

Review

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Review

Developmental Origins of Non-Communicable Chronic Diseases: Role of Fetal Undernutrition and Gut Dysbiosis in Infancy

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Abstract: Globally, there is increasing prevalence of non-communicable chronic diseases (NCCD) like obesity, metabolic syndrome, type2 diabetes mellitus (T2DM), hypertension, allergic asthma and neuro-developmental/psychiatric problems making NCCD a leading cause of disability, morbidity and mortality. Some of these NCCD are presenting at a younger age especially in the socio-economically disadvantaged communities of affluent countries, and in low and middle-income countries undergoing industrialization and socioeconomic transition to more economic prosperity. NCCD are often attributed to unhealthy personal lifestyles, but there may be more at play. Through a case report-based discussion, I will illustrate how environmental exposures during the critical window of life, including in utero and early infancy, can significantly influence health as an adult. I will discuss how establishment of a rich and diverse symbiotic gut microbiota in the first three years of life promotes health while a loss of diversity and abundance of beneficial symbiotic gut microbes can predispose to aforementioned NCCD, and the best practices to establish a symbiotic gut.

Keywords: DOHaD; gut microbiome; dysbiosis; non-communicable diseases

1. Introduction

Globally, there is increasing prevalence of non-communicable chronic diseases (NCCD) like obesity, metabolic syndrome, type2 diabetes mellitus (T2DM), hypertension, allergic asthma and neuro-developmental/psychiatric problems making NCCD a leading cause of disability, morbidity and mortality [1,2]. Some of these NCCD are presenting at a younger age especially in the socio-economically disadvantaged communities of affluent countries, and in low and middle-income countries undergoing industrialization and socioeconomic transition to more economic prosperity. NCCD are often attributed to unhealthy personal lifestyles, but there may be more at play.

Through a case report-based discussion, I will illustrate how environmental exposures during the critical window of life, including in utero and early infancy, can significantly influence health as an adult [3–5]. I will discuss how establishment of a rich and diverse symbiotic gut microbiota in the first three years of life promotes health while a loss of diversity and abundance of beneficial symbiotic gut microbes can predispose to aforementioned NCCD [6–9], and the best practices to establish a symbiotic gut.

2. Case Report

A 21-year-old asymptomatic white male is noted to have an elevated blood pressure (BP) of 134/90mmHg at his annual checkup prior to returning to college. His height is 177.8 cm (5 ft 10 in) and weight is 85.4kg (188 lbs). His BP a year earlier was 125/85 mm Hg. Physical examination findings are normal except for high an elevated BMI of 27 kg/m² (reference healthy 19-24.9). His urinalysis shows proteinuria of 100mg/dl but no red blood cells, white blood cells, or casts in the urine sediment. His serum creatinine is normal at 0.9 mg/dl and serum albumin is 4.5 g/dl. Ultrasonography of the kidneys shows normal echogenicity of both kidneys and normal renal length of 10.9 cm bilaterally.

Since early childhood, his diet has been dominated by ultra-processed foods, including preserved meats with low intake of fruits and vegetables. His average sodium intake is about 3.5 grams per day, while the recommended sodium intake by the by US department of Agriculture (USDA) is less than 2.3 grams per day. Since his middle school years, he has spent a lot of time in academic studies and on digital social media, and engages in low intensity physical exercise only 2 hours/week while US department of Health and Human services recommends 1.5 hours of vigorous intensity exercise per week or 3-5 hours of moderate intensity exercise per week.

Further history obtained to evaluate the cause of his hypertension and proteinuria reveals that he was born to a 24-year-old G1P1 mother by emergency cesarean section at 33 weeks of gestation because of maternal preeclampsia. His very low birth weight of 1.4kg was also less than 5% of expected for his gestational age reflecting intrauterine growth restriction (IUGR). He received cow's milk formula in the first 9 months of life and showed catch-up growth in height and weight by 12 months of age. He had 5 episodes of fever lasting 2-3 days in the first 2 years of life, and he received antibiotics each time for 7 days for presumed otitis media.

The patient's mother, now 45 years old, had smoked cigarettes since she was a teenager, and developed persistent hypertension after the delivery of this child. There is no family history of obesity, diabetes, hypertension, or cardiovascular disease except for mother with hypertension.

3. Risk Factors for NCCD in an Individual Born with IUGR

In ascertaining the cause of proteinuria and hypertension in this young man, his birth history provides clues. Individuals born with IUGR due to inadequate nutrient supply in utero have been noted to have higher risk of certain health problems later in life, including but not limited to hypertension, proteinuria, obesity, T2DM, cardiovascular disease, and neurodevelopmental and psychiatric problems such as impulsive behavior, anxiety, and depression [5,10–18]. The constellation of these problems is a result of developmental conditioning and altered metabolic programming to survive with nutrient deprivation.

The fetus exposed to low caloric supply makes adaptations not only to survive in utero but also to live ex- utero in an anticipated similar nutritionally challenged environment. Some of the adaptations predispose to development of NCCD if the extra uterine environment is different than anticipated, and plenty of nutrition is available. The fetal metabolic changes in response to undernutrition have been well elucidated in a previous report [5] include the following:

- a. slower fetal growth rate by developing insulin resistance to reduce energy demand
- b. developing leptin resistance to decrease energy expenditure, enhance storage of fat, and have less satiety even when food supply is plentiful [18]
- c. redistribution of blood flow by vascular remodeling to allow relatively more nutrition to reach the heart, lungs, brain and adrenals while rationing nutrition distribution to certain other developing organ systems [19,20].
- d. increased fetal exposure to maternal cortisol which in turn alters the hypothalamic pituitary adrenal axis and affects neurodevelopment, resulting in subsequent development of hyper-alert state to forage for food, anxiety, attention deficit hyperactivity disorder, and psychiatric problems[12]

The aforementioned adaptations in response to undernutrition in fetal life in in our patient would have led to his predisposition for chronic kidney disease [21] and NCCD as follows:

- a. Nutritional rationing to the kidneys and premature birth at 33 weeks would have resulted in lower endowment of nephron numbers and increased work load per nephron. Nephrogenesis by arborization occurs until 36 weeks of gestation and no new functioning nephrons are added after birth. The patient described herein lost 3 weeks of nephrogenesis in utero. Increased work load per nephron leads to compensatory hypertrophy of the nephrons but eventually persistent hyperfiltration in the glomeruli and the increased tubular work load results in glomerular damage, proteinuria, hypertension, glomerulosclerosis, and nephron loss. [22] Our patient born with IUGR is also predisposed to hypertension due to smaller diameter of aorta, decreased

distensibility of certain arteries from lower reduced amount of elastin versus collagen in the vessel wall and from increased salt sensitivity.[19,20,23,24]

- b. Insulin resistance, leptin resistance and altered lipid metabolism predispose to obesity, metabolic syndrome, and T2DM [13,17,18]
- c. Nutritional rationing to the pancreas results in lower reduced number of beta cells in the pancreas and this along with insulin resistance, predisposes predisposing him to the development of T2DM [5].
- d. In our patient born with IUGR, the rapid catch up growth by age 1 year due to plentiful postnatal nutrition, is an additional risk factor for the development of obesity, insulin resistance, metabolic dysfunction, and T2DM later in life.[25] .

IUGR, which is often associated with premature birth, is likely to become an increasingly prevalent cause of NCCD. In the USA among live births, the incidence of premature birth (less than 37 weeks of gestation) is approximately 10%, with IUGR in 5%, low birth weight of less than 2500 grams in 8.5%, and very low birth weight of, less than 1500 grams in 1.4% [22]. Advances in neonatal care, including antenatal corticosteroids, surfactant administration, gentle ventilation, parenteral nutrition, and supportive services have markedly improved the outcomes for infants born premature. The majority of the low birth weight and many very low birth weight infants now survive into adulthood but are at greater risk of NCCD. Perinatal history and a higher risk of NCCD in this population should be highlighted in their medical records in order to provide appropriate screening and management.

4. Environment and Epigenetics

Early life nutrition can affect phenotype and disease risk later in life by epigenetic modifications of gene expression.[26]. The transcription of the genes is known to be suppressed or enhanced by cytosine methylation/demethylation within CpG dinucleotides of DNA, and histone modification by deacetylation/acetylation. Furthermore, interfering micro RNAs can inhibit translation of the transcribed mRNA to protein.

Most epigenetic and metabolic programming from dietary and environmental factors occurs during the period of high plasticity of the organism when it can most respond to change. For humans, generally this crucial time is the first 1000 days of life, including 280 days of gestation and 730 days of first 2 years of life and during gametogenesis. Environmental influences on the epigenome, are influenced both by the dose and the developmental timing. [4,25].

5. Developmental Origins of Health and Disease

With the rising prevalence of NCCD in many parts of the world, there is increasing interest in evaluating early life events as contributing factors, since early interventions for preventing NCCD can then be examined and implemented. The developmental origins of health and disease theory (DOHaD) proposes that future health is influenced by environmental exposures during the critical window of life including in utero, infancy, and early childhood. Most studies related to DOHaD have involved focus on early life nutrition, but recently, influences of other environmental exposures from chemicals, hormones, and gastrointestinal microbiome are being investigated.

A long-term human study in Netherlands looked at the offspring of mothers who were exposed to 6 months of famine during pregnancy in the Dutch Hunger winter of 1944-1945 [27]. The famine was the result of blockading of food supply to western Netherlands by the Nazis so the people had to survive on about 800 calories per day. Access to enough food was restored after Allied victory. The pregnant women had good nutrition both proceeding and following the 6 months of undernutrition. It was noted that the offspring of mothers exposed to undernutrition in the first and 2nd trimester had higher risk in adult life of obesity, hypertension, cardiovascular disease, and T2DM but not the offspring exposed to caloric deprivation in the third trimester, underscoring the importance of developmental programming of metabolism in early fetal life.[27].

Studies in Agouti-Viable Yellow mice have shed light on the impact of altered nutrition during pregnancy in modifying disease risk. Compared to wild type mice which have brown coat, Agouti

Viable Yellow mice have a yellow coat, ravenous appetite, become very obese early in life, and have propensity for T2DMs and cancer. Agouti VY mice have a mutant Agouti gene which is constantly turned on. The “yellow” mothers give birth to pups with a range of coat colors from brown to yellow. However, when the yellow mothers were fed a diet rich in genistein, a phytoestrogen from soybean, starting just before conception and throughout pregnancy, the mothers’ diet resulted in change of the phenotype of the offspring. Most of the offspring of these yellow mothers then had brown coat color and they did not develop obesity, T2DM, or cancer[28]. The change in phenotype of the litter resulted from increased methylation of CpG sites in their Agouti gene inhibiting its expression. The extent of this DNA methylation was similar in endodermal, mesodermal, and ectodermal tissues, indicating that genistein acts during early embryonic development. Moreover, this genistein-induced hypermethylation persisted into adulthood, decreasing ectopic *Agouti* expression and protecting offspring from obesity. This study provided the first evidence that in utero dietary genistein affects gene expression and alters susceptibility to obesity in adulthood by permanently altering the epigenome[28].

In another study, Agouti Viable Yellow mice exposed to bisphenol, a chemical found in many kinds of plastic bottles, produced litter with more pups with yellow coat but the phenotype changed to more offspring of brown coat color when the mice fed bisphenol were also given dietary supplements of methyl donors foods [29] like such as choline, folic acid, vitamin B12, and betaine. While bisphenol reduces methylation, a diet rich in methyl donors was able to overcome bisphenol effect and suppress the expression of the Agouti gene.

Honey bees are an excellent case study reflecting how a change in phenotype can result from early life nutrition. While the honeybee queen and worker bees are both females and have exactly the same DNA sequence, they are phenotypically quite different. The queen is larger in size, has life span of 3-4 years, and has large ovaries which can produce 1500 eggs a day but she cannot suck nectar. On the other hand, worker bees are smaller, have a lifespan of only 6 -22 weeks, and have rudimentary ovaries which cannot produce eggs, but they are able to suck nectar from flowers and convert and regurgitate it as thick honey. The differential phenotype of the queen and worker bees is due to epigenetic effects of differential nutrition of the larvae [30,31]. For the first 3 days of life, all developing larvae are fed royal jelly, a product of the hypopharynx of the worker bees. Those few chosen to be raised as queen continue to be fed royal jelly while the other larvae are fed honey only. The differential diet provides substrates for epigenetic writers and erasers and results in suppression or activation of certain genes in the larvae resulting in differential phenotype. The first queen bee to emerge will sting the other developing queen bee larvae to death and if two queen bees emerge at the same time, they fight until only one survives.

Stressors during pregnancy have been linked to later development of hypertension and obesity in offspring [5,32]. Stressors in early life have been shown to result in poor growth. Most epigenetic and metabolic programming from dietary and environmental factors occurs during the period of high plasticity of the organism when it can most respond to change. The altered epigenome, however, can also be transmitted to the off spring resulting in transgenerational inheritance of health or disease risk.[33,34]

A study by Horan highlights transgenerational inheritance. In this study, normal newborn male mice were fed ethinyl estradiol a synthetic estrogen, from birth to day of life 12, and then as adults were mated with normal females. When 3 generations of male mice were exposed to ethinyl estradiol in the neonatal period, 20% of male off springs were infertile. Subsequent exposures of males in neonatal period resulted in fibrotic testes in the off-springs. [35]

Stewart *et al* [36] undernourished rats with a protein deficient diet over 12 generations. When re-fed with a normal diet, it took 3 generations before fetal growth and development were restored to normal. This study suggests that epigenetic change is an adaptive process to respond to the environment; it allows genotypic variation to be preserved through transient environmental changes.

Transgenerational epigenetic inheritance has relevance for social determinants of health since some families and communities are repeatedly exposed to nutritional deprivation and /or certain environmental toxins at workplace or home.[33,34]

6. Role of Gut Microbiome on Health and Risk of NCCD

The environmental factors which can result in altered epigenetic and metabolic programming are not always external to the human body but may be chemicals produced by the microbial flora on and in the human body[7] . Humans are host to trillions of microbes who live in and on our bodies. Diverse families of microbes including bacteria, fungi and viruses live on human skin and mucosal surfaces in a rich ecosystem, like the Amazon rain forest or coral reef. Humans have co- evolved with their environment and the microbes around them. About 95% of human microbiota live in the gastrointestinal tract (gut) and most of them reside in the colon. Humans have 10 times more microbial cells than human cells and have over 3 million microbial genes. Microbiome is the collective genomic information contained within the microbiota. I will use the word microbiome to describe microbial characteristics and effects. The census data of the microbial population is generally evaluated by microbial signatures in stool obtained by shot gun metagenomics and amplification of 16 S ribosomal RNA sequence analysis. Healthy gut microbiota mainly comprises two phyla, Firmicutes and Bacteroidetes, which represent 90% of gut microbiota, but also contain less-represented phyla, such as Proteobacteria, Verrucomicrobia and Actinobacteria and Fusobacteria [37–39] . The phylum Firmicutes includes several genera, of which the majority are *Lactobacillus*, *Bacillus*, *Enterococcus*, *Ruminococcus* and *Clostridium*. Bacteroidetes consists of predominant genera such as *Bacteroides* and *Prevotella*. The Actinobacteria phylum is mainly represented by the *Bifidobacterium* genus. The microbes in the colon thrive on undigested food fibers and resistant starches, and ferment them to produce metabolites which affect human metabolism.

While humans are more complex and intelligent living creatures than many on earth, they have only 23,000 functioning genes, as compared to about 14,000 genes in fruit flies and 46,000 genes in some rice plants[40]. The complexity of human functions is partly dependent on the work outsourced to the microbes. The human gut microbiome serves as the “second genome”. The microbes constantly sense the environment and communicate with the rest of the human body via their metabolites which serve as substrates for the activities of epigenetic modification enzymes and influence the expression of host genes. Since the microbes have short life of hours lifespan and reproduce rapidly compared to humans, their microbiome can more rapidly and effectively induce metabolic changes in the human body in response to environmental exposures. than the human genome.

7. Establishment of Healthy, Symbiotic, Diverse and Abundant Microbiome in Infancy

Despite the vast number of bacteria and complexity found in the adult gut, the microbiota of the infant gut is initially a simple ecosystem which gradually undergoes successional changes until it reaches high diversity. The development of the infant gut microbiota is profoundly influenced by host genotype, gestational age, antibiotic use, mode of delivery, diet and the context in which the infant is born (rural vs urban, presence of siblings, pets and other factors.[41–45] At birth, the founder/pioneer species of the microbiome are acquired from the mother’s birth canal and skin to skin contact.[41,46]. Breast feeding promotes colonization by promoting symbiotic microbes. Human milk has 15% of space for human milk oligonucleotides which do not have much caloric value but selectively promote growth of beneficial microbes like *Bifidobacterium* in the gut. As infants grow, they continue to acquire diverse microbes from a more varied diet of fruits, vegetables, fermented foods, contact with other people, pets, livestock, soil, and things they touch [45]. The founder species help dictate subsequent acquisition of complementary microbes.

The diversity and abundance of beneficial microbial community expands most in the 1st year of life but slows down after age 3 years. By then, each person develops a distinct microbiome which reflects specific combination of microbial species due to their environmental exposures, life style, exercise frequency and dietary habits. [41,47].The diversity and abundance of the gut microbiome is crucial to stability of the microbial population since a rich and biodiverse ecosystem is resistant to change and can bounce back if acutely disturbed from antibiotic therapy or high dose of pathogens.[48]. Diet seems to be one of the most important influences on acquisition of a stable symbiotic microbiome.[45] Colonic microbes thrive on undigested plant fibers and ferment them.

Because of the structural discrepancies between types of fiber, many different enzymes are needed to break it down, and not every species of bacteria produces all the enzymes necessary to break down all types of fiber. Different species of bacteria work together as commensal organisms with varying capabilities to hydrolyze different dietary fibers; therefore, eating a variety of high-fiber foods such as fruits, vegetables, whole grains, and legumes can encourage greater microbial

The rapidly diversifying microbiome in infancy, influences the development of the brain and neural connections, regulates caloric expenditure, satiety and energy balance, and trains the naïve immune system to recognize friends and foes to prevent allergies and autoimmune diseases.

Disruption in acquisition of a stable and diverse microbiome in the first 3 years of life will have lasting adverse effects.

8. How Does the Gut Microbiome in Infancy Influence Future Health and Disease?

The following is an outline of some of the effects of the gut microbes and their metabolites on health:

1. In healthy individuals, symbiotic resident microbes provide competitive growth inhibition to pathogenic microbes and help prevent gut infections.
2. Colonic microbes ferment undigested plant fibers and carbohydrates producing short chain fatty acids (SCFA) like butyrate, propionate, acetate in the process and lower luminal pH, the latter prevents growth of pathogenic bacteria SCFA nourish the gut mucosa and promote the integrity of gut barrier function in many ways including increase in the concentration of tight junctions through the upregulation of genes that encode for tight junction proteins, increased mucus production and inducing both the differentiation and apoptosis of colonic cells[49,50] . The integrity of the intestinal barrier is essential for health since increased intestinal permeability results in translocation of microbial products into systemic circulation, which can promote systemic inflammation and insulin resistance. SCFA produced in the colon enter the blood stream and reach remote organs where they prevent inflammation, increase GLP 1 production, improve glucose homeostasis and increase satiety thus preventing obesity and development of diabetes mellitus [51–54].
3. There is bidirectional communication between the enteric nervous system and central nervous system. In infants, gut microbiome metabolites influence the CNS development affecting maturation of microglia, myelination process and blood brain barrier function. The gut microbes produce various neurotransmitters which affect behavior and mental Health [55–57]. Serotonin produced from dietary tryptophan promotes happiness and satisfaction. Dopamine affects the reward centers of the brain and coping with stress while melatonin production helps promote sleep.
4. Multiple experiments in mice models have shown that altered gut microbiota can cause the synthesis of neurotoxins, which may interfere with neurodevelopment, causing changes in the brain chemistry as well as behavior. Subsequently, these dysbiosis-associated neuronal alterations result in causing behavioral changes such as increased anxiety, depression, and cognitive dysfunction, all of which are characteristic features in autism spectrum disorders. [55,58,59]
5. Early life toxic stress can adversely affect the quality of gut microbiome and thereby affect mental health and predisposition for hypertension. [32,59].
6. Microbial products influence the release & function of gut hormones which affect gut motility, perception of visceral pain, appetite regulation, glucose metabolism, and insulin secretion. Alterations in gut microbiota composition can dysregulate enteroendocrine signaling pathways, contributing to irritable bowel syndrome and metabolic disturbances associated with diabetes mellitus [51,54,60,61].
7. GI microbiome guide the maturation of the naive infant immune system to antigen exposure and primes the immune system toward tolerogenic T cells as compared to proallergic/pro-inflammatory T cell response. It is important for growing infants to be exposed to plenty of both commensal and pathogenic microorganisms for their immune system and central nervous system to develop and function properly. The gut hosts 80% of immune cells in its Peyer patches and through their dendrites, the immune cells are able to sense intestinal luminal chemicals and

learn which microbes and foods are to be tolerated or rejected.[6,62–64]The training of the naïve immune system occurs in the first 3 years of life and confers susceptibility or resistance to allergic or auto immune diseases. [64]

8. GI microbiome metabolites influence caloric balance via effects on energy harvesting from undigested carbohydrates and fibers, and caloric expenditure as well as regulation of appetite, food choices and food cravings. [58,61]. Gut microbiota exhibit diurnal oscillation that can be influenced by feeding rhythms and synchrony of sleep-wake cycle with sun-light and exercise frequency [65,66].
9. The composition of microbiome can influence leanness or obesity, hypertension and metabolic health [19,61,67–69].Exercise frequency has been suggested to increase gut microbial diversity [66] A less diverse and depleted microbiome from antibiotic usage both in livestock and in human infants has been shown to promote later weight gain [70–72].In many studies in both humans and animal models, obesity seems to be associated with a decrease in Bacteroidetes and increase in Firmicutes. In addition, in both humans and mice, recipients of fecal microbiota transplant from obese or lean microbiome exhibit the phenotype of the “donors”. [73,74]

Loss of compositional diversity and abundance of beneficial symbiotic organisms in the gut, changes in their local distribution and metabolic activities, and excessive growth of potentially harmful organisms is labeled as “dysbiosis”. Occurrence of dysbiosis in the first 3 years of life will have lasting adverse effects on health.

9. Increasing Prevalence of Dysbiosis in Industrialized Countries

Recent studies suggest increasing dysbiosis in industrialized countries[70]. There are several reasons for this, some of which are listed.

1. Higher rates of caesarian section instead of natural vaginal delivery. As compared to vaginally delivered babies who show predominance of *Bifidobacterium* species, caesarean-born babies have been shown to lack Bifidobacterium species that are important to postnatal immunity development [43,44].
2. Higher rates of formula feeding instead of breastfeeding during infancy
3. More frequent intake of antibiotics during pregnancy and infancy.
4. Intake of diet low in plant fiber and high in animal protein
5. Less food variety and less intake of local seasonal produce
6. More frequent intake of processed and ultra -processed foods which are high in simple sugars and saturated fat but low in plant fibers.
7. Commercial food production and preservation practices which result in unintended exposure to antibiotics, pesticides and additives in food.
8. Less contact with natural world, therefore less seasonal exposures to local microbes since majority of time at work or home is spent indoors in a sanitized environment with controlled temperature, humidity and filtered air.
9. Asynchrony of sleep- wake cycle with the sun, and prolonged exposure to blue light from electronic devices in the evening both of which disrupt normal circadian rhythm induced physiologic metabolic processes and promote dysbiosis. [65,75]

To summarize, the development of the human microbiome is a dynamic process influenced by various factors, including mode of delivery, feeding practices, early life environmental exposures and sleep-wake rhythm. Core native microbiome is established in the first 3 years of life. Throughout life, the richer and more diverse the microbiome, the better the individual will withstand external threats including unbalanced diet, stress, antibiotic use and diseases. Dysbiosis from microbial decline in the gut in infancy promotes development of obesity, hypertension, T2DM, allergic asthma, food allergies, autoimmune diseases and neuro-developmental/neuro-psychiatric problem. Understanding the consequence of dysbiosis and ways to maintain or restore a healthy gut microbiota composition should be useful in developing promising therapeutic interventions.

10. Best Practices to Establish & Maintain Optimal Microbiome in Infancy and Beyond

In order to obtain long term health, it is important to establish a healthy and diverse gut microbiome in infancy and maintain it long term. The traditional sayings of thousands of years old Indian Ayurveda medicine and of Hippocrates that “all diseases begin in the gut” are corroborated by the studies of microbiome. It appears that man’s best friend is his gut microbiome.

The best practices to establish optimal microbiome start with the pregnant mother; her diet, healthy life style, vaginal delivery, breast feeding and avoidance of exposure to antibiotics. The process continues in infancy and childhood with intake of diverse foods high in fiber which serve as prebiotics, intake of fermented foods which serve as probiotics, plenty of physical activity, and optimal environmental exposures while avoiding or minimizing exposures to toxins, pesticides and antibiotics. A 12- hour period overnight with no food is recommended to optimize health. [76]

Proper sleep hygiene and exercise should be promoted.

While some stress is unavoidable, habitual implementation of strategies to cope with stress should be encouraged like rich social interactions and non-competitive group play.

Potential therapeutic approaches to improve the gut microbiome include supplements of probiotics, postbiotics and fecal microbiota transplantation[77,78]. The best example of the therapeutic effects of microbiome modulation with fecal microbiota transplantation is in patients with recurrent clostridium difficile infection where cure rates of 90-95% have been achieved [79]

11. Touch Points for Prevention of NCCD in Individuals like the Patient in the Case Report

The 21-year-old reported herein was born at 33 weeks of gestation by cesarean section for preeclampsia and had very low birth weight due to IUGR. The latter puts him at risk for development of NCCD in later life. Establishment of healthy microbiome in the gut and optimal diet can potentially prevent NCCD. In an individual like the one mentioned in the case report, this can be done in several ways starting from birth:

1. Skin colonization at birth with the mother’s vaginal flora by placing a sterile normal saline swab in mother’s vagina before caesarian section and gently rubbing it on the baby’s skin as long as mother was not colonized with group B streptococcus [80].
2. Encouragement of the mother to exclusively breastfeed for first 9 months.
3. Antibiotic stewardship during episodes of fever
4. Preventing rapid catch up growth by avoiding overfeeding. The latter is more likely with bottle feeding of formula than with breast feeding.
5. When consuming table food, eating a high fiber diet containing locally produced fruits and vegetables.
6. Avoiding high salt and protein intake to decrease the workload on kidneys which are endowed with less than average number of nephrons.
7. Time restricted eating i.e. eating within a window of 8-12 waking hours thus resulting in overnight fasting for at least 12 hours and preferably 16 hours to allow for metabolic switch from burning glucose to burning stored fat as ketone bodies
8. Increased physical activity
9. To awaken and sleep in rhythm with the sun cycle to have 24- hour circadian coordination of metabolism and energy use
10. Healthy sleeping habits since deep sleep enables much needed repair and cleanup work in the brain and rest of the body
11. Paying special attention to the emotional, physical and mental health of adolescents to prevent transgenerational transmission of illness [33,81].

12. Conclusions

Adverse environmental influences in early life like low birth weight, poor nutrition, exposures to antibiotics and toxins, toxic stress and dysbiosis can influence predisposition for disease late in life, from altered metabolic and epigenetic programming.

1. Elucidating history of early life events is a useful tool in evaluating risk factors for NCCD.
2. Establishment of a rich & diverse symbiotic microbiome is essential for long term health since dysbiosis predisposes to NCCD.

3. Most epigenetic and metabolic programming from dietary or environmental factors occurs during the period of high plasticity of the organism when it can most respond to change. For humans, generally this crucial time is the first 1000 days of life including 280 days of gestation and 730 days of first 2 years of life as well as during gametogenesis.
4. The socioeconomic disparities in health trajectories may in part be mediated by the effects of adverse perinatal influences, unhealthy dietary practices in early childhood and early life stress on gut microbiome.
5. Transgenerational epigenetic inheritance has relevance in social determinants of health since some families and communities are repeatedly exposed to nutritional deprivation, toxic stress and same environmental toxins.
6. Any intervention to prevent and Rx NCCD such as dietary modifications, healthy eating habits and life style changes are best initiated during the period of developmental plasticity to have maximal effect.
7. It is easier to build strong children with healthy gut microbiome than to have to treat adults with NCCD which have origins in childhood

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