

THE NUTRIENT-GENE-HORMONE AXIS

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Abstract

The interaction between Nutrients, Genes and Hormones that significantly influence human physiology and metabolic homeostasis. Emerging evidence from nutrigenomics and nutrigenetics studies unveils the ways that nutrients modulate various downstream hormonal signaling, gene expression and epigenetic profile which then may impact on metabolic outcomes and potential disease risk. Recent researches further declares that every smaller change in dietary habits can trigger substantial shifts in metabolism pathways during interaction with specific genetic variants or mechanism of hormonal regulation. Some nutrient-gene relationships illustrate how genetic variation can alter the efficacy of nutrients, modify enzyme kinetics and impact disease susceptibility. The hormonal mediators like insulin, leptin, cortisol, thyroid hormones and sex-steroid hormones act as essential connectors which helps to integrate nutrient availability during molecular responses across tissues. These hormone functioning pathways helps in to coordinate the balance of energy, regulation of appetite, controls the inflammation, and lipid-glucose homeostasis, all of which are strongly bounded by nutrient intake and genetic predisposition. Individual responses to nutrients vary person to person, emphasizing the importance of understanding personalized metabolic signatures. Such personalized strategies aim to increase nutrient efficiency, lowering the disease risk and improve long-term metabolic resilience. There is still research required between mechanistic findings and therapeutic guidance and further long term, well-characterized controlled studies. Current studies are still evolving and require validation through multi-omic approaches that focuses genomics, metabolomics, proteomics or endocrine profiling. This article describes the present studies on nutrient-gene-hormone axis along with key molecular mechanisms, clinical consequences and possible future approaches for precision nutrition. It further shows how advancements in technologies and biological databases may increases the transition from generalized nutritional advice toward highly individualized interventions.

1. Introduction

Every individual body doesn't have the same response to nutrients and food. That response of nutrients and the food towards the body can be beneficial, or it can also have a negative impact on the body as well. There is also a chance that the

same nutrient intact can respond positively to one person, but for others, it can be harmful, allergic or not that beneficial. This study basically shows the idea of personalized nutrition, according to the individual's needs. There is the single nucleotide polymorphism, which is an inheritable

may be the source of individual differences, which results in a positive and negative response of nutrients. The idea is started of making personalized diet plans according to genetic makeup, but still more study is required on the study of genes and their interaction with food and nutrients to meet the requirements of every individual (1).

Nutrition and genetics are complexly combined to human health, shaping biochemical foundation of the cells and dynamic responses to internal and external challenges. The term nutrigenomics encapsulates how dietary factors influence gene expression programs and epigenetics, hence participate fundamentally in physiological functions (2). In this paradigm, nutrients are not passive fuel but active modulators of transcriptional and chromatin regulation. Vitamins, minerals, fatty acids, amino acids, and various other bioactive compounds engage with nuclear receptors, kinases, and cofactors to activate or deactivate gene switches. Concurrently, dietary methyl donors (such as folate, B12), polyphenols, and other micronutrients simultaneously modifies DNA methylation, histone modifications, and smaller noncoding RNAs in order to offer lasting regulatory memory. Diet influences cellular networks which help directly to regulate metabolic status, ability to withstand oxidative damage, and vulnerability to diseases through these transcriptional and epigenetic pathways (3).

Multiple human interventions and observational studies backup this opinion. For example, specific nutritional additions have also been demonstrated to alter methylation of metabolic loci and affect peripheral tissues' transcriptomes. Animal and cellular experiments also supplement causal relationship or linkage, e.g. polyphenolic compounds modulating histone acetylation or methyl donor influencing chromatin landscape in promoters of metabolic genes. These mechanistic data anchor the concept that what we eat becomes part of our regulatory genome architecture, shaping the ability to adaptive capacity over time (4).

Beyond direct gene modulation, nutrients also have a significant influence on endocrine systems such as connecting diet to hormone biology. A nutrient-centric perspective of endocrinology views dietary components involved in hormone production, secretion, and feedback regulation. For instance, iodine and selenium are necessary substrates for the thyroid hormone biosynthesis, while cholesterol serves a precursor for all steroid hormones (5). Through nutrient mediated signaling pathways, the composition of macronutrients (such as protein, fat, and carbohydrates) can change the activity of pancreatic β -cells and the secretion of insulin. Dietary alterations in adipose tissue gene expression impact production of adipokines, as an example, leptin and adiponectin, modifying systemic hormonal signals. Additionally, diet alters the gut microbiota, that generates metabolites (like short-chain fatty acids, bile acids, neurotransmitter precursors) that influence endocrine axes through gut-brain, gut-liver, or gut-adrenal pathways. Most recent research studies especially focus on how microbiome-derived metabolites may have an influence on the timing of puberty or hypothalamic regulation of endocrine system development (6).

Genes themselves shape hormone function both naturally and in response to dietary changes. Genetic variants (SNPs, regulatory polymorphisms) have impact on the performance of enzymes, receptors, transporters, and signaling molecules throughout hormone biosynthesis and feedback loops (7). In the context of nutrigenetics, these variants interact with dietary exposures. The same dietary intake may produce significantly different hormonal outcomes depending on the genotype. Such as, in metabolic syndrome, certain genetic alleles interacting with high-fat diets boosts dyslipidemia or insulin resistance. Moreover, gene expression programs themselves (which may have been shaped by past epigenetic or transcriptional influences) control the way how endocrine tissues respond to internal and nutritional stimuli. Genome-wide interaction studies (GWIS) and candidate gene & diet analyses increasingly uncover interactions linking diet, genotype, and

hormonal parameters. Although effect sizes are often modest and replication is inconsistent, these data hint at the possibility of tailoring diet to genetics in order to optimize endocrine outcomes (8). The interaction between the nutrient, gene and hormone links with diet, gene regulation, and hormonal responses, basically shows how nutrients changes gene networks and effect of hormones. Understanding this interplay is key to advancing of nutritional research on "nutrient-gene-hormone axis" (9).

2. Nutrient Gene Interactions

Nutritional studies have newly identified the nutrient's function in modulating gene expression and regulating pathways. While not as mainly recognized, presence of nutrients influences gene activity and mechanisms of hormones. The regulatory reaction to a nutrient status observed in multiple cases to be particular for every genotype and especially targeted nutrient dysfunction outcome in modified genetic activity, based on every single genotype (10). Recent studies has shown that the carbohydrates, fatty acids, minerals, and vitamins of all the food components contribute to regulate gene expression. There are some specific examples that shows the nutrient gene interactions and their effects on the body; like folate with MTHFR gene, vitamin D with VDR gene, iron with HFE gene. carbohydrates with TCF7L2 gene, omega 3 fatty acids with FADS gene cluster (11).

2.1. Folate with MTHFR

The MTHFR (Methylenetetrahydrofolate Reductase) is basically a gene which helps in producing an enzyme that plays a significant role in processing folate (vitamin B9) which is a nutrient helps in synthesis of DNA, repair, and in the process of methylation, as well as it also helps in the conversion of homocysteine into methionine. When this process is successfully done, it supports healthy cell division and cardiovascular health (12). Although, regular genetic variations in the MTHFR gene induces a reduction with respect to enzymatic function (Fig. 1). And the most well- observed variant, C677T (rs1801133), causes a change in the enzyme structure, lowering its process and function by up to 60-70% in individuals with the TT genotype. This leads a way to elevated homocysteine levels and reduced availability of active folate in the body. A second variant, A1298C (rs1801131), has lesser effects but can compound problems when combined with C677T (13). Research studies shows that people with these mutations may have a higher risk of cardiovascular diseases, neural tube defects, and pregnancy complications, especially when intake of folate is less in diet. High intake of folate from leafy greens, fortified foods, or supplements can help to normalize the level of homocysteine and balance the reduced enzyme activity (14).

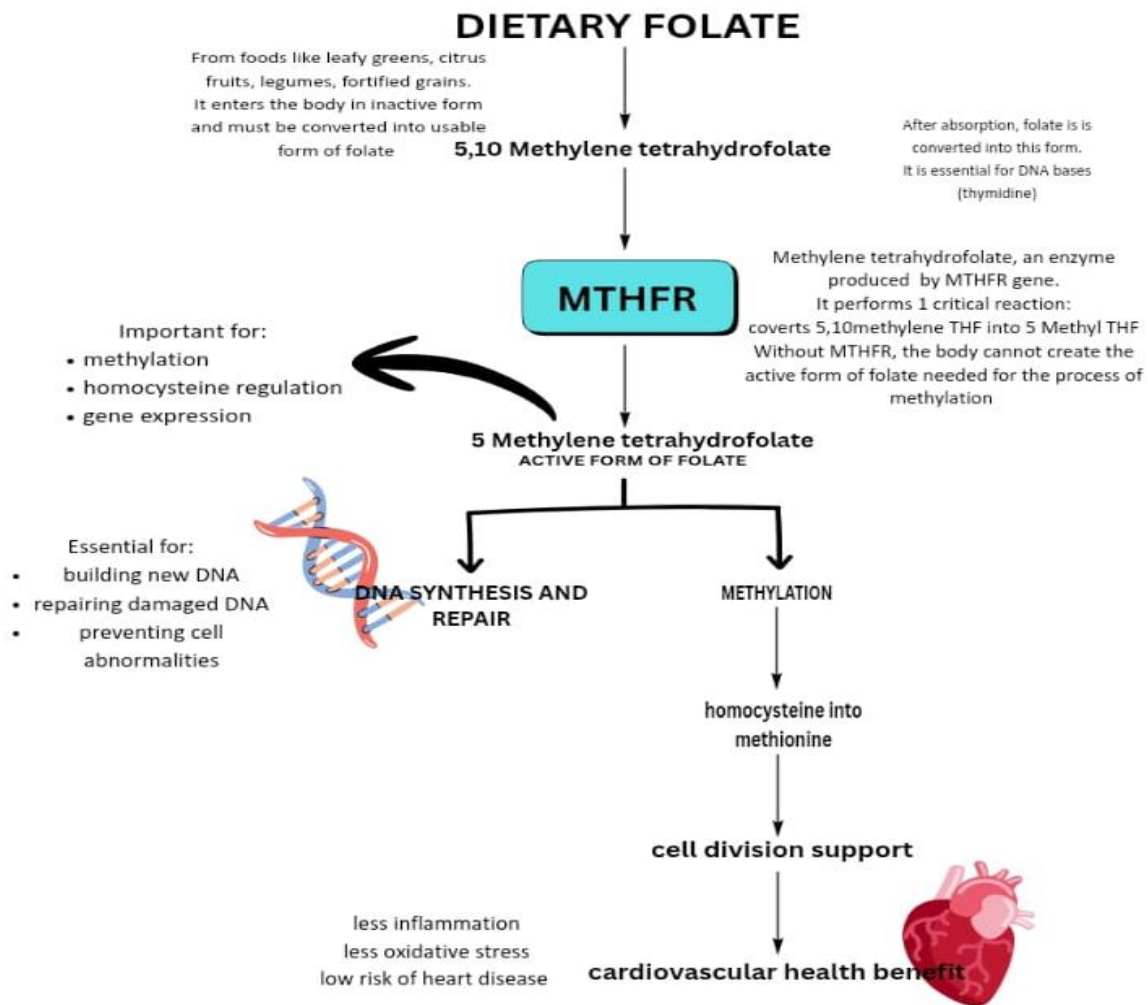


Figure 1. MTHFR with Folate and Folate deficiency complications

2.2. Iron with HFE

The HFE (High Iron Fe) gene regulates the body's absorption and stores iron from food. HFE protein produces by this, for iron uptake management. It interacts with the transferrin receptor on intestinal cells. When this system properly works, the healthy iron levels maintain this by balancing absorption with the body's needs (15). However, different mutations in the HFE gene can discompose this control, leading to excessive iron absorption, known as hereditary hemochromatosis. The most common variant, C282Y (rs1800562), causes alterations in the HFE protein that helps to prevents it from binding to the transferrin receptor. In conclusion, the body further leads to absorb iron even when there is no

need and stores are also full, leading to iron toxicity in the liver, heart, and pancreas. Another variant, H63D (rs1799945), has lower effects but can contribute when combined with C282Y (16) (Fig. 2). Research studies shows that individuals who inherited with two C282Y alleles (homozygous) significantly higher in risk of iron overload disorder, typically have normal iron levels unless they also consume high amounts of iron or alcohol. Initial discoveries and management of dietary intake such as avoiding iron supplements, limiting red meat, and increasing antioxidant intake helps in to control and in prevention of complications like liver damage, diabetes, and heart disease (17).

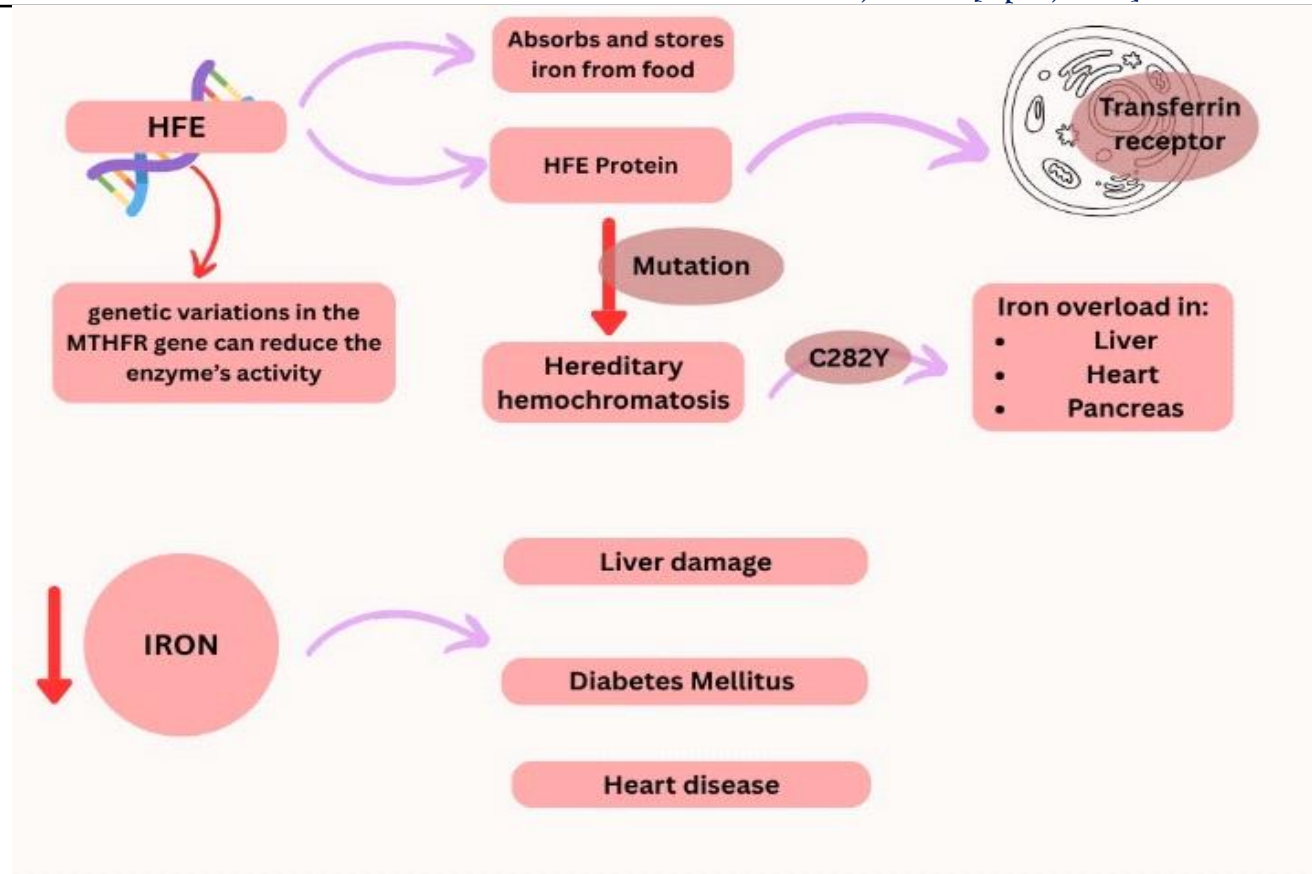


Figure 2. HFE with Iron and Iron deficiency complications

2.3. Vitamin D with VDR

Vitamin D utilize its biochemical and physiological responses usually during interaction with the vitamin D receptor (VDR), which is basically a nuclear hormone receptor encoded with VDR gene. After being activated to its functional form, 1,25-dihydroxyvitamin D, with the retinoid X receptor VDR creates a mixed dimer and binds with response elements of vitamin D (VDREs) in the promoter sequences of responsive genes, transcription regulation (18). This nutrient gene interaction impacts a huge range of physiological or biochemical processes, includes calcium homeostasis, bone metabolism, immune function, and cell proliferation.

Individual responses to vitamin D have been found to be modulated by genetic variation (19). These polymorphisms are also associated with susceptibility to other disorders, including osteoporosis, autoimmune diseases, and some types of cancer. Additionally, researchers claim that by producing antimicrobial peptides like cathelicidin, VDR activation improves innate immunity (Fig. 3). Therefore, the interaction between the nutrient and the gene can demonstrate changes in health outcomes through molecular signaling and genetic variability, as explained by the intermix between vitamin D and the VDR gene (20).

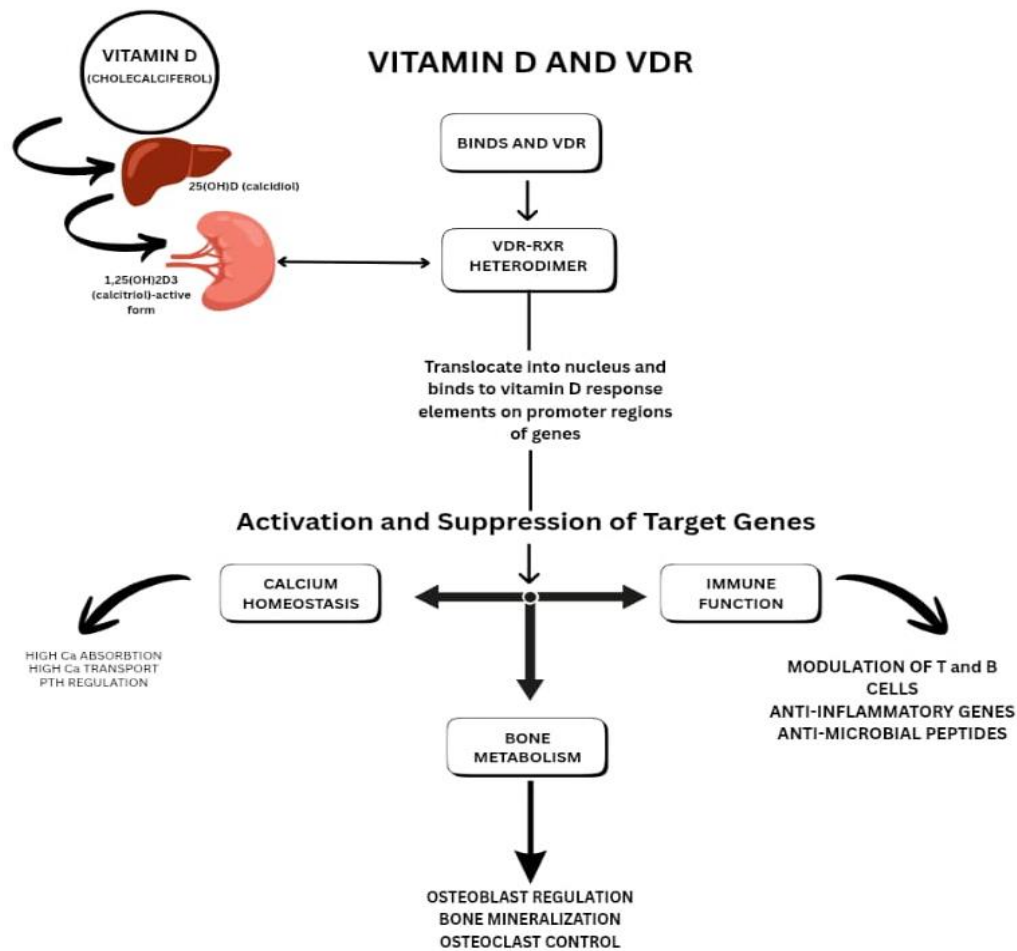


Figure 3. Physiological effect of Vitamin D on VDR

2.4. Carbohydrates and TCF7L2

The interaction between dietary carbohydrates and the TCF7L2 (Transcriptional regulation 7-Like 2) gene is like a well-explained example of a nutrient and gene interaction with important implications for metabolic health, particularly type 2 diabetes (T2D). TCF7L2 plays an important responsibility in the "Wnt signal relay pathway", that impacts on secretion of insulin and metabolism of glucose. Variants in the TCF7L2 gene have been strongly related to the higher risk of Type 2 diabetes. Those individuals carrying such risk allele tend to have defective insulin released

and change in homeostasis of glucose. significantly, research suggests that dietary carbohydrate consumption can modulate the impact of variants like TCF7L2 on diabetes risk (Fig. 4). For instance, high intake of refined carbohydrates or high glycemic load diets may exacerbate the genetic risk conferred by TCF7L2 polymorphisms, while diets rich in whole grains and fiber may mitigate it. This gene diet interaction underscores the potential for personalized nutrition strategies in preventing or managing T2D based on genetic profiles (21, 22).

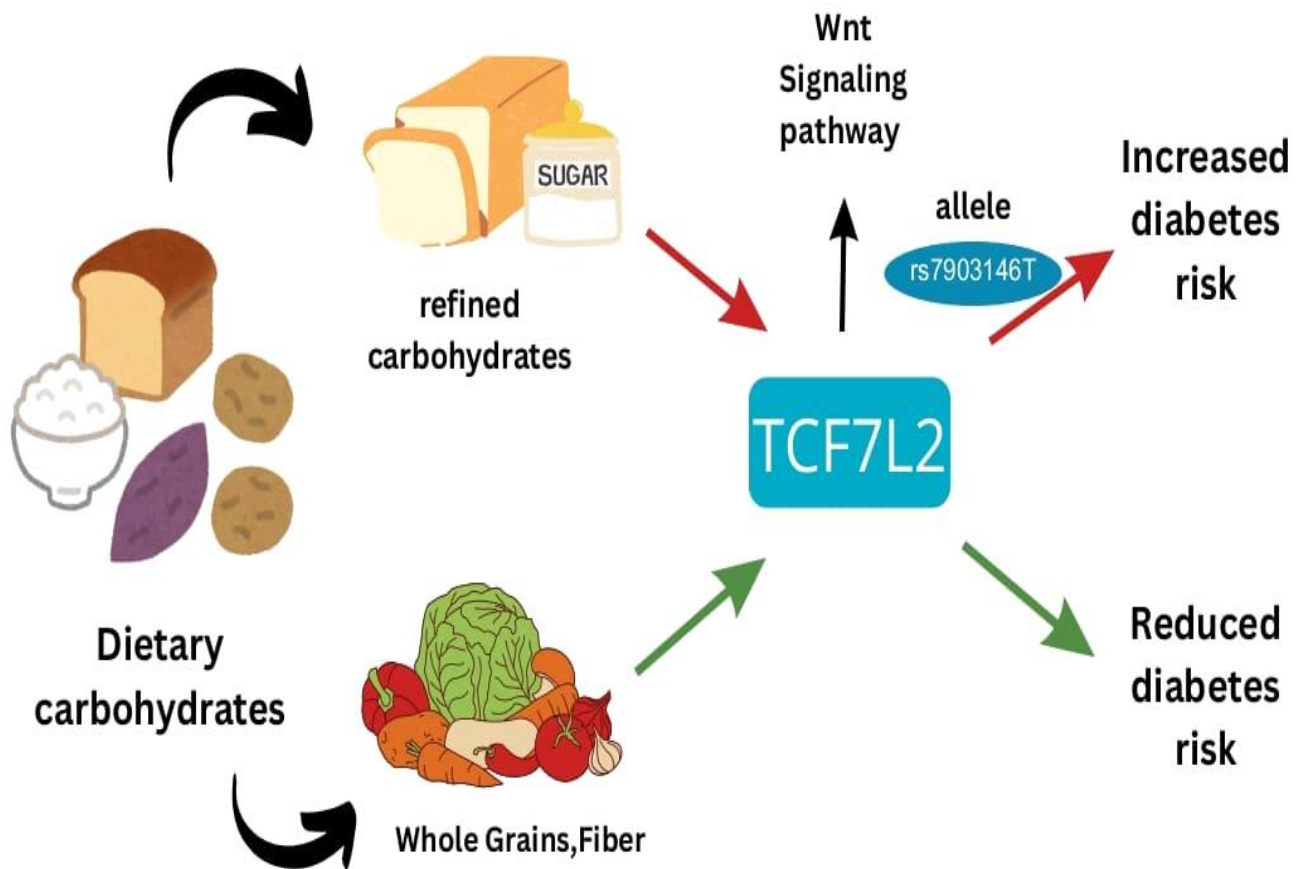


Figure 4. Interactions of dietary carbohydrates with TCF7L2

2.5. Omega fatty acids and FADS gene cluster

The interaction between these fatty acids and the FADS gene cluster (dietary fats desaturase genes, primarily FADS1 and FADS2) is a main example that shows, the nutrient metabolism and health outcomes effected by the genetic variations. The FADS genes specify the enzymes which are responsible in conversion of essential fatty acids like alpha-linolenic acid (ALA) into long-chain healthy fats like, eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), which are crucial for cardiovascular, neurological, and immune health (23). Polymorphisms in the FADS genes, significantly in FADS1 or FADS2, affect the

activeness of this conversion process. As an example, people with such variants might have ability to produce EPA and DHA from dietary ALA, making directly intake of these LC-PUFAs from fish or supplements more important (Fig. 5). One study found that these genetic differences can affects blood lipid profiles and inflammatory markers, potentially modifying the risk of conditions like heart disease. Another study, which finds a gene regulatory indel in the FADS cluster that changes enzyme activity and fatty acid composition in tissues (24).

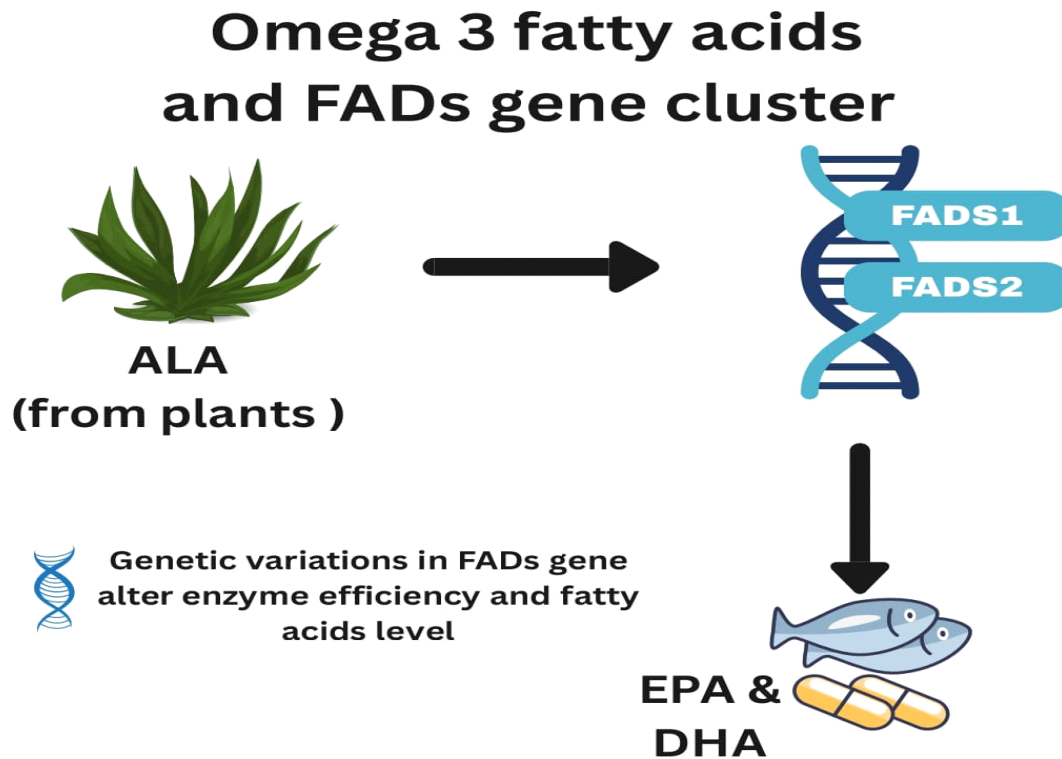


Figure 5. Interaction between omega-3 fatty acids and the FADS gene cluster

3. Gene-Hormone Interactions

There are so several molecular signaling routes eventually regulates specific nuclear gene expression profiles by using the diversity of signal-responsive transcription factors, consisting of nuclear receptor proteins. The formation of DNA based technologies that analyzing signal induced gene expression and TF attachment on a genetic scale shows significantly enhancement in cellular regulating programs controlling the signaling of hormones and regulation of genes (25). Researches of TFs, using genome wide strategies have discovered the study and unpredicted functions of hormone triggered transcription, and also a comprehensive sight is started to observed. During this part, we observed the interaction between genes and hormones that how the genes influence on hormones and how hormones linked to genes to show different mechanisms inside the body. Considering the extensive information available on gene regulation which depends on hormones by nuclear receptors, this evaluation

concentrates on insights obtained from studies of genomes and their function (25, 26).

3.1. MTHFR with Insulin

The MTHFR gene crucially involved in folate metabolism by conversion of 5,10-methylene-THF into 5-methyl-THF, which leads to the regulation of homocysteine levels in the body. This gene exhibit common variation, that's called C677T polymorphism, affects the enzymatic function performance (26). People belong to CT and TT genotypes have normal activity seen in CC type around about 65% and 30%. When this enzyme activity drops, Hcy levels become high, a condition which is known as hyperhomocysteinemia, which cause disturbing in insulin endothelial signaling pathways, in the last, contributing resistance of insulin (IR). In the cited study, women suffering from PCOS who had IR showed higher level of Hcy than those who are not suffering from IR. The different genotypes, as well as T alleles, significantly appeared more often in the IR group

($P < 0.05$), whereas no situation like this was found in healthy participants. This declares that the C677T mutation is specifically connected to insulin resistance in PCOS (Fig. 6). The same patients also raised to have higher triglyceride and overall levels of cholesterol, and within the group with no insulin resistance, TC increases gradually from CC to CT to TT genotypes. These outcomes shows that the MTHFR mutation may increases the threat of IR and imbalance of lipids in PCOS by fluctuating Hcy and disturbing glucose and

lipid metabolism. previous studies have shown that folic acid helps in lowering Hcy and HOMA-IR levels and improve pancreatic function, although this study did not show the data on supplementation. combinedly, the outcome shows that reduced MTHFR activity occurs due to the C677T mutation can elevate Hcy, intermix with insulin and lipid regulation, and enhances the chance of metabolism and cardiovascular issues specially in women with PCOS (27).

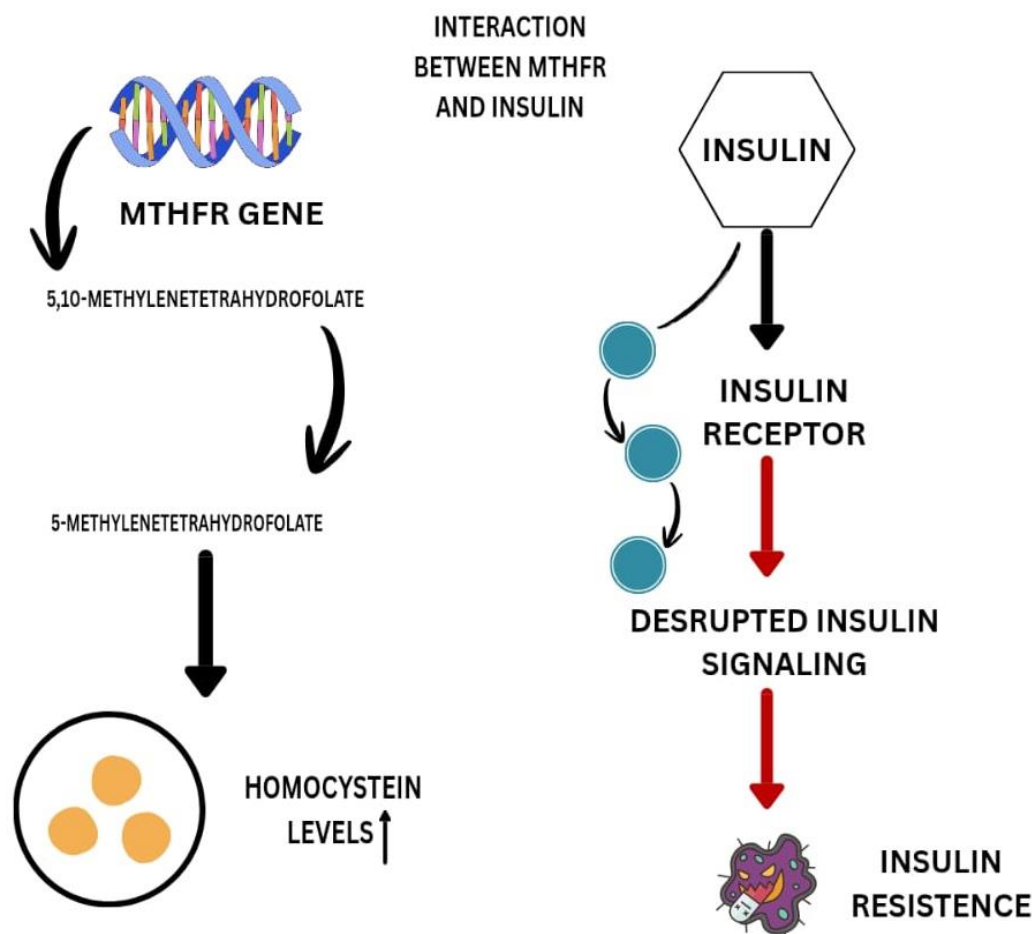


Figure 6. MTHFR gene and insulin metabolism

3.2. VDR Gene and LH Regulation

This study investigates the connection with the vitamin D receptor (VDR) polymorphisms of gene

and in the progression of polycystic ovary syndrome. Nine genetic markers coating almost 65 kb of the vitamin D receptor gene involves,

regulatory region, exon, intron, and UTR sequences were studied. Women with polycystic ovary syndrome normally showed modified sexual hormone production along with alterations in level of cholesterol and triglyceride (TG). In comparison with controls, PCOS patients had higher LH, AMH, prolactin, free and total testosterone, and DHEA-S levels, while FSH was lower, resulting in an elevated LH/FSH ratio. The VDR gene is synthesized in many hormone-regulating tissues such as the pancreas, pituitary, parathyroid, skin, and reproductive organs, resulting its broader impact in metabolic and endocrine function. from the time vitamin D applies its effects through VDR, alterations in this gene may influence glucose metabolism, hormonal regulation, and fertility (28) (Fig. 7).

Among the studied SNPs, important associations were seen with PCOS and its phenotypes. The rs11568820 polymorphism, situated in the VDR gene promoter, modulates transcription levels; the A allele binds more efficiently to the CDX2

transcription factor, enhancing VDR expression. Some studies shows that the GA genotype and A allele may offer protection against PCOS. earlier analyses have linked ApaI and BsmI polymorphisms with high PCOS vulnerability in the women especially of Asia, while the ApaI AA genotype was linked with lower risk and the CC genotype with higher risk. conversely, results for TaqI and FokI variants were irregular, showing little or no linkage with PCOS unless in isolated models. variations in results across populations may affect ethnic genetic diversity and selective evolutionary variations in VDR gene performance. Overall, this study supports the view that VDR gene polymorphisms impact to PCOS risk, likely by changing vitamin D signaling and its downstream effects on reproductive and metabolic pathways. Moreover, large scale multiethnic researches are required to verify these linkages or clarify the gene's role in PCOS pathophysiology (28, 29).

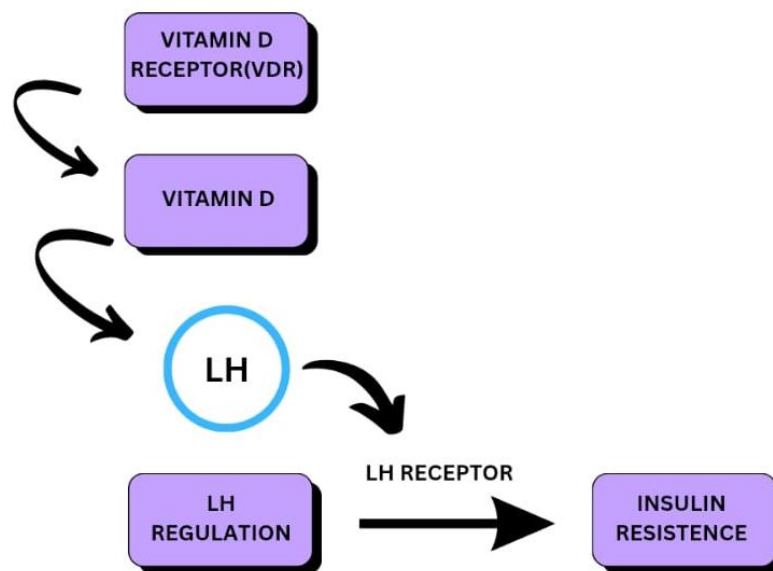


Figure 7. Relationship between VDR and PCOS

3.3. FADS Gene and Insulin Hormone

The type 2 diabetes mellitus is actually a common disorder of metabolism distinguished by lower

secretion of insulin from β cells of pancreas and resistance of insulin in peripheral tissues. Genome wide analysis researchers have verified several

variants of genetics linked with the type 2 diabetes, involving those in the FADS gene cluster. This research focused on the FADS1 polymorphism and its association with type 2 diabetes, along with its effect on the metabolism of omega-3 and 6-fatty acids. According to a study, the total 120 participants from them almost 60 recently diagnosed Type 2 diabetes patients and 60 are healthy controls subjects matched for age, sex, and sociodemographic variables were analyzed. Serum levels of polyunsaturated fatty acids (PUFAs) and the activities of delta-5 desaturase (D5D) and delta-6 desaturase (D6D) enzymes were analyzed using ELISA and gas chromatography, while FADS1 polymorphisms were measured through Sanger sequencing (30).

The results showed a significant fluctuation in genotype and allele frequencies between groups, with C-containing alleles being more common in T2DM patients. The availability of the C allele was independently linked with an increased risk of T2DM, even after adjusting for lipid and inflammatory markers (Fig. 8). Moreover, patients with this allele exhibited lower serum levels of omega-3 and omega-6 fatty acids and drops desaturase enzyme activity. These observations suggest that the FADS1 (rs174547) polymorphism contributes to T2DM susceptibility by impairing fatty acid metabolism and desaturase function, which may in turn influence insulin sensitivity and metabolic health (31).

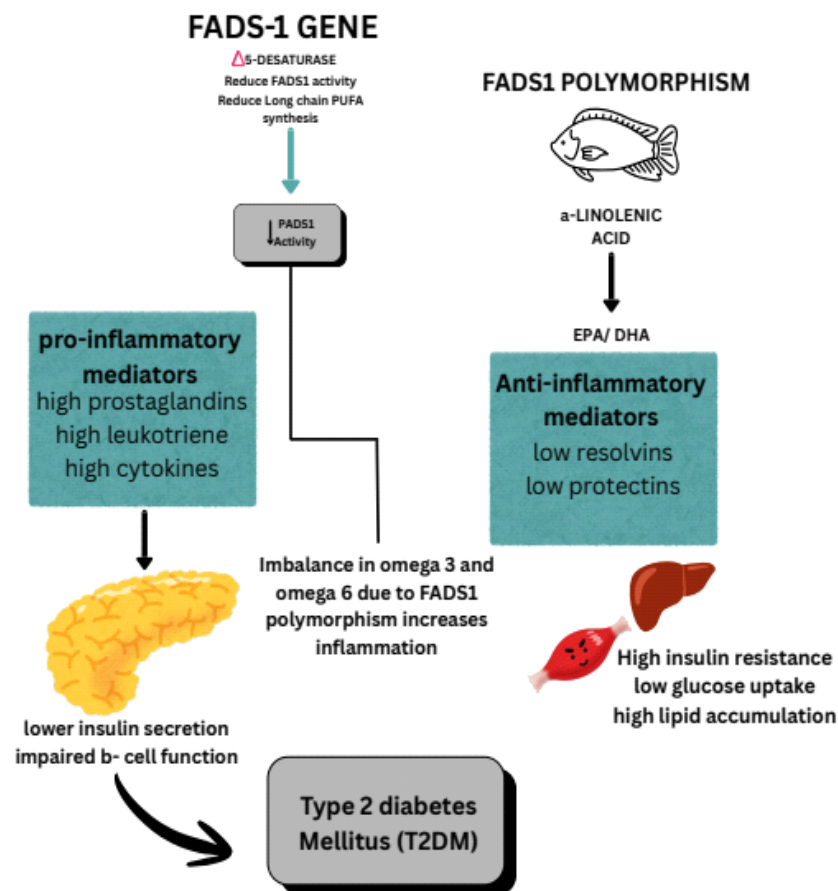


Figure 8. Fatty acids with FADS

3.4. HFE Gene and Follicle Stimulating Hormone

The study intended to examine the connection between the HFE H63D gene mutation and male

infertility by analyzing its association with different clinical and hormonal parameters (Fig. 9). The number of total infertile men is around 148, age between the 17 to 52 years (mean age 29.6 ± 7.2), were involved after excluding individuals with scrotal pathologies, hormonal treatments, systemic illnesses for example diabetes or the type of anemia, and Y-chromosome minor chromosomal deletions. The study evaluated semen sperm density, sperm motility, sperm morphology, testicular size, and levels of serum like FSH, LH, and total testosterone. Results revealed that men with infertility carrying the

mutation of HFE had significantly higher FSH levels and markedly lower motility of sperm ($36.6 \pm 28.1\%$; $P = 0.01$) compared with non-carriers. In addition, allele frequency analysis showed a noticeable variation between men with total sperm motility below and above 50% ($P = 0.001$, $OR = 0.14$, $95\% \text{ CI} = 0.04-0.44$), as well as between those with abnormal versus normal sperm motility ($P = 0.005$, $OR = 3.11$, $95\% \text{ CI} = 1.41-6.86$). These results help to verify that the mutation of HFE is strongly connected with impaired sperm motility and may play a significant role as a genetic risk factor contributing to male infertility (32).

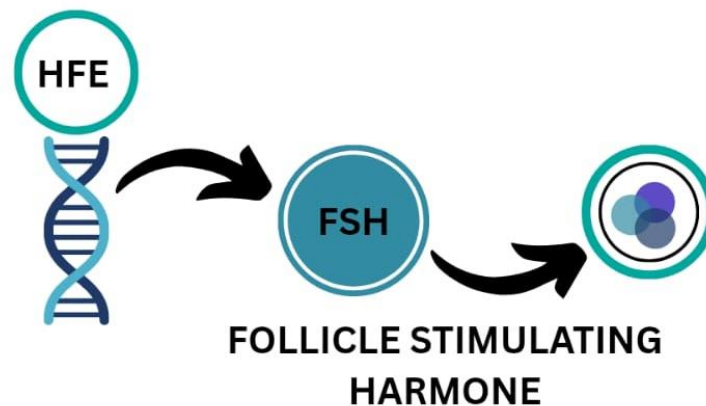


Figure 9. Connection between HFE gene and Male infertility

4. Nutrient-Hormone Interactions

Nutrition strongly have ability to create alteration in the observable characteristics of a dependent genotype, specifically during embryonic and early life stages. there are numerous hormones serves as markers of nutritional status and also their receptors doing a significant responsibility in moderating the result of dietary patterns on numerous genes associated in alterations, development and metabolic processes (33). Nutrition impacts not just only in the production of hormones and metabolic processes it also impacts on hormone receptors, and regulatory processes also occurs as it can be facilitated might by a single nutrient or by complete energy role. Latest researches on the work of early environment affects development via GCs and their receptors, including adult disease (34).

4.1. Folate with thyroid hormone

Thyroid autoimmunity or (AITDs) autoimmune thyroid diseases occur most oftenly that attacks particular organs, which involves Graves' related hyperthyroidism and autoimmune thyroiditis. The key feature of autoimmune thyroid diseases is the penetration of lymphocytes into the butterfly shaped gland in the neck. Auto immune thyroid is characterized by Hashimoto disease, that contains an occurrence rate of about 0.3 to 1.5 per 1,000 people annually. This condition happens approximately 4 to 10 times more frequently in women than in men. Autoimmune thyroid is basically a major contributor to intrinsic hypothyroidism, which is initially indicated by positive serum levels of (TPOAb) and (TgAb), with diffuse low echo areas on thyroid ultrasound (35). Nutritional or dietary patterns are seen to significantly impact the chance of autoimmune

thyroid. Investigations suggests that appropriate consumption or having supplements of vitamin D or selenium, vitamin A, or vitamin B12, iron, magnesium, and vitamin E must help in reduction of the threat of Autoimmune disorder or controls the levels of TPOAb and TgAb. However, recent clinical instructions do not deliver particular dietary suggestions for autoimmune thyroid disorders (36). Folic acid (vitamin B9) is a type of vitamin which is water-soluble which is crucially done a part in one carbon metabolism and metabolism of amino acid (Fig. 10). Folic acid helps in reducing the level of homocysteine (Hcy), by which analysis shows that the supplementations of folic acid can decreases the levels of Hcy by 25%. Deficiency of folate can cause increased

levels of Hcy, elevates the chances of CVDs and different types of autoimmune disorders. Hypothyroidism is repeatedly linked with increased levels of Hcy. In addition, investigations have analyzed that patients suffering from such conditions have reduced folic acid levels, and their hyperhomocysteinemia (HHcy) is correlated along with altered folic acid status. Reduction of Folate levels in the body is directly connected with the risk of various diseases, like iron deficiency, heart disease, or a cancer. Researches also suggested that 16.3% of patients with positive anti-thyroid antibodies facing anemia, with 1.1% having folate deficiency. Moreover, the association between folate and thyroid metabolism remains properly undefined and need further investigations (37).



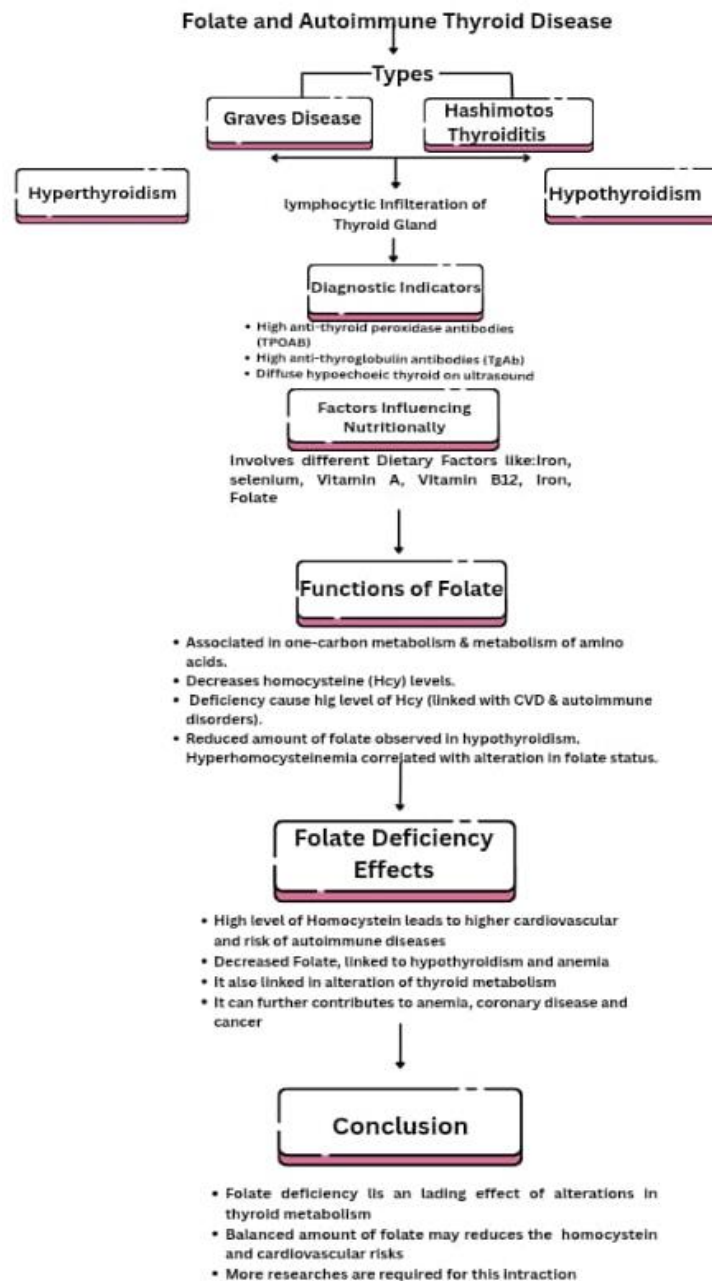


Figure 1.0 Folate interaction with TSH

4.2. Iron with Erythropoietin

Balance or adequate erythropoiesis findings during the production of adequate amount of completely operational fully developed red blood cells that renew aging erythrocytes. For attaining this objective, the spectrum of cell proliferation factors and the elements of iron are essential components which are taken up by precursor cells of erythroid especially for efficient erythrocyte

production (38). Erythropoietin is basically the intricate hormone that is must for productive red cell genesis, and iron is an important mineral needed for oxygen carrying protein formation. EPO allows continuation and proliferation of erythroid early-stage cells by producing intracellular signals leading towards the prevention of apoptosis (Fig. 11). Presence of iron is highly controlled to assure the available supply

for the formation of hemoglobin required during erythropoiesis. Itself iron regulates globin formation at both the transcriptional and translational levels (39). New observations about the intermix between hepcidin, iron availability, and erythropoiesis have designed our understanding of hemoglobin production. Newly

invented erythroid hormone erythroferrone, iron regulatory protein and aconitase shows to perform significant responsibility to regulates erythropoiesis. Innovative treatment agents that regulate iron and erythropoietic regulation are now under advancement (40).

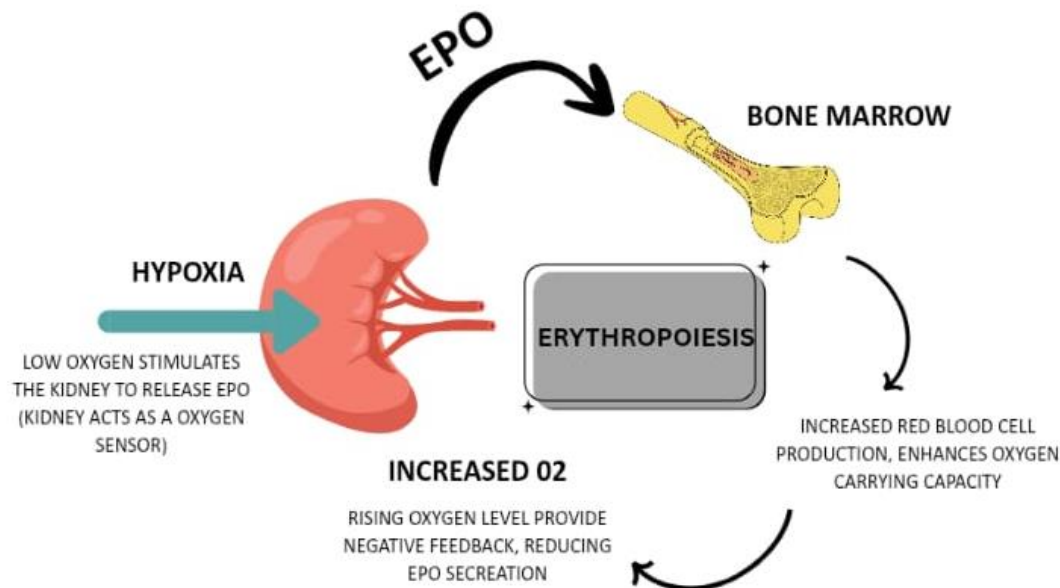


Figure 1.1 Pathway of iron and EPO

4.3. Vitamin D with Calcitonin

Vitamin D shows complicated effects on the human bones such as it helps in the activation of formation of the matrix and maturation of human bones but additionally improves osteoclast activity or it might affect separation of osteogenic precursors. The hormone Calcitonin prevents the primary job of osteoclasts, lowering bone degradation, So, the coupling of D vitamin and the hormone calcitonin may lead to positive bone turnover balance (Fig. 12). The study investigated the assumption that is the long-term administration of high dose vitamin D moderate doses of salmon calcitonin, and balance Ca supplementation could be advantageous in osteoporosis (41). there were 13 women suffering from postmenopausal bone loss was given this special treatment for around 2 to 6 years. No

negative reaction, elevated blood calcium, or excess calcium in urine happened. A noticeable reduction in bone pain was observed. The crack in the bone ratio in 11 patients, vertebral fracture incidence was 240 per 1000 patient years. No changes were observed in the radius using single photon bone densitometry (42).

It is due to only 1 photon, bone density measurement impacts on mostly compact bone, the data results that the intermix of D vitamin and the hormone calcitonin enhances and helps to maintain trabecular bone and protects cortical bone from loss in osteoporosis. Past results suggest that the hormone calcitonin specifically or also along with minor amount of vitamin D enhances density of bones for totally around 2 years. The current data shows a long-term advantageous impacts on the intermix of higher amounts of

vitamin D along with the balance or adequate doses of the hormone calcitonin in post menopause osteoporosis issues (42, 43).

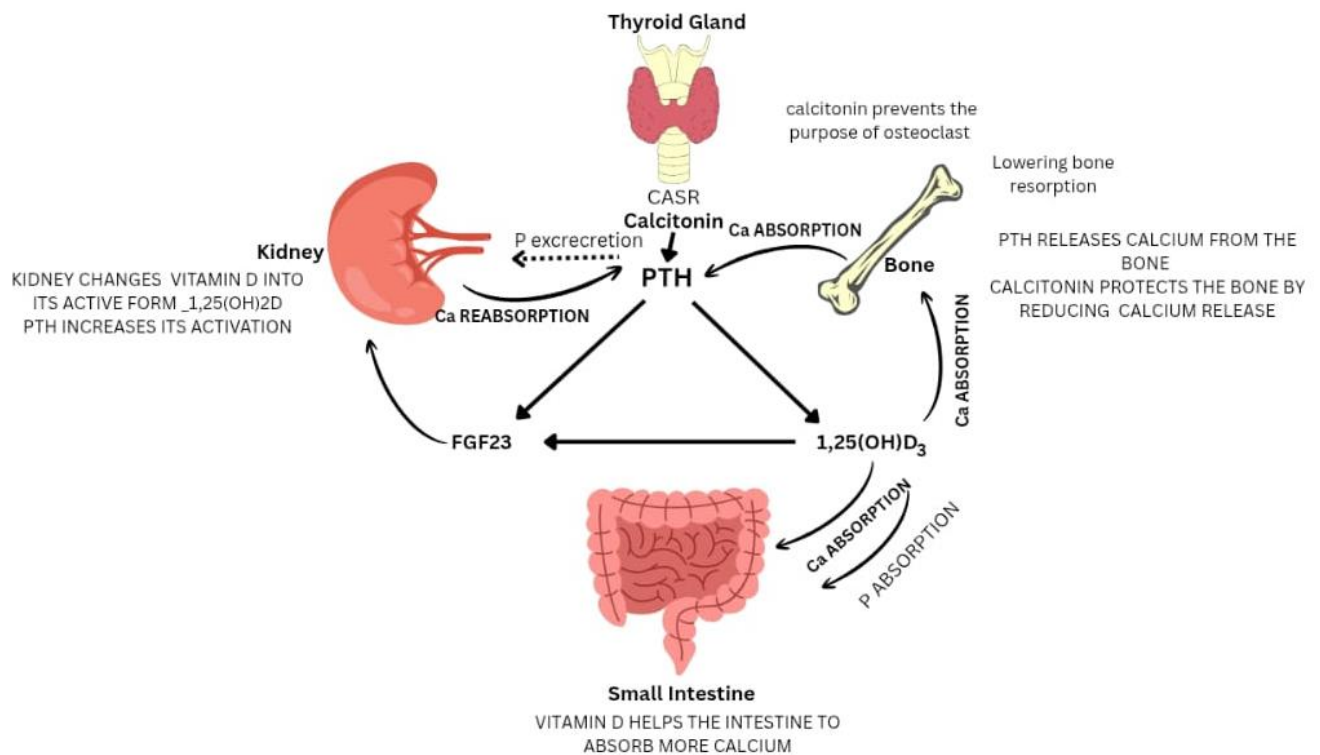


Figure 12. Vitamin D and PTH

4.4. Carbohydrates with Insulin

Defective insulin signaling is a disorder of metabolism which is rising all around the world and it is also associated with few of the most widespread conditions prevalent in modern societies, involve diabetes, CVDs, hypertension, or obesity. Even though therapeutic techniques that helps to manage insulin sensitivity and some are suggested to involve public health strategies to involve modifications in dietary patterns and physical activity are appealing due to their lower cost and risk. We shortly declare some new studies on the functional pathway that influence insulin's various biological activities and investigate the outcomes of carbohydrates on sensitivity of insulin (44). Significantly, we combine some information present related to the effects of plain sugars, starchy carbohydrates involve fiber, slowly

digestible starch involves the basic idea of glycemic index. The present information facilitates the concept that intakes of diets which are high in total amount of carbohydrates does not poorly impacts on insulin sensitivity in compared with high fat diets (45).

Animal studies suggest that plain carbohydrates, in particular type of fructose, have significantly poor effects on different actions of insulin, but those negative impacts have not been shown specifically in human beings (Fig. 13). Higher consumption of non-digestible carbohydrates helps to improve action of insulin and it can also help in the protection from the occurrence of diabetes. The results of dietary patterns with increased or decreased glycemic index on working of insulin are questionable at this present time. For specific results to conclude, predictable researches needs

to be of adequate duration, specifically in targeted populations and evaluate the impact of

physiologically relevant amount of nutrients on specific endpoints of insulin function (44, 46).

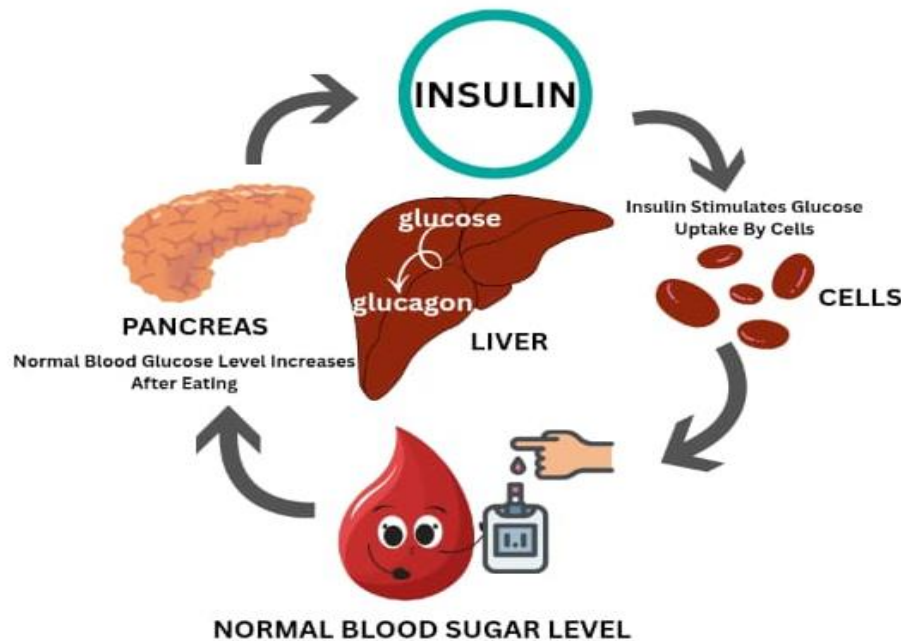


Figure 13. Pathway of Insulin

4.5. Omega Fatty Acids with Insulin

Impaired carbohydrate metabolism is significantly associated with fat consumption of animals and it is the most common practice in those populations who are habitual of eating beef or red meat. Along with these, all those people who are ingesting diets composed of essential fatty acids must have a reduced frequency of diabetes. This is basically a crucially apparent in those areas of the world whose people's diet is greatly rich with omega 3 fatty acids or healthy fats. It is proposed that the diet enriched with good amount of fatty acids increase incorporation of these fatty acids into b cells phospholipid membrane thereby causes

enhancement in secretion of insulin. It is also proved that same alterations developed within the membrane of phospholipid in of peripheral cells composition. Such alterations in the membrane phospholipids would conceptually enhances both receptors of insulin binding receptors affinity and responsiveness, so the enhancement of glucose uptake across the cell membranes. Boosted secretion of insulin and increased sensitivity of insulin stimulated with long term omega 3 or healthy fatty acid consumption would supportively reflects the metabolism of carbohydrates and increase of homeostasis of glucose (46, 47) (Fig. 14).

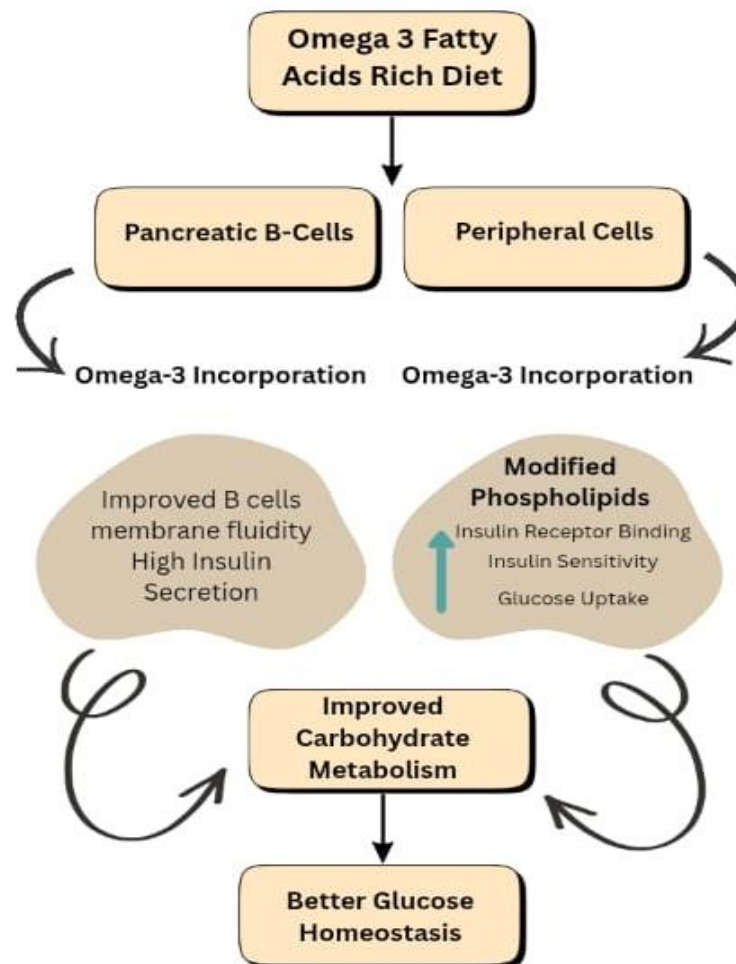


Figure 14. Omega Fatty Acids with Insulin

4.6. Hormonal and Metabolic interactions with Leptin

Body mass excess is the originated from an abnormal lipid stored in white adipose tissue. Latest studies applying genetically obese rodent models has associated with a significant leptin contribution as a regulator of obesity. Leptin is a hormone composed of peptides, synthesized under the control of the obesity gene (*ob*), that is basically secreted by adipocytes and serve a significant contribution in food intake regulation, caloric expenditure and body fat. Receptors of Leptins are synthesized in the central neural network particularly in the afferent satiety regions of the hypothalamus and also in the organs of peripheral system for example in fat mass, skeletal muscle tissue, pancreatic β -cells and hepatic tissue,

that indicates the autocrine and paracrine responsibility of leptin in regulating energy balance (48). In humans, an advanced well-regulated circadian rhythm in the release of leptin is seen along with the increased amount in the middle of the night normally results from progressive hyperinsulinemia of entire day. Leptin plays a double role in maintaining body mass. Leptin demonstrates on overall body fat mass conversely in terms of energy deficit and energy surplus, the progressive alterations in role of plasma leptin concentration like a detector of energy status and reflects the efferent pathways controlling the energy regulations (Fig. 15). Numerous outcomes of leptin on metabolism are linked through association with Insulin and joint actions along with cholecystokinin. Along with the

biological processes, leptin can be impacting medical conditions like adiposity connected to

bone issue, oxidative damage or in abnormal cell division in the body (49).

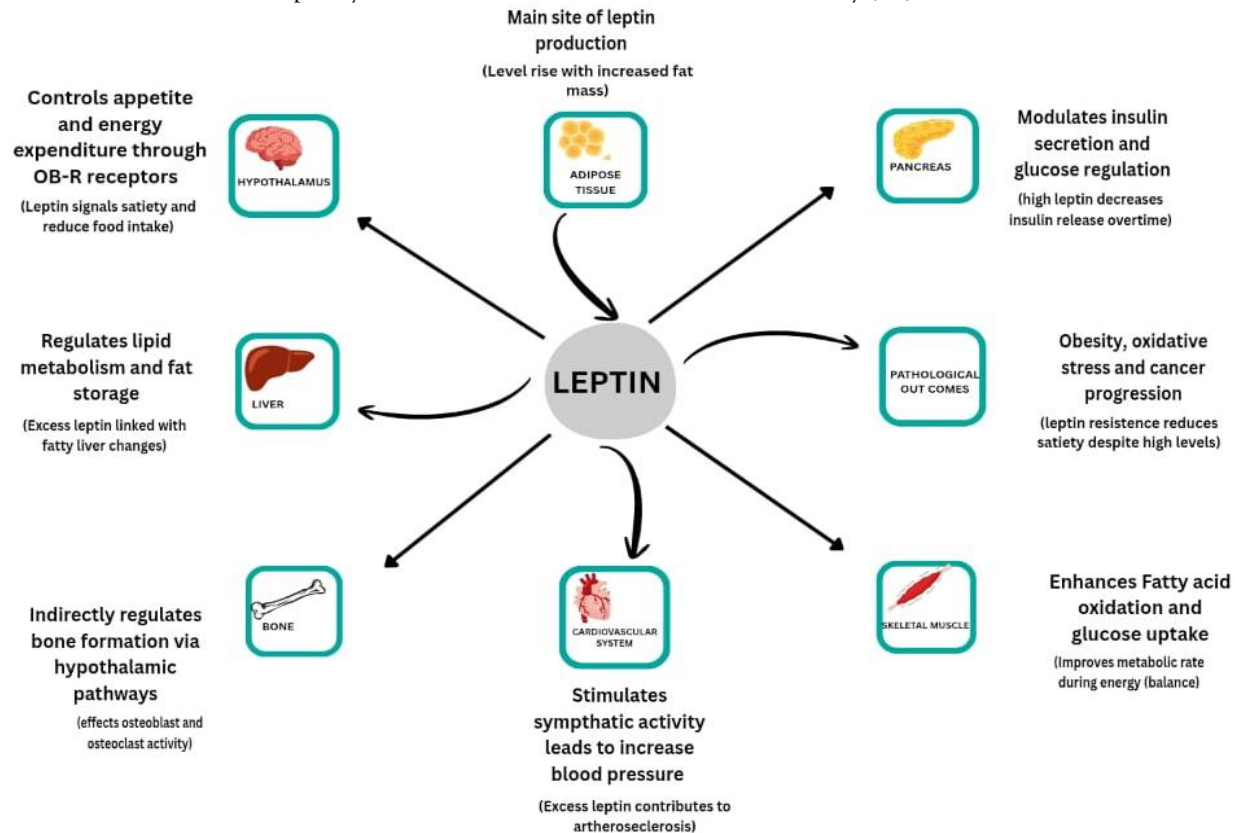


Figure 15. Main stream of Leptin

5. Conclusion

A fundamental framework for comprehending the complex control of human metabolism and health is the nutrient-gene-hormone axis. In addition to being metabolic substrates, nutrients actively influence enzyme activity, receptor activity, cellular signaling, gene regulation, and epigenetic alteration. Hormones including insulin, leptin, erythropoietin, and calcitonin integrate these signals to maintain homeostasis and modulate disease susceptibility, while genetic variations like those in the MTHFR, HFE, VDR, TCF7L2, and FADS clusters significantly impact individual responses to dietary inputs. When evaluating dietary interventions, this axis as a whole highlight the importance of taking into account both genetic background and hormonal milieu. Future research should focus on longitudinal and mechanistic studies that bridge molecular insights with clinical outcomes, ultimately encouraging the

advancement of targeted, customized dietary approaches to optimize metabolic health and prevent chronic disease.

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