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POINT OF VIEW

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Metabolic Diseases: Cellular and Molecular Mechanisms: A Point of View

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Abstract

The Developmental Origins of Health and Disease (DOHaD) framework highlights that unfavorable conditions during fetal development can trigger persistent biological changes, increasing the risk of metabolic disorders in adulthood. While clinical manifestations often appear only later in life, fetal programming produces subtle but permanent structural, functional, and epigenetic modifications in key metabolic organs—including the pancreas, liver, and skeletal muscle. These early alterations weaken physiological resilience and predispose tissues to dysfunction when exposed to postnatal challenges such as poor diet, sedentary behavior, chronic stress, or environmental toxins. Initially, compensatory mechanisms may mask these vulnerabilities, but with aging and cumulative metabolic stress, these reserves decline, culminating in overt conditions such as hypertension, obesity, type 2 diabetes, and vascular disease. Cellular and molecular mechanisms—including epigenetic remodeling, disrupted signaling pathways, mitochondrial impairment, and chronic low-grade inflammation—serve as mediators linking early-life insults to long-term metabolic dysregulation. Because individuals with normal birth weight also develop these disorders with advancing age, it is plausible that such disease clusters have an age-related component. Downstream consequences of metabolic dysfunction—such as oxidative stress, impaired vascular tone, endothelial dysfunction, dysregulated glucose and lipid metabolism, arterial narrowing, and activation of platelet and coagulation pathways—further drive the progression of metabolic risk. By dissecting these mechanisms, it becomes possible to identify early biomarkers and design targeted interventions that halt disease progression before irreversible damage sets in. Thus, integrating developmental biology with molecular medicine offers a powerful opportunity to prevent and treat metabolic disorders rooted in early life. However, contemporary medical practice remains largely disease-focused, emphasizing management of established risk factors. A more forward-looking approach must prioritize early detection, preventive strategies, and lifestyle modification, guided by a deep understanding of the cellular and molecular foundations of metabolic vulnerability.(**International Journal of Biomedicine. 2026;16(2):130-144.**)

Keywords: oxidative stress • inflammation • vascular dysfunction • hypertension • obesity • diabetes • vascular disease

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Abbreviations

CVD, cardiovascular disease; **DOHaD**, developmental origins of health and disease; **FOAD**, fetal origins of adult disease; **LDL**, low-density lipoprotein; **RAAS**, renin–angiotensin–aldosterone system; **T2D**, type 2 diabetes.

Introduction

British Epidemiologist David Barker's hypothesis focused on the "Fetal Origins of Adult Disease" (FOAD), often referred to as the Barker hypothesis, which proposed that adverse influences during critical periods of fetal development, particularly related to nutrition and the intrauterine environment, could "program" the fetus for increased susceptibility to a range of chronic diseases later in life.[1-19] These diseases, termed metabolic diseases, include hypertension, obesity, type 2 diabetes (T2D), vascular diseases, neurodegenerative diseases, and, to some extent, even cancer.[20-22] Low birth weight, a marker of poor fetal growth, has been linked to a higher risk of coronary artery disease, hypertension, and stroke in adulthood. Studies have shown associations between fetal undernutrition and increased risk of obesity, insulin resistance, and T2D.[2-5]

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Research also suggests a link between fetal programming and the development of certain neurological conditions, including Parkinson's and Alzheimer's disease.[20] The FOAD hypothesis has also been explored in relation to cancer development and progression. Barker's hypothesis highlights the crucial role of early developmental influences, especially during the fetal period, in shaping long-term health outcomes and disease susceptibility.[1-5]

Metabolic disturbances during fetal development can trigger adult-onset metabolic diseases through several interconnected mechanisms, primarily linked to fetal programming and epigenetic modifications.[23,24] The fetal pancreas produces hormones like insulin and glucagon during key developmental periods. Maternal malnutrition or metabolic disorders can disrupt pancreatic development by altering transcription factors and signaling pathways, thereby reducing β-cell mass and function.[25,26] This deficiency can reduce insulin production and impair glucose sensing, thereby increasing the offspring's risk of T2D. The fetal liver is also a major target of programming, with its size and later function being shaped by the intrauterine environment.[27,28] Suboptimal nutrition during gestation can alter the expression of genes involved in hepatic energy production, leading to increased hepatic gluconeogenesis and insulin resistance in adulthood. This can contribute to hyperglycemia and the development of T2D. The fetal liver is also a major target of programming, with its size and later function being shaped by the intrauterine environment. Suboptimal nutrition during gestation can alter the expression of genes involved in hepatic energy production, leading to increased hepatic gluconeogenesis and insulin resistance in adulthood. This can contribute to hyperglycemia and the development of T2D. Maternal obesity or a high-fat diet during pregnancy can induce epigenetic changes in fetal adipose tissue, leading to increased adipogenesis and a predisposition to obesity in adulthood.[29,30]

Epigenetic changes are alterations in gene expression that do not involve changes in the DNA sequence itself but can be transmitted to subsequent cell divisions and even generations. [31] *DNA Methylation:* This involves adding methyl groups to CpG islands in DNA, often silencing gene expression. For example, studies have shown altered DNA methylation patterns in the insulin-like growth factor 2 (IGF2) gene in individuals exposed to prenatal famine, which is linked to increased risk of metabolic diseases.[32] *Histone Modifications:* These include modifications like acetylation and methylation of histone proteins, which can affect chromatin structure and gene accessibility. These modifications can alter the expression of genes involved in key metabolic pathways.[33] *MicroRNAs (miRNAs):* These small non-coding RNAs regulate gene expression by binding to target mRNAs, thereby affecting protein synthesis. Adverse intrauterine environments can alter miRNA expression profiles, thereby influencing metabolic pathways such as insulin signaling, lipid metabolism, and food intake.[34]

Fetal exposure to abnormal levels of hormones, such as insulin, glucocorticoids, and insulin-like growth factors, can permanently affect organ development and function, predisposing individuals to metabolic diseases.[35] Maternal high-fat diets can affect hypothalamic gene expression in the offspring, leading to leptin resistance and altered regulation of appetite and energy balance.[36] In essence, metabolic disturbances during critical windows of fetal development can trigger long-lasting structural and functional changes in key metabolic organs, such as the pancreas and liver, often mediated by epigenetic modifications.[37] These changes can impair glucose homeostasis, insulin sensitivity, and lipid metabolism, increasing the risk of developing metabolic diseases such as T2D, obesity, and metabolic syndrome in adulthood. If fetal metabolic disturbances are the root cause of adult-onset metabolic diseases, why is there a delay of several years to develop these chronic diseases? What epigenetic factors trigger or initiate the risks for the development of metabolic diseases? Answers to such questions are the key to our understanding of the "developmental origins of health and disease" (DOHaD) hypothesis.[38,39]

The delay between fetal programming and the onset of adult metabolic diseases is due to several interacting factors that cumulatively affect outcomes over time. Fetal programming causes permanent, often subtle, changes in the structure and function of key metabolic organs (like the pancreas, liver, and muscle) and systems.[40,41] These changes might not be severe enough to cause problems immediately, but they leave these organs with reduced capacity or altered responses to later environmental challenges. Epigenetic marks (like DNA methylation and histone modifications) can be permanently altered by the fetal environment, affecting gene expression throughout life.[42,43] These changes can prime genes involved in metabolic regulation to respond differently to stimuli, but the full impact may only become evident when combined with other factors over time. The postnatal environment plays a crucial role in triggering the manifestation of fetal programming effects. *Factors like diet*: An unhealthy diet, especially one high in fat and sugar, can place extra stress on organs already compromised by fetal programming.[36, 37] *Lifestyle:* A sedentary lifestyle further exacerbates the risks of developing metabolic disorders.[44] *Stress:* Chronic stress can disrupt hormonal balance and metabolic function, particularly in individuals with pre-existing vulnerabilities. [47] *Environmental factors:* Exposure to certain chemicals or toxins can interact with fetal programming, further increasing disease risk.[47,48]

Gradual Accumulation of Damage: Metabolic diseases often involve the gradual accumulation of damage to organs and tissues over time.[48,49] For example, insulin resistance develops progressively, leading to declining β-cell function and eventual diabetes.[50] Fetal programming creates a predisposition, but the full disease state requires the added impact of aging and other risk factors. *Compensatory Mechanisms*: In early life, the body's compensatory mechanisms may be able to mask the effects of fetal programming.[51,52] For instance, the pancreas may initially compensate for reduced β-cell mass by increasing insulin secretion.[53] However, these mechanisms may eventually be overwhelmed by the combined effects of aging, poor lifestyle choices, and other factors, leading to the development of metabolic diseases. In essence, delay is not a sign that the fetal insult is not the root cause, but rather that it sets the stage for future problems that unfold over time in combination with later-life exposures and the natural aging process.[50-53]

Fetal Origin of Adult Diseases

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.[3,10-13,16-19] The studies with the 'Mysore Cohort' were among the first in a low-and middle-income country to test DOHaD concepts, with a predicted association between small size at birth and adult coronary heart disease, insulin resistance, and low lung function.[10] The Mysore Parthenon study findings suggest that exposure to maternal nutritional deficiencies, as well as overnutrition, 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.[11] 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 and 1966.[10] The FOAD, a concept first popularized by Dr. David Barker, has since led to many studies that have provided evidence that certain diseases have links to fetal origins. The concept of the fetal origin of adult disease has been extended well beyond cardiovascular disease (CVD) and now includes investigations into the development of the central nervous system and the early origins of adult mental health and cognitive function.[54-59] Given that epigenetic alterations during fetal development may cause several adult metabolic diseases, as well as diseases of the nervous system, we would like to see future research focus on possible intervention strategies to halt, reverse, or prevent these epigenetic modulations of fetal metabolism.

New Hypothesis on Fetal Origin of Adult Diseases

Obesity is a well-recognized risk factor for T2D. A landmark discovery from Children's National Hospital, Washington, DC, has been described as a potential "game changer" in detecting obesity-related complications. According to a hospital news release, physician-scientist Dr. Robert Freishtat and his colleagues have shown that "early intervention and prevention of obesity-related illness may soon be possible." It is well established that visceral adipose tissue (belly fat) is strongly associated with serious complications of obesity, including cardiovascular disease and insulin resistance leading to diabetes. What had remained unclear until recently, however, were the precise mechanisms by which excess visceral fat triggers these conditions. Dr. Freishtat's team demonstrated that as visceral fat accumulates, adipocytes undergo changes and begin releasing a distinct set of exosomes compared to those released by lean fat cells. These altered exosomal signals disrupt critical biological pathways, impairing the body's ability to regulate glucose and cholesterol. Dr. Freishtat has likened exosomes to "biological tweets"—brief molecular messages that enable cell-to-cell communication and influence gene expression. In their exploratory studies, the team collected adipose tissue from lean and obese female patients and used modified bead-based flow cytometry to isolate and compare exosomal miRNAs. They concluded that the successful identification of these exosomes paves the way for the development of diagnostic tests that could enable early intervention or even the prevention of obesity-related diseases.[60-62]

Similarly, microvesicles (MVs) released by multiple cell types carry mRNA and miRNA, remaining in the extracellular space to mediate intercellular signaling—functionally echoing Dr. Freishtat's "biological tweets." Importantly, these vesicles play a role in epigenetic reprogramming of host cell metabolism. Building on these findings, we contacted Dr. Freishtat to explore a potential US–India collaborative project on the role of maternal exosomal miRNAs in reprogramming fetal genetic material and gene expression. The Diabetes Research Group at King Edward Memorial (KEM) Hospital, Pune, had already established a large biobank of maternal and fetal tissues. With the leadership of Professor C.S. Yajnik, we initiated preliminary studies. Genotypic Technology, Bengaluru, partnered to provide rapid miRNA assays. Encouraging early results enabled the team to secure funding from the U.S. National Institutes of Health (NIH) for further research.[62] Based on these observations, a "new hypothesis" has emerged regarding the FOAD: maternal and cord blood adipocyte-derived exosomal miRNAs that regulate adipogenesis are associated with higher infant adiposity.[63] As body fat increases during obesity, fat cells change and release different exosomes than lean adipocytes. These altered signals interfere with key metabolic processes, ultimately reducing the body's capacity to manage sugar and cholesterol effectively.

Cardiometabolic Diseases

Cardiometabolic diseases, including hypertension, excess weight, obesity, T2D, and vascular disorders, have risen markedly in incidence and prevalence worldwide. [64-70] A cascade of pathological events contributes to the progression of these conditions and the onset of acute arterial complications. Key factors include oxidative stress, vascular inflammation, obesity, diabetes, endothelial dysfunction, arterial stiffness, subclinical atherosclerosis, growth and rupture of atherosclerotic plaques, arterial stenosis, and activation of platelet and coagulation pathways. Hypertension, obesity, and T2D are central drivers of this process. An imbalance between free radicals and antioxidants promotes widespread cellular and tissue damage, particularly in blood vessels. Persistent vascular inflammation is a critical mechanism that initiates structural changes in the arteries. Over time, vessel walls lose elasticity and become rigid—an independent predictor of cardiovascular risk. Fatty streaks and early lesions evolve into advanced lipid-rich plaques within the arterial wall. When these plaques rupture, thrombogenic material is exposed, triggering platelet activation and blood clot (thrombus) formation. Depending on the site of obstruction, this process can result in acute clinical events such as myocardial infarction (coronary arteries), ischemic stroke (cerebral arteries), or peripheral artery disease (limb arteries).

Altered Endothelial Metabolism: Vascular Dysfunction

Altered endothelial metabolism leading to vascular dysfunction is widely recognized as one of the earliest indicators for the progression of vascular disease. This damage to the endothelium—the thin layer of cells lining blood vessels—can precede and predict the onset of atherosclerosis and subsequent cardiovascular events.[71-73] Endothelial cells (ECs) adapt their metabolic pathways in response to stressors

like hyperglycemia, hyperlipidemia, and hypertension. This metabolic reprogramming disrupts vascular homeostasis, leading to inflammation, impaired vasodilation, and oxidative stress that characterize endothelial dysfunction. Endothelial cells typically favor glycolysis over mitochondrial oxidative phosphorylation, even in the presence of sufficient oxygen. However, under stressful conditions such as hypoxia or inflammation, this preference is heightened. This shift can promote the production of inflammatory and pro-atherogenic molecules. Excess reactive oxygen species (ROS) from metabolic shifts—such as from uncoupled endothelial nitric oxide synthase (eNOS) and NADPH oxidase activation—damage ECs and oxidize lipoproteins. ROS also react with nitric oxide (NO) to produce peroxynitrite, reducing NO bioavailability and inhibiting its anti-inflammatory and vasodilatory effects. NO, a key molecule for regulating vascular tone and inhibiting inflammation, is a metabolic product of the amino acid L-arginine through the eNOS enzyme. In metabolic disease, NO bioavailability is reduced due to reduced L-arginine, or eNOS coupling.

In metabolic disease, NO availability is reduced by reduced L-arginine availability and by inhibition of various endogenous enzymes by lipid hydroperoxides and oxidized lipoproteins (Figure 1). In hyperlipidemia, ECs exposed to oxidized LDL (ox-LDL) express adhesion molecules that cause platelets to adhere to the arterial wall. Macrophages consume these lipids to become foam cells, the earliest visible signs of atherosclerosis. Insulin resistance impairs the insulin-mediated signaling pathway(P13K/AKT/eNOS) that typically stimulates NO production. This causes an imbalance between vasoactive molecules such as prostacyclin and NO, and vasoconstrictive molecules such as endothelin-1, prostaglandins (PG), PGG2, PGH2, and thromboxane A2. In hyperglycemia, excess glucose reacts with proteins and lipids to form AGEs. When AGEs bind with ECs, they promote inflammation and oxidative stress. Hyperglycemia also alters the balance in the production of vasoconstrictive prostaglandins and vasodilatory metabolites.[74]

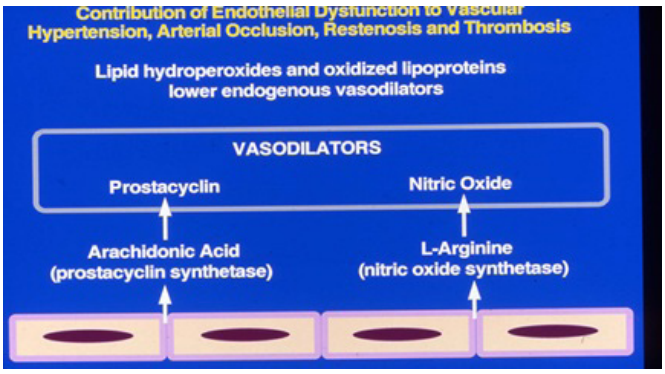
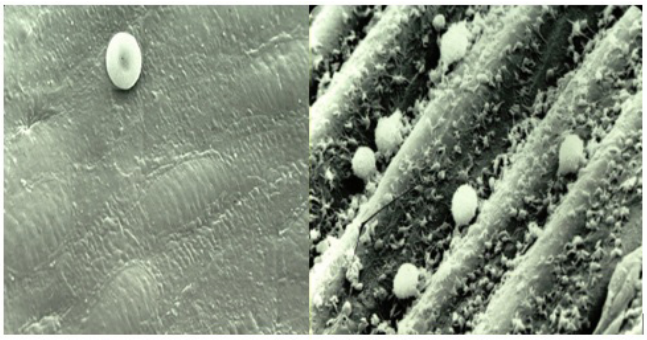


Figure 1. *Lipid Hydroperoxides and Oxidized lipoproteins lower endogenous Vasodilators (Schematic representation, prepared by the University of Minnesota Medical Artists).*

Hypertension

Intrauterine growth restriction (IUGR) leads to a reduced number of nephrons at birth, a condition that predisposes an individual to salt-sensitive hypertension later in life through compensatory hyperfiltration and epigenetic changes to the renin–angiotensin–aldosterone system (RAAS). This process is part of the «developmental origins of adult disease» theory, which posits that adverse events during critical periods of fetal development can have permanent effects on organ structure and function.[75] Endothelial dysfunction is a hallmark of programmed hypertension. Mitochondrial ROS production impairs nitric oxide (NO) bioavailability.[76] Excessive ROS production, often due to mitochondrial dysfunction, leads to endothelial activation, inflammation, and vascular disease by affecting NO release,[77] while histone modifications in endothelial nitric oxide synthase (eNOS) genes suppress vasodilatory capacity.[78] These changes, along with an altered balance between vasodilators and vasoconstrictors induced by hyperglycemia, lead to increased vascular stiffness and heightened sympathetic activity.[74]

Changes in signaling pathways in vascular endothelial cells and vascular smooth muscle cells (VSMCs) are key molecular mechanisms that trigger vascular dysfunction and promote the development of hypertension (Figure 2).[79]



A B

Figure 2. *A: Healthy Endothelium. B: Dysfunctional Endothelium. (Courtesy: Professor (Late) James G White, University of Minnesota Medical School)*

Molecular pathways influencing blood vessels can be broadly categorized into two groups. The first indirectly regulates vascular sympathetic activity through mechanisms such as RAAS, immune signaling, and redox pathways. The second directly affects vascular functions, including calcium signaling, NO-(NOsGC)-cGMP pathways, and vascular remodeling. The indirect pathways form a complex network that primarily induces vasoconstriction via direct mechanisms. For instance, sympathetic disorders often promote vasoconstriction by activating calcium channels, while RAAS not only activates calcium channels but also drives vascular remodeling. While endothelial and smooth muscle cell signaling pathways are the primary drivers of vascular tone, platelets critically modulate this system. By tipping the PGI_2/TXA_2 balance toward vasoconstriction, platelet dysfunction directly contributes to hypertension and its cardiovascular complications (Figure 3).[74]

In terms of therapeutic application, molecular pathways involved in vascular regulation, such as calcium signaling, NO-(NOsGC)-cGMP, RAAS, and sympathetic activity, have demonstrated clear efficacy in clinical practice. [80-82] Modern

medicine increasingly views hypertension not as a standalone disease but as a significant risk factor for vascular disorders.[83] The primary goal of blood pressure management is to reduce cardiovascular events, much as controlling blood lipids or glucose levels. It is essential to recognize that the molecular basis of hypertension lies in vascular dysfunction and/or altered vascular volume. A deeper understanding of these mechanisms is crucial for advancing research on the signaling pathways underlying hypertension.

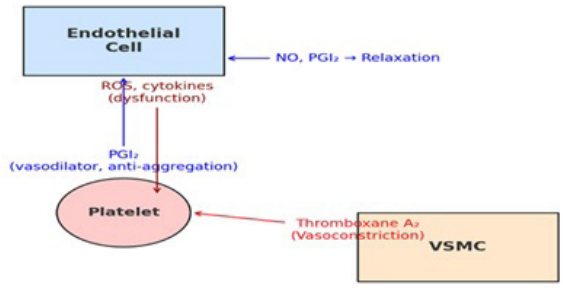


Figure 3. *Cros-talk between endothelial cells, vascular smooth muscle cells, and platelets (Prepared by Open AI-ChatGPT)*

Obesity

Compared to Europeans and Americans, South Asians and East Asians tend to develop central abdominal obesity and T2D at a lower body mass index (BMI). Advances in high-throughput genotyping technologies have enabled large-scale genome-wide association studies (GWAS), uncovering hundreds of genetic loci linked to BMI and waist-to-hip ratio (WHR), primarily in European populations. A major limitation of such studies is the overwhelming number of genes associated with these risks. For instance, a large meta-analysis of BMI-associated single-nucleotide polymorphisms (SNPs) identified more than 750 SNPs linked to susceptibility genes, including specific variants. Among them, the FTO (alpha-ketoglutarate-dependent dioxygenase) gene emerged as a strong contributor to polygenic obesity. Despite these findings, the molecular mechanisms driving this complex disorder remain poorly understood, and the variation in fat distribution across global populations is still unexplained. Obesity is now recognized as the leading public health challenge worldwide, yet the strikingly different fat distribution patterns in nearly half the global population remain a mystery. Central abdominal obesity is considered a major risk factor for T2D. Globally, the highest prevalence of T2D is observed in the United States, followed by China and India. This indicates that fat distribution alone is not the sole determinant; rather, factors such as poor dietary habits, poor nutritional quality, sedentary lifestyle, and broader socio-economic conditions contribute significantly to the development of metabolic disease.[84]

Brown fat and white fat are two distinct types of adipose tissue with opposite roles in energy metabolism, and their balance influences obesity and metabolic health (Figure 4, Table 1). (94). White adipose tissue (WAT) is the ‘storage fat’ that stores excess energy in the form of triglycerides. It is usually distributed subcutaneously and viscerally around internal organs. Excess visceral fat accumulation is strongly linked to insulin resistance, T2D, CVD, and chronic inflammation. These tissues secrete adipokines (leptin, adiponectin, resistin, TNF-α, IL-6). In obesity, secretion patterns shift towards the generation of pro-inflammatory signals, driving systemic metabolic dysfunction.[86,87] Whereas brown adipose tissue (BAT) burns energy to produce heat using uncoupling protein 1 (UCP1) in mitochondria.[88] More abundant in newborns, in adults, in areas like the neck, supraclavicular regions, and around large blood vessels. In obesity, BAT activity is reduced, leading to reduced energy expenditure and favoring fat accumulation. Active BAT helps maintain body weight by increasing energy expenditure, improving glucose and lipid metabolism, and insulin sensitivity. White fat cells can sometimes transform into beige adipocytes under certain stimuli (cold exposure, exercise, some hormones). This process, called “browning of white fat” is a potential therapeutic strategy against obesity.[89] Exercise increases irisin and other myokines that promote browning of fat. Dietary factors that promote this process include capsaicin, catechins, caffeine, and omega-3 fatty acids.

Excess maternal nutrition or gestational diabetes can also further aggravate obesity risk by enhancing adipogenesis through altered PPARγ and C/EBPα signaling, thereby expanding adipocyte progenitor pools.[29] Research from INSERM, France, highlights that dysregulated adipose progenitor cells (APCs) and abnormal perinatal adipogenesis, mediated by epigenetic mechanisms, are key drivers of long-term adipose dysfunction in offspring of obese mothers.[90]Additionally, mitogen-activated protein kinases (MAPKs), including ERK1/2, JNK, and p38MAPK, play critical roles in regulating appetite, adipogenesis, glucose homeostasis, and thermogenesis. While landmark studies on liraglutide, a GLP-1 receptor agonist, have demonstrated remarkable success in obesity management, such therapeutic strategies do not address the fundamental cellular and molecular mechanisms underlying obesity.[91]

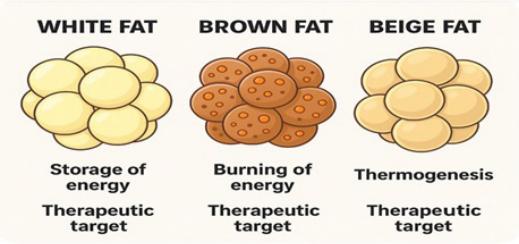


Figure 4*. Different types of adipose tissue. (Created by Open Ai-Chat GPT)*

Table 1.

Schematic diagram shows the differences between white fat, brown fat, and beige fat. (Developed by OpenAI ChatGPT).

Category	White Fat (WAT)	Brown Fat (BAT)	Beige Fat (Brite)
Main Function	Energy storage (triglycerides)	Energy burning (thermogenesis)	Intermediate; inducible thermogenesi
Color & Structure	White/yellow; large lipid droplets	Brown; multilocular lipid droplets	Light brown; appear within WAT
Mitochondria	Few	Very high	Moderate
UCP1 Presence	Absent	Abundant	Inducible
Effect on Obesity	Promotes obesity, insulin resistance	Protects against obesity, improves r	Can counteract obesity if activated
Therapeutic Target	Convert to beige fat (browning)	Activate to increase energy expendi	Induce browning via cold, exercise, d

Diabetes Mellitus

The combined effects, such as DNA methylation and histone modifications, can suppress pancreatic and duodenal homeobox 1 (PDX1) and hepatocyte nuclear factor 4 alpha (HNF4a), leading to oxidative stress and mitochondrial defects, and resulting in insufficient ATP generation in pancreatic β-cells.[92,93] This severely limits glucose-stimulated insulin release and contributes to the dysfunction seen in T2D.[94] Skeletal muscle is a major site for glucose uptake after meals, primarily facilitated by the glucose transporter type 4 (GLUT4). Programming of this tissue, often associated with insulin-resistant states, affects glucose metabolism through two main avenues. *Reduced mitochondrial oxidative capacity*: This refers to a decline in the mitochondria's ability to efficiently generate energy through oxidative phosphorylation. A lower oxidative capacity reduces the muscle's glucose demand, leaving more glucose in the bloodstream.[95] *Reduced GLUT4 expression*: Insulin and exercise typically trigger GLUT4 translocation from the cell's interior to the plasma membrane to facilitate glucose entry.[96] In programmed muscle, GLUT4 expression or translocation is reduced, limiting the cell's ability to clear glucose from the blood.

The liver is the primary organ responsible for endogenous glucose production, a process that is normally suppressed by insulin. In states of insulin resistance, this process becomes unregulated and contributes significantly to hyperglycemia, particularly during fasting. The two key proteins involved are: *FOXO1*: A transcription factor that activates the expression of genes involved in gluconeogenesis, such as glucose-6-phosphatase (G6Pc) and phosphoenolpyruvate carboxykinase (PEPCK).[97] Normally, insulin signaling via Akt phosphorylates FOXO1, sequestering it in the cytoplasm and inactivating it. In insulin resistance, this suppression is impaired, and active FOXO1 remains in the nucleus, promoting glucose production. *PGC-1α*: A transcriptional co-activator that collaborates with transcription factors like FOXO1 to boost the expression of gluconeogenic enzymes.[98] The combined effect of these dysfunctional pathways is systemic hyperglycemia. *In fasting states*: The liver increases its glucose production through hyperactivated gluconeogenesis, flooding the bloodstream with glucose. *Upon feeding*: The impaired glucose uptake by skeletal muscle means that ingested glucose is not efficiently cleared from the blood, further worsening hyperglycemia.[99] This vicious cycle demonstrates a central aspect of metabolic disorders like T2D, where tissue-specific defects converge to cause persistently high blood sugar.

FOXO1 activation: The transcription factor Forkhead box O1 (FOXO1) is a key regulator of hepatic gluconeogenesis (the production of glucose from non-carbohydrate sources).[100] Normally, insulin signaling activates Akt, which phosphorylates FOXO1 and sends it out of the cell's nucleus, effectively turning it off. In insulin-resistant states, this phosphorylation is impaired, and FOXO1 remains active in the nucleus. Active FOXO1 promotes the transcription of key gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), thereby increasing the liver's production of glucose.

PGC-1α hyperactivation: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a transcriptional coactivator that works with FOXO1 to regulate gluconeogenesis.[98] Similar to FOXO1, PGC-1α is typically activated during fasting to stimulate hepatic glucose production. In the context of the described programming, increased activity leads to persistently elevated glucose production, contributing to fasting hyperglycemia. This cycle of reduced glucose uptake and increased production is a classic feature of insulin resistance and T2D.[101]

Hyperglycemia promotes a prothrombotic milieu by facilitating platelet activation, perturbing coagulation pathways, and impairing fibrinolytic mechanisms.[102] The underlying pathophysiological processes involve oxidative stress, endothelial dysfunction characterized by diminished nitric oxide bioavailability, accumulation of advanced glycation end products (AGEs), elevated circulating coagulation factors, augmented platelet aggregation, and decreased fibrinolytic enzyme activity.[103] *Endothelial Dysfunction*: Sustained hyperglycemia induces oxidative and inflammatory stress within the vascular endothelium, resulting in impaired endothelial function. This dysfunction is associated with reduced synthesis of nitric oxide (NO) and prostaglandin I_2, both of which inhibit platelet aggregation. Consequently, endothelial impairment contributes to a prothrombotic state. *Platelet Activation*: Hyperglycemia directly modulates platelet behavior by increasing their sensitivity to activating stimuli and promoting aggregation.[74,104] Additionally, it enhances the release of platelet-derived microparticles and strengthens the binding affinity for specific coagulation factors, collectively amplifying thrombotic potential.[105]

In a unique study conducted at the University of Minnesota, in collaboration with Dr. Jonathan Gerrard, we investigated alterations in arachidonic acid metabolism in drug-induced diabetic rats.[74] Diabetes was induced in these animals by streptozotocin injection. We assessed prostanoid production in platelets and vascular tissues by measuring stable metabolites of radiolabeled arachidonic acid, specifically thromboxane and prostacyclin. In diabetic rats, thromboxane production was elevated, whereas prostacyclin production was reduced compared with control animals (Figure 5). Remarkably, transplantation of pancreatic islet cells into diabetic rats restored prostaglandin production to normal levels, demonstrating that the shift in prostanoid balance toward a pro-thrombotic state was disease-specific.

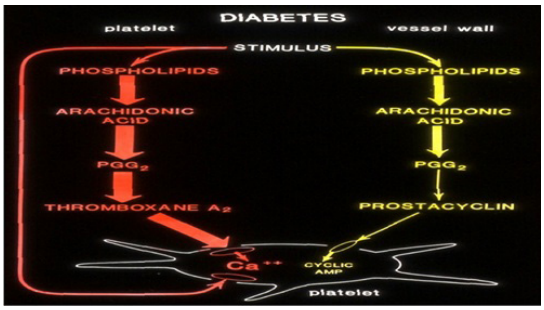


Figure 5. *Altered Prostanoid Metabolism in Drug-Induced Diabetes Rat Model (Courtesy: My Associate, Dr. Jonathan Gerrard, University of Minnesota).*

Clinical complications associated with chronic hyperglycemia include microvascular dysfunction that contributes to the development of peripheral neuropathy, retinopathy, and nephropathy, primarily as a result of arterial and capillary insufficiency.[106] Prolonged hyperglycemia activates multiple biochemical pathways that damage vascular endothelial cells.[104] Excess intracellular glucose increases flux through the polyol pathway, leading to sorbitol accumulation, osmotic stress, and depletion of NADPH, thereby reducing antioxidant defenses, including glutathione. Concurrently, hyperglycemia enhances the formation of advanced glycation end products (AGEs), which cross-link with proteins in the vascular basement membrane and interact with receptors for AGEs (RAGE) on endothelial and inflammatory cells, triggering oxidative stress and inflammatory signaling[107,108] Activation of protein kinase C (PKC), particularly the β-isoform, further promotes vasoconstriction, increased vascular permeability, and basement membrane thickening by upregulating endothelin-1, vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGF-β).[109] Additionally, increased glucose auto-oxidation and mitochondrial overproduction of reactive oxygen species (ROS) exacerbate endothelial dysfunction by impairing nitric oxide (NO) bioavailability and promoting prothrombotic and proinflammatory states.[74,78] Collectively, these mechanisms result in capillary rarefaction, reduced tissue perfusion, and ischemic injury to nerves, retinal microvessels, and renal glomeruli, which are the pathological hallmarks of diabetic microangiopathy.

Occlusive Arterial Disease

Occlusive arterial disease develops primarily as a consequence of atherosclerosis, a chronic, progressive condition involving structural and functional alterations of the arterial wall.[110] The process begins with endothelial injury, often triggered by factors such as hypertension, hyperglycemia, dyslipidemia, smoking, or oxidative stress. [111] Damage to the endothelium leads to a loss of vascular homeostasis, characterized by reduced nitric oxide (NO) availability, increased permeability to lipids, and enhanced expression of adhesion molecules that promote the recruitment of circulating platelets, monocytes, and T lymphocytes (Figure 6).[112] Once within the intima, monocytes differentiate into macrophages, which engulf oxidized low-density lipoproteins (oxLDL) through scavenger receptors, transforming into foam cells—the hallmark of early fatty streak lesions.[113] This process is amplified by reactive oxygen species (ROS), which not only oxidize lipids but also activate redox-sensitive transcription factors such as NF-κB, leading to the production of inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6). These cytokines sustain local inflammation, attract more immune cells, and promote smooth muscle cell migration from the media to the intima.[114]

Vascular smooth muscle cells (VSMCs), once in the intimal layer, undergo phenotypic switching from a contractile to a synthetic state, enabling them to proliferate, secrete extracellular matrix components, and take up lipids.[115] Signaling pathways involving Bruton's tyrosine kinase (BTK) have been implicated in regulating macrophage activation, VSMC behavior, and lipid metabolism within the plaque microenvironment.[116] At the molecular level, microRNAs (miRNAs) play critical regulatory roles by modulating gene expression involved in inflammation, lipid metabolism, and cell survival. For instance, certain miRNAs suppress endothelial repair mechanisms or enhance pro-inflammatory signaling, further aggravating vascular dysfunction.[117] Over time, these processes culminate in the formation of fibroatheromatous plaques, composed of lipid cores, necrotic debris, inflammatory cells, and fibrotic tissue.[118] Continued oxidative and inflammatory stress may weaken the fibrous cap, predisposing it to rupture. Plaque rupture exposes thrombogenic material to circulating blood, triggering platelet activation and thrombus formation that can abruptly obstruct blood flow, manifesting clinically as myocardial infarction, stroke, or peripheral arterial occlusion.[119] In summary, occlusive arterial disease represents a complex interplay between endothelial dysfunction, oxidative stress, immune activation, lipid metabolism, and molecular signaling networks (including BTK and miRNAs). Together, these events perpetuate a self-amplifying cycle of inflammation and vascular injury that drives the progression from early atherosclerosis to advanced, clinically significant arterial occlusion.

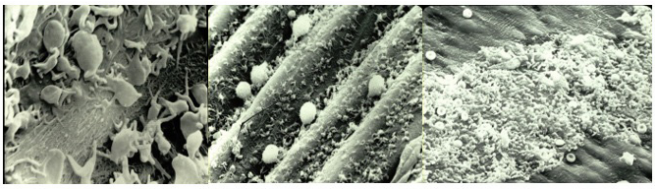


Figure 6. *Platelet Interactions with the arterial vessel wall. (Courtesy: My associate, (Late) Professor James G. White, University of Minnesota).*

Prothrombotic role of blood platelets

Prothrombotic conditions at the vascular wall arise from an imbalance between antithrombotic and prothrombotic mediators produced by endothelial cells and circulating platelets (Figure 7).

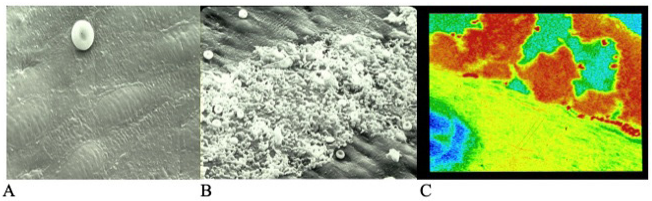


Figure 7. *Platelet Interaction with healthy endothelium (A), Platelet interaction with dysfunctional endothelium (B), and subendothelium (C).(Courtesy: My associate, (Late) Professor James G White, University of Minnesota).*

Under physiological conditions, vasodilators and antithrombotic agents such as prostacyclin (PGI_2), thrombomodulin, protein C, plasminogen activators, and heparin-like glycosaminoglycans maintain endothelial integrity and inhibit platelet aggregation and fibrin formation.[68-70] However, oxidative stress, inflammation, or hyperglycemia can disrupt this equilibrium, leading to

enhanced synthesis and release of prothrombotic factors, including platelet-activating factor (PAF), von Willebrand factor (vWF), plasminogen activator inhibitors, endothelial proteases, and tissue factor. These molecules promote platelet adhesion, activation, and aggregation, while concurrently stimulating the coagulation cascade through thrombin generation and fibrin deposition. Additionally, increased production of prostanoids such as prostaglandins G_2 and H_2, and thromboxane A_2, augments vasoconstriction and platelet aggregation, further amplifying the prothrombotic milieu that predisposes to vascular occlusion and ischemic events.[74]

Ionized calcium acts as the primary bioregulator, with numerous biochemical mechanisms modulating the availability of free cytosolic calcium.[120] Signal transduction begins when agonists bind to specific receptors, leading to the stimulation of effector enzymes via transmembrane GTP-binding proteins (Figure 8). Key enzymes that regulate calcium levels via secondary messengers include phospholipase C, phospholipase A2, phospholipase D, adenyl cyclases, and guanyl cyclases. Phospholipase-C activation results in the hydrolysis of phosphatidylinositol trisphosphate, generating the secondary messengers 1, 2-diacylglycerol (1, 2-DG) and inositol trisphosphate (IP3).[121] Signal transduction mechanisms are similar to agonist-induced transmembrane signaling. Platelet antagonists act at the membrane receptors, inducing transmembrane signals that result in the formation of second messengers, cyclic AMP (cAMP) and cyclic GMP (cGMP).[122] These second messengers lower cytosolic calcium levels and thereby limit the availability of free calcium needed for platelet activation, leading to the assembly of actin, contraction of cytoskeletal proteins, and secretion of granule contents.[120-122]

Figure 8. *Signal transduction, formation of second messengers. (Schematic representation prepared by the University of Minnesota Artists).*

Occlusive Arterial Events

All major arteries are susceptible to oxidative stress–induced endothelial injury, a fundamental initiating event in the pathogenesis of atherosclerosis.[123,124] Under normal physiological conditions, the vascular endothelium serves as a critical regulator of vascular homeostasis by maintaining vasodilation through nitric oxide (NO) production, inhibiting platelet aggregation, and preventing smooth muscle proliferation. However, chronic exposure to oxidative stress—arising from metabolic abnormalities such as hyperglycemia, dyslipidemia, hypertension, and smoking—leads to excessive generation of reactive oxygen species (ROS).[125] These reactive species rapidly inactivate NO, impairing endothelial-dependent vasodilation, and promoting a pro-inflammatory, pro-coagulant, and vasoconstrictive milieu.

Endothelial dysfunction enhances vascular permeability, facilitating subendothelial accumulation of LDL. Oxidative modification of LDL within the intima results in the formation of oxidized LDL (oxLDL), which acts as a potent chemoattractant for circulating monocytes and T lymphocytes.[126] Upon infiltration, monocytes differentiate into macrophages that internalize oxLDL via scavenger receptors, giving rise to foam cells, the earliest morphological feature of fatty streaks. The local inflammatory environment perpetuates the release of cytokines, chemokines, and growth factors that stimulate vascular smooth muscle cell (VSMC) migration and proliferation into the intima. These VSMCs contribute to extracellular matrix deposition, leading to the development of a fibrofatty atheromatous plaque.[127] As the lesion matures, persistent inflammation and oxidative stress weaken the fibrous cap via macrophage-derived matrix metalloproteinases (MMPs), rendering the plaque unstable and prone to rupture. Plaque rupture exposes thrombogenic core material to circulating blood, activating platelets and the coagulation cascade, culminating in thrombus formation and acute vascular occlusion. [128,129]

The clinical consequences of such occlusive arterial disease are determined by the vascular territory affected. In coronary arteries, it manifests as myocardial ischemia and infarction; in cerebral vessels, as transient ischemic attacks or ischemic stroke; and in peripheral arteries, as critical limb ischemia or gangrene.[130] Similarly, involvement of renal and retinal microvasculature results in ischemic nephropathy and retinopathy, respectively.[131] Collectively, oxidative stress–driven endothelial dysfunction integrates metabolic, inflammatory, and vascular mechanisms, forming the central axis of atherogenesis. This progressive process not only underlies the structural narrowing (stenosis) of arteries but also predisposes to acute ischemic events that compromise perfusion and the functional integrity of vital organs. Therapeutic implications: Understanding the molecular interplay between oxidative stress, inflammation, and endothelial dysfunction provides a strong rationale for targeted interventions.[132,133] Strategies that restore redox balance—such as antioxidants, NADPH oxidase inhibitors, and mitochondrial ROS modulators—alongside agents that enhance endothelial NO bioavailability or suppress vascular inflammation (e.g., statins, anti-cytokine therapies, and BTK inhibitors), hold promise in preventing or attenuating the progression of atherosclerotic vascular disease.[132,133]

Discussion

Cardiovascular diseases (CVDs) remain the foremost cause of death worldwide. Of the 20.5 million CVD-related deaths reported in 2021, nearly 80% occurred in low- and middle-income countries.[134] Much of the foundational understanding of CVD pathophysiology stems from the landmark Framingham Heart Study, which identified key risk factors such as hypertension, diabetes, and smoking. The study also underscored several critical contributors to heart disease—elevated cholesterol (particularly LDL or “bad”

cholesterol), obesity, physical inactivity, family history, age, and sex. It has been estimated that the complete elimination of cardiovascular diseases could extend average life expectancy by approximately 11 years.[135] The INTERHEART study further demonstrated that nine modifiable risk factors account for over 90% of the global risk of myocardial infarction across diverse regions and populations, implying that effective management of these factors could prevent most premature heart attacks.[136] Similarly, Khera and colleagues at Harvard University showed that even among individuals with a high genetic predisposition, adherence to a healthy lifestyle reduced the relative risk of coronary artery disease by nearly 50%.[137] Research from Imperial College London revealed a decline in cardiovascular mortality but a concurrent rise in diabetes-related deaths in high-income countries. Between 1980 and 2009, age-standardized cardiometabolic mortality decreased across 26 industrialized nations, with reductions in modifiable risk factors contributing to 49% of the decline in men and 40% in women. However, no country has yet succeeded in reversing or halting the increasing incidence of vascular diseases.[69]

In a monograph we published in 2001 titled "Coronary Artery Disease in South Asians," world-renowned cardiovascular epidemiologist Professor Henry Blackburn of the University of Minnesota emphasized, "The ultimate health goal is not merely to control disease or reduce high risk, but to prevent high risk from developing in the first place—both in individuals and across entire populations."[138] According to the Cleveland Clinic, healthy lifestyle habits could prevent up to 80% of chronic diseases, most of which are linked to modifiable risk factors—a finding supported by numerous studies and public health organizations. Despite this evidence, modern healthcare continues to focus largely on managing diagnosed conditions such as hypertension, T2D, obesity, and vascular diseases, rather than preventing them. The future of medicine, however, lies in proactive prevention, targeting modifiable risks and promoting a longer, healthier lifespan.[70,139] Our current understanding of the cellular and molecular mechanisms underlying cardiometabolic risk and the development of metabolic diseases has advanced substantially. In this review, we summarize these mechanisms, including oxidative stress, dysregulated lipid and glucose metabolism, endothelial dysfunction, arterial injury, atherosclerosis, and acute vascular events. In addition to lifestyle modification, early detection of metabolic dysfunction and targeted intervention at the cellular and molecular levels may significantly enhance the prevention and management of chronic metabolic diseases.

The concept of the FOAD, originally proposed by Dr. David Barker, has evolved into the DOHaD paradigm.[1-4] This hypothesis suggests that the intrauterine environment, including maternal nutrition, hormonal milieu, and metabolic status, profoundly influences fetal organ development and long-term health outcomes. Evidence from the Mysore Cohort and subsequent Mysore Parthenon Studies demonstrated that low birth weight, a marker of suboptimal fetal nutrition, was associated with an increased risk of coronary heart disease, insulin resistance, and metabolic dysfunction in adulthood.[10-12] Furthermore, maternal undernutrition or overnutrition—often coexisting in low- and middle-income countries—was found to exert dual adverse effects on offspring, predisposing them to metabolic and cardiovascular diseases. A new mechanistic hypothesis has emerged from studies led by Dr. Robert Freishtat's team at Children's National Hospital and collaborative work with Indian research institutions. Their work focuses on adipocyte-derived exosomal microRNAs (miRNAs) that mediate intercellular communication and epigenetic regulation.[60] In obesity, visceral adipocytes release altered exosomes that contain specific miRNAs, which reprogram metabolic pathways in distant tissues—impairing glucose and lipid homeostasis.[62,63] Extending this concept, maternal exosomal miRNAs may cross the placenta and modify fetal gene expression, influencing adipogenesis and lifelong susceptibility to obesity and T2D. This finding integrates epigenetic regulation into the DOHaD framework and opens avenues for early diagnosis and intervention.

The global rise in cardiometabolic diseases—including hypertension, obesity, T2D, and vascular dysfunction—reflects an interplay between metabolic, oxidative, and inflammatory processes.[64-70,140] ***Endothelial Dysfunction***: A pivotal early marker of vascular disease, characterized by reduced nitric oxide (NO) bioavailability due to oxidative stress and metabolic imbalance.[71-73] ***Hypertension***: Linked to fetal growth restriction, nephron deficit, and persistent activation of the renin–angiotensin–aldosterone system (RAAS), representing a developmental programming effect.[74-77] ***Obesity***: Differences in adipose tissue function—white (WAT), brown (BAT), and beige fat—determine metabolic efficiency. Maternal obesity and gestational diabetes further aggravate fetal adipogenesis via altered PPARγ and MAPK signaling, increasing long-term obesity risk.[84-87] ***Diabetes Mellitus***: Epigenetic modifications suppress critical pancreatic genes (PDX1, HNF4α), impairing β-cell function and insulin secretion. In peripheral tissues, reduced GLUT4 expression and mitochondrial dysfunction diminish glucose uptake, perpetuating hyperglycemia and insulin resistance.[92-99]

Atherosclerosis underlies occlusive arterial diseases through a cascade initiated by endothelial injury. Hyperglycemia, dyslipidemia, and hypertension increase oxidative stress, leading to lipid oxidation (ox-LDL formation), activation of inflammatory cytokines (TNF-α, IL-1β, IL-6), smooth muscle proliferation, and plaque formation.[123-127] Platelets play a prothrombotic role, amplifying vascular injury by promoting imbalanced prostanoid signaling and elevating thromboxane A_2. Experimental evidence, such as prostanoid imbalance in diabetic rats, confirms this metabolic-vascular linkage. In advanced stages, these mechanisms culminate in ischemic events—myocardial infarction, stroke, or peripheral artery disease—reflecting the systemic consequences of metabolic dysregulation. Despite advances in understanding molecular pathways—calcium signaling, NO–cGMP cascades, and redox regulation—clinical outcomes rely heavily on modifiable risk factor control. Historical and contemporary studies (Framingham, INTERHEART, Harvard's Khera et al.)[136,137] converge on the same conclusion: lifestyle modification—including balanced nutrition, physical activity, and smoking cessation—remains the most effective preventive strategy. Modern medicine must transition from a reactive model of disease management to a

proactive prevention model, emphasizing early identification of epigenetic and metabolic markers of disease susceptibility.

Conclusions

The cumulative evidence from decades of global and Indian research underscores that adult metabolic and cardiovascular diseases originate, in part, from adverse intrauterine environments that induce epigenetic reprogramming of key metabolic pathways. The integration of exosomal signaling, maternal nutrition, and oxidative stress into the DOHaD framework provides a unified model linking fetal events to adult pathology. Cardiometabolic diseases—spanning obesity, diabetes, hypertension, and vascular disorders—share a common axis of endothelial dysfunction, oxidative stress, and inflammation. While molecular research has identified numerous therapeutic targets, the greatest impact will come from early-life interventions and preventive strategies that address maternal and fetal health, aiming to halt the intergenerational transmission of disease risk. Ultimately, the future of medicine lies not merely in treating disease but in preventing high-risk states from developing, thereby promoting healthier aging and reducing the global burden of chronic cardiometabolic disorders.

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