensive studies are needed to understand what specific nutrients are deficient and how they influence the fetal growth. Similarly, we need to fully understand the role of PKC- epsilon as well as adipocyte-derived exosomal miRNA in the reprogramming of fetal fat metabolism, so that appropriate interventions could be developed.

We know from the above-mentioned studies, that PKCε makes the fat cells sick. We also know that 'sick fat cells' if we can use that terminology, shed exosomes containing miRNA, capable of sending 'biological tweets' to other cells. In view of the fact, that in any given situation multiple miRNAs are involved, we need to identify the collective functional role of these sets of miRNAs. In a recent study Lee and associates have demonstrated that miRNA-101b attenuates cardiomyocyte hypertrophy by inhibiting Protein Kinase C epsilon signaling [63]. PKCs play many roles in cell signaling in different tissues. As we have noted earlier, inhibition of PKCε prevents hepatic insulin resistance. Many observations have also indicated that PKC signaling pathways regulate important events in neurogenerative pathophysiology of Alzheimer's disease. What is of great significance is that FOAD seems to promote not only CMDs at a later stage in life but also neurological diseases. Further research is needed to firmly establish the role of PKCε and exosomal miRNA in adiposopathy (Adipocyte pathology).

In this overview, we have briefly discussed the early studies at the Mission Hospital, Mysore, where it all started, and provided the incentive for further extensive studies related to the size at birth, weight at birth, and other altered features representing, the intrauterine growth retardation, which led to the 'thrifty gene' and the Barker's hypothesis, on fetal origin of adult diseases. We have briefly discussed the role of visceral adiposity, that is characteristic feature of the Asian phenotype, compared to the uniform dispersal of body fat in most Caucasian subjects. We also have discussed the possible role if any of protein Kinas C-epsilon in fat cells and their role in adipocyte pathology. We have briefly discussed the seminal findings of Robert Freishtat's group at the Children' National Hospital, Washington DC, which has been heralded as a game changer in the diagnosis of obesity-related disorders. As it is an ongoing investigation, we have limited our discussion on the findings of this study. Since, this opens a new field of investigation at the cellular and molecular level, we have described

this phenomenon, as the 'new hypothesis' for the fetal origin of adult diseases. There is considerable discussion on the possible role of miRNA and mRNA, in the cellular signaling pathways as well as, specifically on the development of metabolic risks, metabolic diseases, and in the area of cardiovascular physiology and pathology. We feel strongly, that this will be a great area of interest for some time to come, for the various experts trying to develop a personalized and precision healthcare.

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