ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS

Review Article

Developmental Origin of Cardiometabolic Diseases: Role of Free Fatty Acids

Gundu HR Rao*

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

***Corresponding Author:** Gundu HR Rao, Emeritus Professor, Laboratory Medicine and Pathology, Director, Thrombosis Research, Lillehei Heart Institute, University of Minnesota, Minneapolis, Minnesota, USA.

Received: September 09, 2022; **Published:** September 15, 2022

Abstract

Framingham Heart Study is a one-of-a-kind observational study, which discovered probable causes for developing risk for cardiovascular diseases (CVDs). Based on this information, a large multinational, standardized case control study concluded, "that management of modifiable risks for CVDs, significantly reduced premature mortality". Data are available from birth records at the Mission Hospital Mysore, India, that altered biometric features (birth weight and length) of a new-born, predetermines their acquiring metabolic diseases in later life. Studies done at the UK and India, helped develop a concept, "Foetal Origin of Adult Diseases". British lifecourse epidemiologists have proposed, that adverse nutrition in early life measured by birth weight, birth length, are responsible for the 'developmental origin of adult diseases'. Despite these observations, to this day, we do not know the exact underlying molecular mechanisms, that predispose these new-born children, to metabolic diseases in later life. Take home message is that altered metabolism at any time in life course, could lead to the development of risks for metabolic diseases. There are many gaps in our understanding of this concept. Much of the earlier work has focused on the role of micronutrients such as folic acid, iron, zinc. calcium and multivitamins. Although need for Omega 3-fatty acids during this crucial growth period is noted, definitive studies are lacking to demonstrate the role of essential fatty acid deficiency in the development of later life adult diseases. Some of the recent bilateral studies of researchers from the USA and India, suggest, a role for maternal microRNA in foetal programming of adiposity-related metabolic changes in the growing foetus, as well as that of the offspring's. A large number of nutritionally deprived children are born in lower and middle-income countries and these children are 'at risk' for developing chronic metabolic diseases later in their adult life. Better understanding of the underlying molecular mechanisms, role of microRNAs, gene expression, and epigenetic factors that play a role in foetal programming, will help develop appropriate interventions and preventive strategies.

Keywords: *Cardiometabolic Diseases; Fatty Acids*

Introduction

Framingham Heart Study (FHS) is a population-based, observational study, that was initiated by the United States Public Health Service in 1948 in Framingham, Massachusetts, to prospectively investigate the epidemiology and risk factors for cardiovascular disease [1]. On October 11, 2023, the FHS will celebrate 75 years, one of the longest epidemiological studies. This seminal study, provided significant insights into the epidemiology of this complex disease and for the first time, described risk factors that promote the development of cardiovascular disease. By the 1940s, cardiovascular disease had become the number one cause of mortality and has retained this status to

this day. According to the World Health Organization (WHO), cardiovascular diseases (CVDs) are the leading cause of death worldwide, taking an estimated 17.9 million lives each year. More than one third of these deaths occur prematurely, in people under 70 years of age. INTERHEART, a large, international, standardized, case-control study demonstrated the beneficial effects of robust management of potentially modifiable risk factors in reducing premature mortality [2].

Despite the fact a much earlier study (Mysore Cohort Study), demonstrated a risk factor related to intrauterine growth retardation and malnutrition, in the foetal programming for the development of metabolic diseases, very little attention is paid to alleviate this known risk. Since 1934, Holdsworth Memorial Hospital (HMH), also known simply as Mission Hospital Mysore, India, has kept meticulous anthropometric records of new-born children. Earlier studies indicated, that more than 30% of the children born in this hospital were of low birth weight. Studies described as Parthenon Cohort Studies was funded by Parthenon Trust, Switzerland, the Wellcome Trust, UK, and the Department for the International Development, UK, and the Medical Research Council, UK [3]. Further studies from this hospital and the King Edward Memorial Hospital, Pune, India, showed that these children with low birth weight, suffered from intrauterine growth retardation. British Epidemiologist Professor David Barker, collaborated with these groups, and developed the now famous 'Barker Hypothesis', which postulates, that number of organ structures and associated functions, undergo programming during embryonic and fetal life [4]. Extensive studies in the UK and India, led to the development of a novel concept, and demonstration of Fetal Origin of Adult Diseases (FOAD). Professor Barker proposed, that adverse nutrition in early life measured by birth weight, was responsible for the 'developmental origin of health and disease (DOHaD)' [5]. The importance of this discovery, has prompted Cambridge University press, to establish an exclusive professional journal on this topic: *Journal of Developmental Origin of Adult Diseases* [6]. The very existence of this meticulous birth record at HMH, Mysore, remained relatively unknown, till Indian Council of Medical Research, India, established a birth cohort study in 1969 at five centres: New Delhi, Mumbai, Pune, Mysore and Vellore. These studies were funded for five years. Babies were measured in detail at birth and through infancy, childhood, and adolescence [7]. In 1993 Medical Research Council (MRC) of the UK, established an Epidemiology Resource Centre at HMH, Mysore, and initiated a research program to assess the importance of early life, on adult diseases of this population (Mysore Cohort Study).

In a country like India, anywhere from 30-50% of the new-born children are of low birth weight. Therefore, according to 'foetal origins' hypothesis, one should expect this condition to contribute significantly to the development of metabolic diseases such as hypertension, type-2 diabetes, and obesity epidemic. However, according to Prof. Yajnik, lead investigator of the Pune Maternal Nutrition Study Group, the higher prevalence of these disorders in urban compared to rural areas, suggests, significance of prenatal and postnatal factors [8]. Although studies from leading epidemiologists had suggested the role of altered intrauterine growth, as the cause for the development of adult metabolic diseases such as hypertension, excess weight, obesity, type-2 diabetes and vascular diseases, no serious attention was paid to this newly discovered risk factor, at the national level, till the Indian Council of Medical Research (ICMR)-INCLEN Collaboration, undertook a nationwide survey engaging faculty from 265 institutions, to identify top research priorities in the Maternal, New-born, Child Health and Nutrition (MNCHN) themes for 2016 - 2025 [9]. This realization occurred almost quarter century after, Prof Barker proposed his hypothesis in the early 1990s [10-14]. Fully realizing the importance of these studies at the HMH, Mysore, we established a chapter of our professional society, South Asian Society on Atherosclerosis and Thrombosis (SASAT) at this campus: (www.sasat.org) [15].

Based on their observations, researchers from the Maternal Nutrition Study Pune, and Professor Barker's group from Southampton, UK concluded that, "Small Indian babies have small abdominal viscera and low muscle mass, but preserve body fat during their intrauterine development. This body composition may persist postnatally and predispose to an insulin resistant state" [16]. Three decades after the proposal of the Barker hypothesis, a new hypothesis is being proposed, based on the work of researchers from the Children's National Hospital (CNH), Washington DC. A news release from the CNH says: "The work that CNH 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 is direct relationship between the amount of visceral adipose, or belly fat a person has, and development of some of the most common metabolic diseases such as hypertension, obesity, type-2 diabetes and vascular diseases. What remained unclear, were the precise mechanisms of how the increase in belly fat, triggers the adult onset diseases" [17]. According to Robert Freishtat, "as the visceral fat grows, somewhere on the path of obesity development, the metabolism of fat tissue changes and begins to release different exosomes than lean adipose cells do. These new messages 'tweets', disrupt some important processes that eventually prevent body from effectively dealing with sugar and cholesterol metabolism [18,19]".

In order to explore the role of maternal exosomes on the foetal programming of adipose metabolism, researchers of CNH Washington DC, developed a bilateral research project with the Pune Maternal Nutrition Study Group at King Edward Memorial (KEM) Hospital, Pune. The project was funded by the National Institutes of Health (NIH), USA [19]. They proposed to leverage existing longitudinal biorepository data from the Indian maternal-infant pairs, test the association between maternal adipocyte-derived exosomes and infant adiposity. They hypothesized, that if successful, this project could identify potential therapeutic target and provide early interventions, that could address, prevalent metabolic conditions, such as diabetes and obesity in India. A professional society (www.sasat.rog) started by the author of this article, was responsible for initiation of several bilateral research projects, between the US scientists and the Indian scientists, as well as with the Indian Council of Medical Research (ICMR). Some of the major collaborators included, University of Minnesota, Florida International University, University of Alabama, Madras Diabetes Research Foundation (MDRF), Chennai, India, as well as CNH, Washington DC. The investigating teams from these institutions, had a longstanding international collaboration between the US and India [19,20].

Biological anthropology, low birth weight (LBW), altered nutrition, and foetal programming of adult metabolism

According to Professor David Barker, when faced with adversity of malnutrition, a foetus will undergo remodelling, thereby altering structure and function of various organs, to preserve neurodevelopment and promote survival. The word programming refers, to the fact that whatever the stimuli (exosomes or exposomes, epigenetic factors) during the foetal development, generates permanent changes, that persist throughout one's lifespan. Though a very attractive hypothesis, lacks experimental proof of such memory of genetic programming, and a possible trigger, for the development of risk factors for metabolic diseases, at a later time in life. Earliest population-based study, on the effect of maternal malnutrition on the growing foetus, is that of Dutch famine of 1944-45. The daily nutrition intake of pregnant women of this cohort was supposed to be between 400 - 1000 calories. The study found, that adults whose mothers were exposed to the famine during the early gestation period, demonstrated reduced glucose intolerance, revealed more atherogenic lipid profile, and higher body mass index, characteristic features of metabolic diseases [21]. It is assumed, that micronutrient deficiencies are common among women in low-income countries, and therefore, may affect pregnancy outcomes. Because of this global view, findings of the Maternal Micronutrient Supplementation Group of the Medical Research Council (MRC) Resource Centre, of Southampton, UK, becomes very relevant. They have reported beneficial effects of multiple micronutrients supplementation with iron plus folic acid in pregnancy outcomes. Supplementation resulted in small increase in birthweight and a reduction in the prevalence of LBW of about 10% [14]. A multinational study on the effect of lipid based nutrient supplements (LNS) on pregnancy outcome of HIV positive pregnant women concluded that, "Further research to investigate the impact of LNS on various aspects of foetal growth in HIV infected women is warranted [22].

The Mysore Birth Records Cohort Study comprised men and women born in Holdsworth Memorial Hospital (HMH), between 1934 and 1966. The purpose of this study was, to determine association if any, between the size and weight at birth, length at birth and development of adult metabolic diseases, cognitive function, including age-related cognitive decline. Study findings demonstrated, that lower birth weight was associated with higher risk of coronary artery disease in adult life. Type-2 diabetes was found to be associated with shorter length at birth than weight, and higher maternal weight. The prevalence of dementia and depression was 3% and 19% respectively. Despite the extensive studies done on this topic at various centres, in a review article published in 2015, in *Int J. Epidemiology*, the authors of

this bilateral study indicate, that they are currently recruiting subjects to study: 1) cognitive function as a continuous measure, obtained by administering a battery of cognitive tests developed, validated and normed in India by the 10/66 Dementia Research group; 2) a structured clinical mental state interview (Geriatric Mental State), an extended informant interview, the History and Aetiology Schedule, a structured neurological assessment (NEUROEX) and the Neuropsychiatric Inventory to diagnose dementia and other mental disorders.

Although we have access to the research data on this topic, for more than half a century, little is known on the role of fatty acids in the development of adult diseases. Essential fatty acids (EFAs) of the N3 and N6 long chain polyunsaturated fatty acids (PUFAs), are essential for the neurodevelopment in early life. These fatty acids are passed on from mother to infants via placenta, thus facilitating the incorporation, into foetal tissues such as brain and adipose. Because humans cannot synthesize these fatty acids, they need to be consumed as a part of the diet or acquired from the mother during the intrauterine growth or during the breast feeding stage. Therefore, to a great extent, the PUFA status of the developing infant depends on that of its mother [23-26]. There seems to be a significant decrease in the docosahexaenoic acid (DHA) during pregnancy. Furthermore, the neonatal status of DHA, correlates positively with birth weight, birth length, and head circumference. Therefore, there is a need for maternal DHA supplementation during pregnancy, to prevent intrauterine growth alterations. A longitudinal study on the role of PUFAs suggested the importance of circulating PUFAs, in their distinct pathophysiological roles, and in glucose homeostasis in pregnancy [27]. Since our interest for decades has been in the area of cardiometabolic diseases, in this overview, we will briefly discuss the role of poly unsaturated fatty acids (PUFAs), in haemostasis and thrombosis.

Friedman and associates from the Pennsylvania State University, Hershey, PA, described platelet dysfunction in neonates, with essential fatty acid deficiency [28]. They studied platelet aggregation response to ADP and found impaired response to this known agonist. They also have reported that this observed dysfunction was normal after these infants recovered from deficient state. Based on their observations they concluded, that a deficiency of arachidonic acid, the precursor of thromboxane $A_{2,}$ is correlated with an impairment of the aggregation of platelets, a phenomenon mediated by thromboxane A_2. A colleague of ours Professor M J Stuart, from the State University of New York, Syracuse, NY, described that healthy new-borns maintain normal platelet counts, with a platelet ultrastructure, that does not differ from adults. She further states, that transient hypo responsiveness is most marked in platelets from preterm infants [29]. These and other earlier observations are however speculative, as they did not measure the availability of platelet membrane associated fatty acids, release of arachidonic acid upon stimulation, or the formation of bioactive thromboxanes upon stimulation. Furthermore, as we have described earlier, platelet aggregation response to agonists could be obtained independent of thromboxanes.

Role of PUFAs in haemostasis and thrombosis

Agonist mediated activation of platelets lead to a chain of signalling events [29,30]. Agonists such as thrombin, adenosine diphosphate (ADP), epinephrine and thromboxane A_2 act at the G-protein-coupled transmembrane receptor and initiate activation signalling pathways (Figure 1). GTP-binding proteins (G proteins) act as transducers of signals, between the transmembrane domain receptors, and a variety of enzymes and ion channels. The G-protein subunit undergoes a confirmational change, leading to the exchange of its bound GDP for GTP. Receptor mediated signalling results, in the hydrolysis of GTP to GDP, and activation of phospholipase C (PLC). This enzyme acts on membrane-associated phospholipids (inositol phosphates) and generates second messengers like inositol 1- 4'-5' trisphosphate (IP_3) and diacylglycerol (2-DAG). IP_3 mobilizes cytosolic calcium from membrane stores, elevates cytosolic calcium, activates phospholipase A_2 and releases arachidonic acid (AA). AA is converted by cyclooxygenases (COX) to prostaglandin endoperoxides (PG) PGG_2 and PGH_2 and thromboxane $A_{2,}$ all potent platelet agonists, which in turn activate platelet membrane associated receptors. This signalling mechanism is one of the common pathways to activate platelet membrane glycoprotein (GP) domains such as GP 11b/111a, which facilitates fibrinogen binding, promotes development of stickiness, and induces platelet aggregation.

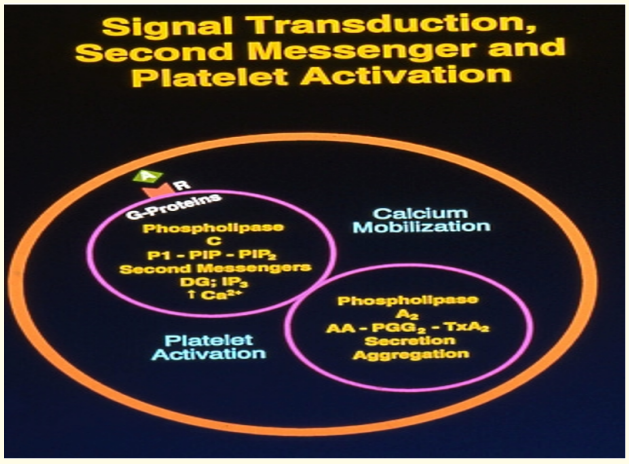

Figure 1: *Activation signalling pathways (Courtesy: Gundu H. R. Rao, University of Minnesota).*

Role of free fatty acids in the development of metabolic risk factors

Increased plasma glucose and free fatty acids, contribute to inflammation as well as oxidative stress [31]. Whereas, Omega-3 fatty acids seem to decrease oxidative stress and inflammation [32]. These two early risk factors of metabolic diseases, as well as infectious diseases (viral), share a common mechanism, oxidative stress. Oxidative stress occurs, due to an imbalance in the production and consumption of reactive oxygen species. Increases in reactive oxygen species, also can lead to chronic inflammation. Furthermore, these risk factors also can induce endothelial dysfunction, one of the earliest modifiable risk factor, for metabolic disease, as well as for the severity of infectious diseases, caused by viral disease such as COVID and HIV [33,34]. Furthermore, altered metabolic state also induces endothelial dysfunction (ED), which is an early event in atherosclerosis, obesity, diabetes and vascular diseases. Earlier research suggested, that the early risk factors such as inflammation, oxidative stress, excess weight were responsible for the development of ED [35]. A recent article published in Circulation Research by George King of Joslin Diabetes Centre, Boston, MA, describes a series of studies, explaining the relationship among insulin, fats, and vascular system. According to their findings, endothelial cells drive the body's metabolism [36]. According to these researchers, insulin resistance can increase atherosclerotic and cardiovascular risk by inducing ED, decreasing nitric oxide (NO) production, increasing the levels of vasoconstrictors, and accelerating arterial inflammation.

Oxidative stress develops, when an imbalance exists between free radical formation and the capability of cells and tissue to clear them. Excess of hydroxyl radical and peroxynitrite cause lipid peroxidation, thus damaging cell membranes and lipoproteins. The hydroperoxyl adducts of linoleic acid and eicosapentaenoic acid, inhibit the COX enzymes in platelets and lowers the endogenous levels of vasodilators (Figure 2) [37]. Redox homeostasis in biological systems is maintained by two distinct mechanisms; the enzymatic systems including superoxide dismutase, ascorbate peroxidase, guaiacol peroxidase, glutathione-S-transferase and catalase; the non-enzymatic compounds like ascorbic acid, reduced glutathione, α-tocopherols carotenoids, phenols, flavonoids and proline [38]. Studies from our laboratory at the University of Minnesota demonstrated, that platelet levels of glutathione are reduced under stress and the glutathione deficient platelets exhibit altered arachidonic metabolism [38,39].

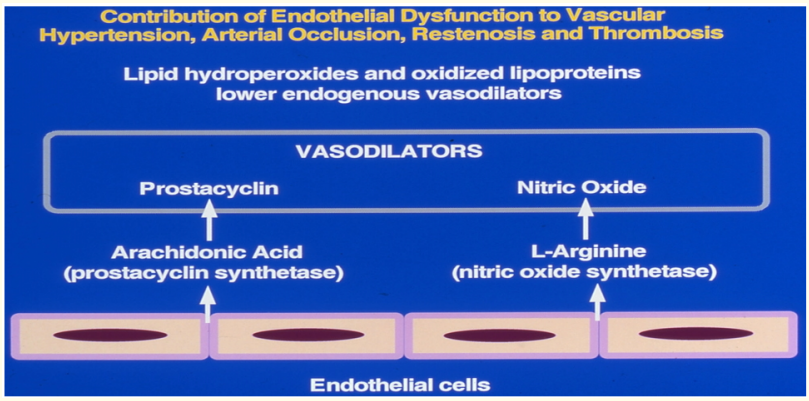

Figure 2: *Lipid hydroperoxides lower endogenous vasodilators (Courtesy: Gundu H. R. Rao, University of Minnesota).*

Further studies from our laboratory demonstrated, that similar altered metabolism of arachidonic acid occurs during experimentally induced diabetes conditions. In our exploratory studies, rats were rendered diabetic by injection of streptozotocin, and the ability of platelets and vessel wall tissue to make prostanoids from the substrate arachidonic acid (AA), were compared with the matched controls. We evaluated AA incorporation, release of AA and conversion of radiolabelled AA, to thromboxanes (thromboxane B_2) and prostacyclin (6-Keto $PGF_1\alpha$). The stable metabolites of the respective, active derivatives of AA by platelets and the vessel wall tissues [40]. Conversion of AA to proaggregatory thromboxanes, was higher in the diabetic rats and the vasodilatory prostacyclin was less, suggesting a shift to prothrombotic state. The changes observed both in the platelet and vessel wall production of AA, was normalized by pancreatic islet cell transplantation, suggesting a disease specific effect. Large longitudinal studies on arterial stiffness, pulse wave velocity (PWV) changes, and intima-medial thickness have concluded, that such conditions precede hypertension, and metabolic diseases in preterm babies, children, and youth [41-44]. Furthermore, accelerated cognitive decline has been observed, in individuals with highest PWV compared to lowest PWV individuals [45]. From these studies, one can assume that insulin resistance, elevated blood glucose, and increased free fatty acids, can increase atherosclerotic and cardiovascular risk by inducing ED by decreasing nitric oxide (NO) production, lowering vasodilators via PG pathway, increasing vasoactive thromboxane production and accelerating arterial inflammation.

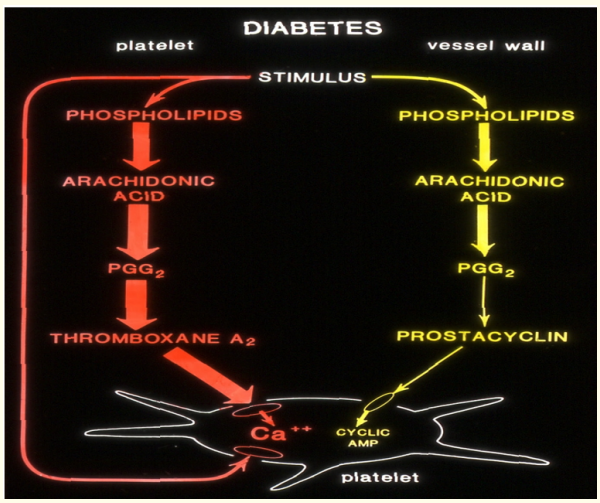

Figure 3: *AA conversion to thromboxanes and prostacyclins in diabetic rats (Courtesy: Gundu H. R. Rao, University of Minnesota).*

Discussions

British Epidemiologist, Professor David Barker, who traced roots of chronic adult diseases in later life to early life programming of metabolic pathways, became the director of the Medical Research Council (MRC), Environment Epidemiology Unit in Southampton in 1984. It is interesting to note, that his PhD thesis was on prenatal influences and subnormal intelligence, a fore runner to his later work on foetal programming of adult diseases [46]. After he stepped down as the director of this unit, he continued to work at what is now called the MRC Lifecourse Epidemiology Unit, which is headed by Professor Caroline Fall at University of Southampton, UK. Researchers at the MRC International Nutrition Group, and London School of Hygiene report that, "Considerable evidence now exists, that early exposure to nutritional deprivation, can have a long term consequence to health, with low birth weight, now considered a risk factor for later health outcomes, such as coronary heart disease, stroke, type-2 diabetes, and the metabolic syndrome" [47]. They further elaborate this concept, "There is considerable evidence, that foetal and early postnatal undernutrition, can invoke the following changes: metabolic adaptations that affect variables such as hepatic enzyme profiles, lipoprotein profiles, clotting factor production, anatomical adaptations, that affect end organ glucose uptake, renal resource handling, endocrine adaptations, that affect pituitary-adrenal systems, insulin signalling, and leptin levels".

In view of these observations one can confidently predict, that a large number of new-born babies with poor nutrition and low birth weight, are 'at risk' for developing metabolic diseases later in life. One can also argue, that not only foetal and post-natal nutrition is important, but also of the 'would be' mother [48]. According to a global report by the United Nations, more than half of all undernourished people (418 million) live in Asia. More than 2.3 billion people globally, lack year-round access to adequate food. Nutritional restrictions in the first 1000 days of life, seem to impair or delay the physical and cognitive development of the individual, and have long-term consequences for their health. There are various ongoing studies, to characterize the metabolic derangements induced by various forms of early-life malnutrition [49]. In spite of the massive data available on this topic from the UK and India, what we would like to convince our readers is the fact, that metabolic alterations occur at all stages of development and therefore, early diagnosis of the various risk factors for the development of metabolic disease, is critical for robust management of the modifiable risk and prevention of premature death by these diseases.

INTERHEART study, a large, international, standardized, case-control study, designed to assess the importance of risk factor modification, indeed demonstrated, that robust management of modifiable risk factors, have the potential to prevent most premature cases of myocardial infarction (MI) [50]. Researchers at Harvard university on the other hand demonstrated, that even in the presence of non-modifiable risks (genetic), a healthy lifestyle, prevents premature death by MI. Based on their study they concluded, "that across four studies involving 55,685 participants, genetic and lifestyle factors were independently associated with susceptibility to coronary artery disease. They found that a favourable lifestyle was associated with a nearly 50% lower risk of coronary disease than was unfavourable lifestyle" [51]. On the other hand, at the University of Minnesota a new concept was developed to address the development of the 'disease itself', instead of focusing on risk factor management. Prof Jay Cohn, at the University of Minnesota, has successfully shown that disease score, calculated from 10 non-invasive radiological tests, can be used to detect cardiovascular disease in early stages [52].

Early diagnosis of the risks, management of the risks and prevention of metabolic diseases

According to the United Nations International Children's Emergency Fund (UNICEF), with the birth of 25 million children per year, India accounts for nearly one fifth of the global child births [53]. Even with the low end figure of 30% low birth weight children, it runs into over 7.5 million children 'at risk' for developing metabolic diseases per year. One of the findings of David Barker was, 'antenatal stress of placental insufficiency', which programs metabolic alterations in beta cell function. The increase in insulin sensitivity then persists, into adult life and promotes, the development of metabolic abnormalities, such as oxidative stress, inflammation, vascular dysfunction, hypertension, obesity, diabetes and vascular diseases. The free fatty acids on the other hand, can cause insulin resistance, generate lipid

metabolites (diacylglycerol), lower vasodilatory metabolites (NO, PGE_1, PGI_2), increase proinflammatory cytokines such as (TNF-α) IL-1ß, IL-6, MCP1 and induce oxidative and endoplasmic reticulum stress. In view of these observations, studies have to be initiated at the earliest stages of development, to understand mechanisms that precipitate these conditions so that one can introduce appropriate interventions. The Pune Maternal Nutrition Study (PMNS) set up cohort in six villages near Pune city in 1994. The study objective was to explore associations of maternal diet, physical activity, and nutritional status, with birth outcomes and to trace the evolution of cardiometabolic risks in children. In 2012, when the cohort was aged 18 years, this cohort study was converted to randomised control intervention study (PRIYA), testing the effect of vitamin B_{12} supplementation of the young F_1 men and women on foetal growth, epigenetic marks and macrometabolic outcomes in the next (F_2) generation. The PRIYA trial and the 24-year follow-up of the PMN, are ongoing.

In HIV-1-infected women, poor nutrient status has been associated, with faster progression of HIV-1 disease, and adverse birth outcomes. Harvard School of Public Health, assessed the effects of vitamin A and multivitamins, on birth outcomes in such women. The researchers found, that multivitamin supplementation was a low-cost way of substantially decreasing adverse outcomes, and increasing T-cell counts in HIV-1-infected women [54,55]. According to the Cochrane review, four relatively large, well-conducted randomised controlled trials on the benefits of micronutrient supplementation, have been conducted in pregnant lactating women infected with HIV [55]. Multiple micronutrient supplements, seem to confer multiple benefits, to pregnant women and their offspring. Studies on Long-term clinical benefits, adverse effects, and optimal formulation of multiple micronutrient supplements, as well as macronutrients, require further investigation in pregnant women in general, in low-and middle-income countries. Recent studies from India (ICMR-INDIAB National Study), have recommended macronutrients for obtaining remission and prevention of diabetes in Asian Indians, based on a data driven optimization modelling [56]. INTERGROWTH-21st a multicentre study, did a comprehensive evaluation of how the maternal exposome, influences the biology of the early human growth and development [57]. They analysed the relationships between the size at birth and maternal metabolite signatures, for foetal phenotypes as measure of the exposome, and found different foetal phenotypes, that influenced the postnatal growth, adiposity, and neurodevelopment. They also found that the extreme phenotypes, had early-pregnancy metabolite: 5-hydroxy eicosapentaenoic acid and 11-phosphatidylcholines, linked to oxylipin or saturated fatty acid side chains.

Studies at the Mission Hospital Mysore (Cohort Profile: MHM), were among the first in a low-and middle-income country, to test the developmental origins of health and disease (DOHaD) [11]. Whereas the Mysore Parthenon Cohort was established at MHM, to examine the long-term effects of maternal glucose and nutritional status, on cardiovascular disease risk factors in the offspring [3]. This ongoing study provides extensive data on serial anthropometry and body composition, physiological and biochemical measures, dietary intake, nutritional status, physical activity measures, stress reactivity measures and cognitive function, and socio-demographic parameters of the offspring. Data on anthropometry, cardiovascular risk factors, and nutritional status, are available for mother during pregnancy, anthropometry and risk factor measures are available for both parents at follow-up. Although it is well known that long chain omega-3 fatty acid status during pregnancy, may influence new-born anthropometry and duration of gestation, evidence from randomized clinical trials in low-and middle-income countries is limited. In order to develop some molecular basis for these foetal programming, Dr Rao facilitated the development of a bilateral research project between the CNH Washington DC researchers, and the Maternal Nutrition Study Group at Pune, India. This study was funded by the National Institutes of Health USA [19]. These studies were developed based on the discoveries made at CNH, Washington DC on the role of adipocyte-derived maternal exosomes, as an obesity-related maternal factor capable of driving abnormal foetal cardiometabolic development, and to be an interorgan mediator of cardiometabolic disease, in obese children and adults [18].

Since researchers at CNH had developed techniques to isolate these exosomes from body fluids, specific objectives of the proposed studies were, to test the association between maternal adipocyte-derived exosomes and infant adiposity. The Specific Aims of the proposed NIH/R21, focused on clinical data and biospecimens (e.g. maternal blood, urine and infant cord blood, amniotic fluid) from Indian maternal-infant pairs, that are part of a long-term longitudinal cohort studies, run by our Indian colleagues at the King Edward Memorial

Hospital, Pune. This exosomal testing was an exciting, new research opportunity, that has the potential to transform, current thinking about the pathogenesis of childhood obesity and cardiometabolic diseases. Moreover, the project is likely to identify potential therapeutic targets, for the primary prevention of these diseases.

Despite Barker's hypothesis, which postulates, that a number of organ structures and associated functions, undergo programming during embryonic foetal life, which determines the set of physiological and metabolic responses that carry to adult hood, well thought-out studies have not been done to address all aspects of this speculative hypothesis. What evidence we have is sketchy, inconclusive and at best, provide limited solutions. Emerging technologies may provide access to the genetic basis of foetal programming and gene expression, under various stressful situations. Recent studies indicate that whole genome sequence could be used for determining the health status of new-born children, including during foetal development stage [58]. Experts at National Centre for Advancing Translational Sciences and at the NIH Gene Therapy Group unanimously agree, "that whole-genome sequencing (of all infants) is the way to go in the future." Furthermore, studies on the role of maternal exosomes, exposomes, and other epigenetic factors that influence the early growth of the foetus, will give us greater insights into the foetal programming, that may influence later adult health and disease.

To address issues related to the early life influences, that underlie the developmental origin of adult diseases, we have established a consortium, at the Children's National Hospital in Washington, DC. The Scientific Consortium of Non-Communicable Diseases Prevention Across Generations (SCNR-G), was formed in 2020 at the Children's National Hospital, Washington DC. This consortium serves as a catalyst for international scientists, and health care workers to develop, basic, applied, interventional, collaborative projects, and to translate results to patients and their families. Professor Gundu Rao serves as the Chair of this Global platform (www.SCNR-G.org). Mission of the consortium is to provide global DOHaD leadership and a catalytic platform for collaborative surveillance, prevention, and treatment of NCDs. Vision of the SCNR-G is, to collaboratively work with partners to identify early risks, reduce risks, prevent morbidity and mortality related to NCDs, through focused diagnostics and novel interventions, in the earliest stages of human development. Prof. Gundu Rao is also the founder Chief Executive Officer of the professional society, South Asian Society on Atherosclerosis and Thrombosis (www.sast.rog).

Conclusion

Vascular diseases of the heart and brain together, are responsible for the largest number of mortality and morbidity worldwide. Cardiovascular disease is the leading cause of mortality worldwide and is associated with 17.8 million deaths annually. What we have learnt in the last half a century is, effective management of the known modifiable risks for developing CVDs, significantly reduces premature mortality. Despite this knowledge from large clinical studies, we have not been able to reduce, reverse, of prevent metabolic diseases such as hypertension, obesity, type-2 diabetes and vascular diseases. All of these diseases have increased rapidly, in the last three decades to epidemic proportions. We have learnt from the earlier studies, that the low birth babies are indeed 'thin-fat babies'. Obesity is not only a disease by itself, but also is a risk factor for other adiposity related clinical complications, as well as for the severity of infectious diseases such as Covid-19. We and others have been advocating robust developments of holistic risk prevention strategies, rather than focusing on the risk management. In order to develop such prevention strategies, we need to identify early signs (diagnostic features or bio markers) of the disease, underlying causes or molecular mechanism involved, and then plan appropriate interventions. According to recent reports, 829 million people globally are undernourished. The leading, renowned lifestyle expert Professor Dean Ornish says, "Although heart disease and diabetes kill more people than all other diseases combined, these are preventable and even reversible for at least 95% of people today, by changing our diet and lifestyle".

Despite the fact that the thesis topic of British Epidemiologist, Professor David Barker was on 'prenatal influences on subnormal intelligence', not much is known on the mechanisms involved in predisposing these new-born children, to cognition problems in adult life. This is to some extent true, of how prenatal nutritional deficiencies predispose, these low birth weight children to excess metabolic diseases

in later life. Barker hypothesis speculated that 'prenatal stress', nutritional insufficiency, or other metabolic disturbances, programmed pancreatic beta cells in these low birth weight children, to produce altered insulin sensitivity, which persisted to adult life and was responsible, for the development of metabolic diseases in later life. Based on this observational conclusion, multiple studies have been conducted in different countries, to find observation-based evidence, to support this hypothesis or to develop interventions, for preventing the ill effects of foetal programming on altered metabolism in adult life. Barkers hypothesis was discussed by experts in the early 90s, and studies were instituted in India, as well as in the UK, to address the foetal nutrition as well as that of the mother. At the King George Memorial Hospital, Pune, a dedicated team was formed to address maternal nutrition in particular, Pune Maternal Nutrition Group, which is active to this day. Having said that, it is important to remind the readers that at the national level no major study was initiated to look at this very important problem till 2015.

The Indian Council of Medical Research undertook a nationwide study, engaging faculty from 256 institutions, to identify top research priorities in the Maternal, New-born and Child Health and Nutrition Initiative (CHNRI) from 2016-2025. This was one of the most extensive studies conducted by this premier institute, under the guidance of the, then Director of the ICMR, Dr Soumya Swaminathan (Current Chief Scientist at WHO). According to their report, research ideas were pooled from 498 experts located in different parts of India, scored by 893 experts. This exercise was one of the largest use of CHNRI methodology. Study group concluded that, "prioritization of research options are only valuable if they are put to use, and we hope that donors will take advantage of this prioritized list of research options". We would like to emphasize that this exercise was an effort to meet the requirements of the Sustainable Development Goals of the United Nations (UN). Majority of countries (193) of the UN adopted the resolutions of the UN for Sustainable Development Goals (SDG). According a UN report only 20 out of 193 countries are actively participating in this program. Many countries require Official Development Assistance to encourage growth and trade. Yet, aid levels are falling and donor countries have not lived up to their pledge to ramp up development assistance. What we want to emphasize here is, even in such an extensive one-of-a-kind national study, the topic of our interest, which we consider of great public health importance, is barley discussed. We have just made a new beginning by establishing a global platform; 'Scientific Consortium of Non-Communicable Diseases Prevention Across Generations' at the Children's National Hospital, Washington DC. We have initiated bilateral studies with the Pune Maternal Nutrition Study Group. We have met Emeritus Professor Caroline Fall (Hertfordshire birth cohort) of the MRC Life course Epidemiology Centre at the University of Southampton, UK, who is the leader of the MRC Epidemiology group at the Mission Hospital, Mysore.

What we need now is a consortium of interested stakeholders, who can work in concert, and develop needed resources, to address the issues related to this unique 'maternal-child' nutrition issues. We and others currently working on these topics, feel that early diagnosis of the underlying causes will provide opportunities to develop appropriate interventions. As we have described in this review, developmental origin of risks for developing metabolic diseases, could occur as early as in prenatal stages, or any time during the life course. Therefore, it is essential to look at this phenomenon with a new perspective, so that the emphasis is on early risk stratification and prevention, than 'modifiable risk management' and reduction of premature mortality.

Bibliography

1. Mahmood SS., *et al*. "The Framingham Heart Study and the Epidemiology of Cardiovascular Disease: A Historic Perspective". *Lancet* 383.9921 (2014): 999-1008.

2. Yusuf S., *et al*. "Effect of modifiable risk factors associated with myocardial infarction in 52 countries (the INTEHEART study): case-control study". *Lancet* 364.9438 (2004): P937-P952.

3. Krishnaveni GV., *et al*. "Cohort Profile: Mysore Parthenon Birth Cohort". *International Journal of Epidemiology* 44.1 (2014): 28-36.

4. Barker DJ. "Fetal origins of coronary heart disease". *British Medical Journal* 311 (1995): 171-174.

5. Barker DJP. "The Developmental Origin of Adult Diseases". *The Journal of the American College of Nutrition* 23.6 (2004): 5885-5955.

6. Journal of Developmental Origin of Adult Diseases. Cambridge University Press.

7. Rao GHR and Bharathi M. "Mother and Child Nutrition; First Major Step for Prevention of Cardio-Metabolic Disorders". *Journal of Cardiology Cases* 109 (2016): 179-186.

8. Yajnik C. "Interaction of perturbations in intrauterine growth and growth during childhood on the risk of adult-onset disease". *Proceedings of the Nutrition Society* 59.2 (2000): 257-265.

9. Arora NK., *et al*. "Research Priorities in Maternal, Newborn, and Child Nutrition for India: An Indian Council of Medical Research-INCLEN Initiative". *Indian Journal of Medical Research* 145.5 (2017): 611-622.

10. Barker DJ., *et al*. "Fetal and placental size and risk of hypertension in adult life". *British Medical Journal* 301 (1990): 259-262.

11. Krishna M., *et al*. "Cohort Profile: The 1934-66 Mysore Birth Records Cohort in South India". *International Journal of Epidemiology* 44.6 (2015): 1833-1841.

12. Khandelwal S and Reddy KS. "Eliciting a policy response for the rising epidemic of overweight-obesity in India". *Obesity Reviews* 14.2 (2013): 114-125.

13. India State-Level Disease Burden Initiative Malnutrition Collaborators: The burden of child and maternal nutrition and trends in its indicators in the states of India: the Global Burden of Disease Study 1990-2017". *Lancet* 3.12 (2019): 855-870.

14. Fall CH., *et al*. "Micronutrient supplementation Study Group Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation". *Food and Nutrition Bulletin* 30 (2009): S533-S546.

15. Rao GHR. "Contributions of South Asian Society on Atherosclerosis and Thrombosis and Indian Society of Atherosclerosis Research to our understanding of Atherosclerosis and Thrombosis". *Journal of Clinical and Preventive Cardiology* 5.2 (2016): 67-72.

16. Yajnik CS., *et al*. "Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study". *International Journal of Obesity* 27 (2003): 173-180.

17. Rao GHR. "Fetal origin of Adult Cardiometabolic Diseases: Micronutrient and micro RNA Interventions". *Endocrinology and Metabolism Research Institute* 4.3 (2019).

18. Ferrante SC., *et al*. "Adipocyte-derived exosomal miRNA: a novel mechanism for obesity-related disease". *Pediatric Research* 77 (2015): 447-454.

19. Freishtat R. "Maternal Adipocyte-derived Exosomes in the Thin-Fat Baby Paradox. Fogarty International Research Grant". *National Institutes of Health (NIH)* (2020).

20. NIH grant funded by Fogarty International Centre (2001 to 2016), Myron Gross, University of Minnesota, Dale Williams, Florida International University, Cora Lewis, University of Alabama and V. Mohan, Madras Diabetes Research Foundation, Chennai (2016).

21. Roseboom TJ., *et al*. "Effects of prenatal exposure to Dutch famine on adult disease in later life: an overview". *Molecular and Cellular Endocrinology* 185 (2001): 93-98.

22. Nikhoma M., *et al*. "Lipid based nutrient supplements during pregnancy may improve foetal growth in HIV infected women-A cohort study". *PLOS ONE* 14.5 (2019): e0215760.

23. Honstra G. "Essential fatty acids in mothers and their neonates". *The American Journal of Clinical Nutrition* 5 (2000): 1262S-9S.

24. Rump P., *et al*. "Essential fatty acid composition in plasma of phospholipids and birth weight: a study in term neonates". *The American Journal of Clinical Nutrition* 73 (2001): 797-806.

25. Wang E., *et al*. "Longitudinal associations of plasma fatty acids in pregnancy with neonatal anthropometry: Results from the NICHD Fetal Growth Studies-Singleton Cohort". *Nutrients* 14.3 (2022): 592.

26. Zhu Y., *et al*. Plasma phospholipid n-3 and n-6 polyunsaturated fatty acids in relation of cardiometabolic markers and gestational diabetes: A longitudinal study with the prospective NICHD Fetal Growth Studies.

27. Friedman Z., *et al*. "Platelet dysfunction in the neonate with essential fatty acid deficiency". *The Journal of Pediatrics* 90.3 (1977): 439-443.

28. Stuart MJ. "Platelet function in the neonate". *The American Journal of Pediatric Hematology/Oncology Journal* 1.3 (1979): 227-234.

29. Rao GHR. "Signal transduction, second messengers and platelet pharmacology". *Pharmacology* 13 (1994): 39-44.

30. Rao GHR. "Signal transduction, second messengers and platelet pharmacology". In: Env. Physiol. (Mallick BN and Singh R, Editions.), Narosa Publishing House, Delhi (1994).

31. Tripathy D., *et al*. "Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects". *Diabetes* 52.12 (2003): 2882-2887.

32. Meital LT., *et al*. "Omega-3 fatty acids decrease oxidative stress and inflammation in macrophages from patients with small abdominal aortic aneurysm". *Scientific Reports* 9 (2019): 12978.

33. Ghosh A., *et al*. "Role free fatty acids in endothelial dysfunction". *Journal of Biomedical Science* 24.50 (2017).

34. Rao GHR. "Coronavirus Disease; Long COVID: Global War Against a Novel Virus". *EC Clinical and Medical Case Reports* 5.8 (2022): 14-28.

35. Ivanov A., *et al*. "". *Oxidative Medicine and Cellular Longevity* (2016): 8910396.

36. Park K., *et al*. "Endothelial cells induced progenitors into brown fat reduce atherosclerosis". *Circulation Research* 131 (2022): 168-183.

37. Das K and Roychoudhury A. "Reactive oxygen species (ROS) and response of antioxidants as ROS-scavengers during environmental stress in plants". *Frontiers in Environmental Science* 2 (2014): 53.

38. Hill TD., *et al*. "Role of glutathione and glutathione peroxidase in human platelet arachidonic acid metabolism". *Prostaglandins* 38 (1989): 21-32.

39. Hill TD., *et al*. "The influence of glutathione depleting agents on human platelet function". *Thrombosis Research* 53 (1989): 457-467.

40. Gerrard JM., *et al*. "Alteration in the balance of prostaglandin and thromboxane synthesis in diabetic rats". *Translational Research: The Journal of Laboratory and Clinical Medicine* 95.6 (1980): P950-958.

41. Rao GHR. "Altered Glucose Metabolism and Acute Vascular Events". *Journal of Clinical Cardiology and Diagnostics* 4.1 (2022): 9-16.

42. Agbaje AO. "Arterial stiffness precedes hypertension and metabolic risks in youth: a review". *Journal of Hypertension* (2022).

43. Chainoglou A., *et al*. "Arterial stiffness and nocturnal hypertension in preterm children and adolescents". *Journal of Hypertension* 40.9 (2022): 1751-1757.

44. Agbaje AO., *et al*. "Effects of arterial and carotid intima-medial thickness progression on the risk of overweight/obesity and elevated blood pressure/hypertension: a cross-lagged cohort study". *Hypertensin* 79.1 (2022): 159-169.

45. Araghi M., *et al*. "Association of aortic stiffness with cognitive decline: Whitehall 11 longitudinal cohort study". *European Journal of Epidemiology* 35.9 (2020): 861-869.

46. Cooper C. "David Barker (1938-2013)". *Nature* (2013).

47. Prentice AM and Moore SE. "Early programming of adult diseases in resource poor countries". *Archives of Disease in Childhood* 90.4 (2004).

48. M: Maternal nutrition and low birth-weight-what is really important?" *Indian Journal of Medical Research* 130 (2009): 600-608.

49. Mayneris-Perxachs J and Swann JR. "Metabolic phenotyping of malnutrition during the first 1000 days of life". *European Journal of Nutrition* 58.3 (2019): 909-930.

50. Yusuf S., *et al*. "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART Study): case control study". *Lancet* 364.9438 (2004): P937-952.

51. Khera AV., *et al*. "Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Artery Disease". *The New England Journal of Medicine* 375 (2016): 2349-2358.

52. Cohn J., *et al*. "Screening for early detection of cardiovascular disease in asymptomatic individuals". *American Heart Journal* 146 (2003): 679-685.

53. UNICEF/WHO Low birthweight: country, regional and global estimates. New York, NY: UNICEF (2004).

54. Fawzi WW., *et al*. "Randomized trial of effects vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania". *Lancet* 351 (1998): 1577-1582.

55. Siegfried N., *et al*. "Micronutrient supplementation in pregnant wone with HIV infection". *The Cochrane Database of Systematic Reviews* 3 (2012): CD009755.

56. Anjana RM., *et al*. "Macronutrient recommendation for remission and prevention of diabetes in Asian Indians based on data-driven optimization model: The ICMR-INDIAB National Study". *Diabetic Care* (2022): dc220627.

57. Villar J., *et al*. "Association between foetal abdominal growth trajectories, maternal metabolite signatures early in pregnancy, and childhood growth and adiposity: prospective observational multinational INTERBIO-21st foetal study". *The Lancet Diabetes and Endocrinology* (2022).

58. Gammon K. "Revealing the hidden impact of whole genome sequencing for new-borns". *New Scientist* 3401 (2022).

Volume 5 Issue 10 October 2022