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# Obesity, Diabetes Mellitus, and Vascular Impediment as Consequences of Excess Processed Food Consumption

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## Abstract

Regular intake of ready-to-eat meals is related to obesity and several noninfectious illnesses, such as cardiovascular diseases, hypertension, diabetes mellitus (DM), and tumors. Processed foods contain high calories and are often enhanced with excess refined sugar, saturated and trans fat, $Na^+$ and phosphate-containing taste enhancers, and preservatives. Studies showed that monosodium glutamate (MSG) induces raised echelons of oxidative stress, and excessive hepatic lipogenesis is concomitant to obesity and type 2 diabetes mellitus (T2DM). Likewise, more than standard salt intake adversely affects the cardiovascular system, renal system, and central nervous system (CNS), especially the brain. Globally, excessive utilization of phosphate-containing preservatives and additives contributes unswervingly to excessive phosphate intake through food. In addition, communities and even health experts, including medical doctors, are not well-informed about the adverse effects of phosphate preservatives on human health. Dietary phosphate excess often leads to phosphate toxicity, ultimately potentiating kidney disease development. The mechanisms involved in phosphate-related adverse effects are not explainable. Study reports suggested that high blood level of phosphate causes vascular ossification through the deposition of $Ca^{2+}$ and substantially alters fibroblast growth factor-23 (FGF23) and calcitriol.

**Categories:** Cardiology, Endocrinology/Diabetes/Metabolism, Epidemiology/Public Health
**Keywords:** blood vessels, phosphate, preservatives, food additives, freshly, oven to table, precooked food, prepackaged food, unhealthy food, junk food

## Introduction And Background

Current studies regarding the consumption of ready-prepared foods and their consequences reliably reported a significant correlation between obesity, several noninfectious illnesses (noncommunicable diseases (NCDs)), cardiovascular diseases, hypertension, several types of malignancies, and many more [1-5]. For the last few decades, obesity has appeared as a significant public health issue globally [6]. One US study reported that 35.65% of the adult population was obese in 2009-2010, and no statistically substantial transformation was observed when equated with 2003-2008 [5]. Obesity linked with high consumption of ready-to-eat meals equally exists in low- and middle-income countries (LMICs) and high-income countries (HICs) [7-12]. The World Health Organization (WHO) stated in 2020 that “39% of adults aged 18 years and over were overweight in 2016, and 13% were obese.” Furthermore, the WHO outlined overweight as a “body mass index (BMI) more than or equivalent to 25, and obesity as a BMI above or equally 30” [13]. Additionally, it has been apprised that by 2030, 38% and 20% of the overall global grownup people will be overweight and obese, respectively [14]. The current manuscript will elaborate on the relation of fast-food consumption with obesity and its cardiovascular relevance. Processed food contains a high quantity of calories. These foods often contain excess refined sugar, saturated and trans fat, $Na^+$ and phosphate-containing taste enhancers, and preservatives [15,16]. Most processed food contains highly refined carbohydrates that alter insulin physiology and promote adipose tissue deposition [17,18]. Studies have revealed that extremely treated foodstuffs with extra lipid substances and sugar-sweetened beverages change neurobiological reward pathways involved in eating behaviors, taking over the brain’s emotional and motivational pathways and encouraging food cravings and excessive food intake [19-21].

### Materials and methods

This review explains the probable processes relevant to processed food and obesity, linking diabetes mellitus (DM) with vascular impediments and implications. The literature search was based on electronic archiving through Google Scholar, ScienceDirect, PubMed, and ResearchGate. The listing of references of allied papers was checked to obtain additional literature. Keywords include diabetes, obesity, food additives, food preservatives, processed foods, ready-to-eat foods, phosphate toxicity, vascular calcification, cardiovascular diseases, renal impairment in phosphate toxicity, and mitochondrial dysfunction. Papers published earlier than 2000 and written in languages other than English were discarded, as well as those papers with full texts that are not available through interlibrary collaboration. Before inclusion in this study, a manual check of

appropriate articles was conducted. Duplicate articles were removed carefully. After the separate evaluation and addition of the nominated pieces of literature, a supplementary discussion was conducted to sort out every doubt, issue, error, or bias concerning particular articles.

# Review

## Brief portrayal regarding obesity and ultra-processed food

One recent British study revealed that eating ultra-processed food regularly statistically significantly increases the possibility of obesity [22]. The British National Diet and Nutrition Survey (2008-2016) revealed through model analysis that among British people who eat prepackaged food, the highest (¼) group was correlated with 1.66 kg/$m^2$ greater BMI, 3.56 cm higher waist circumference (WC), and 90% elevated odds for living with obesity than the bottommost group [23]. Similarly, another Korean study revealed that women who derived 26.8% of the total calories of daily need from extremely processed food (top ¼) had 0.61 kg/$m^2$ inflated body mass index, 1.34 cm raised WC, 51% high-level odds of the presence of obesity (BMI > 25 kg/$m^2$; odds ratio (OR): 1.51; 95% confidence interval (CI): 1.14-1.99; p = 0.0037), and 64% greater odds of central obesity (men: WC ⩾ 90 cm; women: WC ⩾ 85 cm; OR: 1.64; 95% CI: 1.24-2.16; p = 0.0004) when compared with lowest ¼ eaters of unhealthy junk food [24]. In the same way, one recent Australian study reported that a diet containing a lion's share of convenience food is statistically significantly (p ⩽ 0.001) correlated with obesity. This study developed adjusted results and stated that those Australians who eat the highest ¼ ultra-processed food had statistically significantly (p > 0.05) more BMI and WC and had additional odds for obesity and abdominal obesity than individuals of the lowermost ¼ [25]. The US population who derived 74.2%-100% calories from ready-to-eat junk food was correlated with 1.61 parts of raised BMI, bigger WC, and central obesity than those who derived 0%-36.5% energy from similar convenience food [26]. A Brazilian study reported an almost comparable picture. The adjusted result said that Brazilians consume the highest portion of prepackaged unhealthy food, and a high BMI level increases the possibility of developing statistically important additional WC than individuals who consume a minor portion [27]. Therefore, it is globally well known that prepackaged junk foods, because of their high amounts of sugar, $Na^+$, and fat, cause obesity and several NCDs [1,7,16,28-32].

*A Brief Depiction Regarding Food Additives and Preservatives*

Foodstuff additions (preservatives, artificial sweeteners, emulsifiers, dyes, and color) are commonly utilized throughout the globe [33-35] to increase a vendible quality by increasing aroma, color, texture, appearance, and taste [36]. These agents are frequently correlated with multiple health hazards with hypersensitive reactions, e.g., diarrhea, abdominal discomfort, and colicky pains (digestive); nervous hyperactivity, insomnia, and irritability; glucose intolerance in healthy human subjects (endocrine); and dysbiosis [37-40]. Commonly used food additives are cheap [41] and widely used in commercial food processing. The most commonly used food additives, including preservatives, are monosodium glutamate (MSG), phosphate, synthetic food coloring agent, $NaNO_2$, high-fructose containing liquid, synthetic sweetening agent, $C_{23}H_{23}FN_4O_7Zn$ (Irish moss), $C_7H_5NaO_2$, trans-unsaturated fatty acids, bacterial polysaccharide, synthetic seasoning agent, fermenting fungus, NaCl, $C_3H_6O_2$, disodium pyrophosphate ($Na_2H_2P_2O_7$), benzene-based carboxylic acid ($C_6H_5CO_2H$), $C_4H_6NaO_4$-, and phosphorus and its congeners [42-44]. The currently FDA-approved food and color lists can be retrieved at https://www.fda.gov/food/food-ingredients-packaging/food-additive-listings and https://www.fda.gov/industry/color-additive-inventories/color-additive-status-list, respectively.

*Monosodium Glutamate in Food and Health*

MSG, a $Na^+$ salt of α-amino acid ($C_5H_9NO_4$), is one of the most widely utilized taste enhancers by food manufacturers throughout the globe. MSG gives an exclusive flavor to the foodstuffs termed "umami" or "savory taste," unlike the four principal tastes sweet, sour, salty, and bitter [45]. Besides, food safety regulatory organizations think MSG ingestion to be harmless, although considerable preclinical and clinical research has called into question MSG health risk exclusively subsequent to chronic ingestion.

Glutamate has several physiological functions (Figure *1*), such as acting as a substrate for energy creation in the intestinal epithelial cell lining, an intermediate in the cellular protein metabolic process, and the forerunner of important metabolites such as glutathione (GSH) (oxidative stress modulator) or N-acetyl glutamate (metabolic regulator) and also a central nervous system (CNS) excitatory neurotransmitter [46]. Glutamate receptors are expressed in other neuronal cells, including lymphocytes, thymocytes, and neutrophils [47]. An experimental study showed that MSG resulted in the development of obesity within six days because of a shoddy but insistent inflammatory condition, going along with pro-inflammatory cytokine step-up and suppressed adiponectin gene process, which is probably related to being overweight [48]. Moreover, MSG-induced enhanced strata of oxidative stress and extreme hepatic lipogenesis are encouragingly connected to obesity and T2DM [49]. Cellular hyperexcitability could be an essential contributing and pathogenic factor of cancer through the stimulation of voltage-gated $Na^+$ passage, excitatory ligand glutamate, and non-neuronal excitative receptors [50].

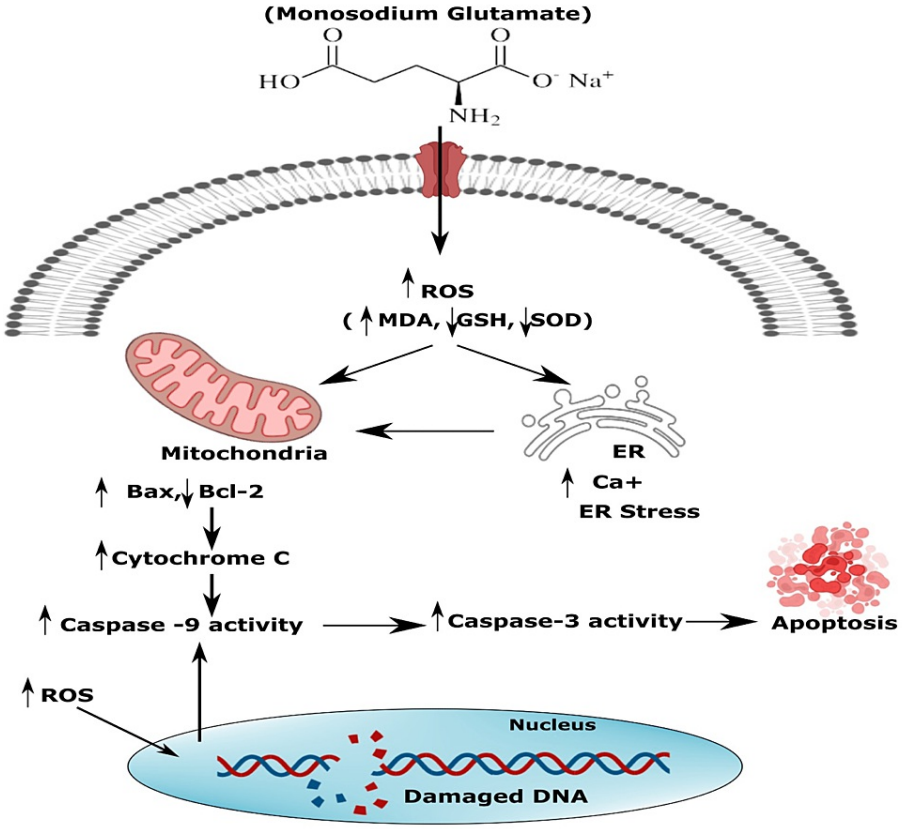


**FIGURE 1: Molecular mechanics of cellular death provoked by MSG.**

MSG: monosodium glutamate; ROS: reactive oxygen species; MDA: malondialdehyde; GSH: glutathione; SOD: superoxide dismutase; ER: endoplasmic reticulum

Image credit: Susmita Sinha

*Sodium Chloride (Salt) as Food Preservative*

Salt (sodium chloride) has been used as a food preservative conventionally, limiting the development of foodborne pathogens and decomposition organisms by reducing water content. $Na^+$ is an important nutrient for sustaining well-being when consumed moderately, and excess intake causes several health complications, such as cardiovascular disorders [51]. Bread, cheeses, processed meat, soy sauce, bacon, and spreads are the leading causes of high $Na^+$ in modern foodstuffs [52]. NaCl is vital in ultimate taste enhancement, consistency, long shelf life, customer palatability, and germ-free and reasonable preparations of several treated meat foodstuffs [53]. In recent decades, preclinical, clinical, and epidemiological research have shown substantial and clinically important relations in collecting health-related problems for salt consumption above 4 g per day. Furthermore, high salt intake adversely affects vasculature, cardiovascular, renal, and central nervous systems, especially the brain [54].

*Source of Phosphorus in Diet*

Phosphorus is an essential micronutrient that originates predominantly from the phosphorus-comprising complex $PO_4^{3-}$ and is absorbed in the intestine from consumed food and food additives and circulated in the blood as inorganic phosphate (Pi). Again, plant sources (hard-shelled edible fruits, legumes, and whole grains) and animal sources (dairy, flesh, fish, and eggs) of phosphorus are available adequately as foodstuffs in nature. The natural phosphorus supply is in the crystalized state of carboxylic acid derivatives and hydroxyapatite [55,56]. Individuals who take vegetarian diets express reduced serum phosphorus echelons and declined fibroblast growth factor-23 (FGF23); additionally, plant-origin phosphorus is often associated with a salt of phytic acid (myo-inositol 1,2,3,4,5,6-hexakis dihydrogen phosphates), poorly assimilated (<40%) through our digestive tract [57]. However, studies showed that excess phosphate is one of the more important and dangerous reasons for cardiac problems and can even lead to death with or without negotiated renal function [58,59]. Elevated levels of $PO_4^{3-}$ are commonly linked with ossification of vessels,

cardiovascular problems including left ventricular failure (LVF), defective endothelium function, and progression in declined kidney function [60].

*Phosphate Homeostasis in Healthy Adults*

The normal phosphorus level is 2.5-4.5 mg/dL (0.81-1.45 mmol/L). High serum levels of phosphorus in our system are described as plasma phosphate over 4.5 mg/dL due to illness or too much consumption of food [61]. Equilibrium in $PO_4^{3-}$ is regulated through the intestinal absorption of dietary sources, bony storage and release, and renal elimination. The principal endocrine control of the phosphate biotransformation process includes calcitriol, parathyroid hormone (PTH), and FGF23. In addition, about 60%-70% of dietetic phosphorus goes to the blood through the small gut, mostly through an energy-dependent Na/Pi symport [62]. Calcitriol excites gastrointestinal Na/Pi symport, thus augmenting $PO_4^{3-}$ absorption, but calcitriol controls only 30% of intestinal absorption [63].

Typically, the quantity of $PO_4^{3-}$ eliminated through the kidney usually equals that absorbed through the intestinal epithelial wall. Again, PTH decreased $PO_4^{3-}$ reabsorption from the proximal convoluted tubule by inferring Na/Pi cotransporters, although PTH promotes bone resorption and raises serum $PO_4^{3-}$ levels among individuals with healthy renal physiology. Nevertheless, PTH has a dominant role in renal function in excreting $PO_4^{3-}$, which ultimately reduces its concentration in blood [64]. Another regulator, FGF23, is generated by osteocytes, and osteoblasts are recognized as the primary cause of excessive phosphate excretion in urine and are accountable for regulating $PO_4^{3-}$ [65]. Raised urinary $PO_4^{3-}$ elimination and declining phosphate absorption from the gut occur due to reduced calcitriol synthesis by hindering 1α-hydroxylase [66]. FGF23 requires a Klotho cofactor to bind its receptor (FGFR-1c) to exert its bioactivities. Thus, FGF23 is effective only in tissues that can yield Klotho (distal convoluted tubule of the kidneys, parathyroid glands, and the brain). FGF23 and α-Klotho, parathormone, calcitriol, and a number of phosphate transporters in the renal and gastrointestinal systems regulate phosphate homeostasis. Again, genetically persuading hyperphosphatemia origins widespread tissue damage, especially in essential organs [67].

Researchers found that a transmembrane protein Klotho has various possessions on the physiological control of inorganic electrolytes, principally $Ca^{2+}$ and $PO_4^{3-}$, and energy biotransformation through the hormonal action of FGF [68]. Klotho is expressed in several organs such as kidneys (distal convoluted tubules), parathyroid glands, liver, brain, and adipose tissue [69]. Among the FGFs, FGF23 can hinder the actions of 1α-hydroxylase and Na/Pi symporter in the kidneys from affecting the general systemic $PO_4^{3-}$ balance (Figure *2*) [70].

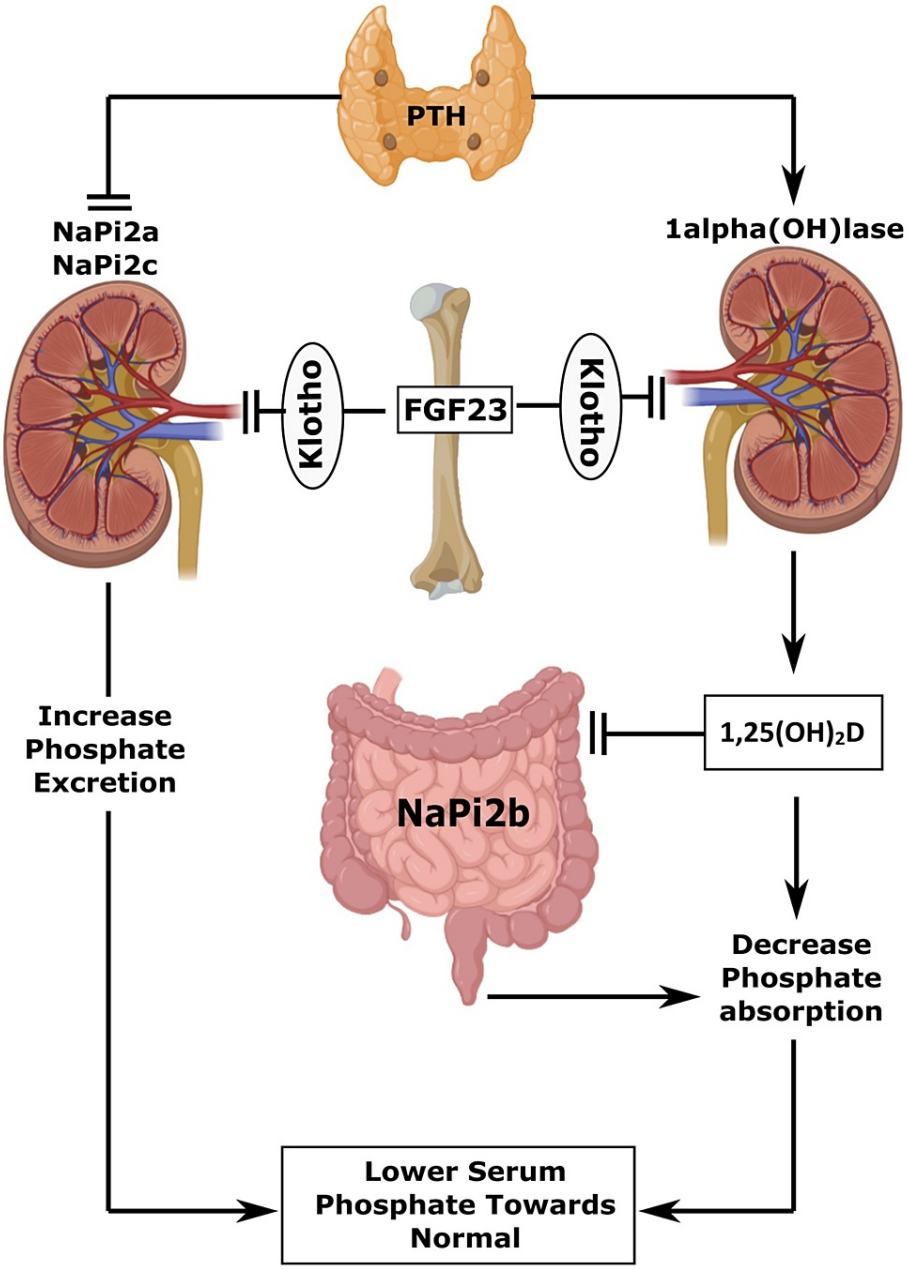


**FIGURE 2: Diagrammatic representation of phosphate balance in humans.**

PTH: parathyroid hormone; FGF23: fibroblast growth factor-23

Image credit: Susmita Sinha

*The Use of Inorganic Phosphate as a Food Preserver*

The addition of $Na^+$ salt in food was practiced through ancient times and as early as 5,000-10,000 years [71]. With the advancement of food knowledge, people have started to avoid sodium salt as a food preservative and additive to protect themselves [72]. The increasing severity of hypertension and its prevalence due to high salt-containing food intake in LMICs and high-income countries (HICs) results in the wide application of inorganic $PO_4^{3-}$ as a foodstuff preserver [73-75]. In the human diet, a significant source of phosphate is foodstuffs originating from milk, fish, and other types of flesh. Approximately 40%-60% phosphate absorption occurs in the gut, which is then carried into the body fluid and distributed across the body, including the renal system [76]. It has been observed that inorganic phosphorus/phosphate is used as preservatives in as high as 100% of factory-processed diets [77]. Factory-processed foods frequently contain

food preservatives, often hidden as hazardous toxic elements. In addition, community people and health professionals are unaware of phosphate-containing food preservative-induced toxicity [78]. Excessive phosphate intake results from adding more phosphate to foods and unavailability of hyperphosphatemia-related sufficient information. Previous reports showed that consuming treated foodstuffs (containing inorganic phosphates as preservatives) is associated with several noninfectious illnesses such as T2DM, hypertension, heart muscle dysfunction, obesity, and carcinomas, which are increasing globally [79-81].

*Obesity and Insulin Resistance*

The modern lifestyle, especially among urbanized in both minimal to average earning and higher earning states, is pervaded by excessive prepackaged food, containing high calories, and is often correlated with low-energy-consuming work [82-85]. High calories with low fiber-containing food and modern jobs that require sitting for a prolonged time that primes to increase weight and fat deposition determine a prevaricate energy equilibrium [86-89]. Thereby, upsetting energy balance frequently disrupts the homeostasis of the liver and adipose tissue. This is expected to be accomplished by instigating the pro-inflammation of immune cells heading toward peripheral insulin resistance (IR) [90-96]. These pathologies ultimately culminate in metabolic syndrome (MetS), represented as multiple noncommunicable diseases, principally abdominal or central obesity, chronically raised blood pressure, dyslipidemia, IR/impaired insulin glucose metabolism, and steatohepatitis [97-99].

Over the last 25 years, multiple studies reported that fatty tissue hyperplasia and hypertrophy frequently correlated with the negative impact of adipose tissue metabolic equilibrium [100,101]. Additionally, various studies said that tumor necrosis factor-alpha (TNF-α) was significantly raised among obese individuals, eventually rooted in IR, and surfaced the notion of an inflammatory element of obesity [86,102-105]. This inflammatory pathological issue is known as “meta-inflammation,” a clinical disease of chronic, low-grade inflammation noticed among obese patients [106,107]. This subthreshold inflammation, mainly observed in white adipose tissue (WAT), causes regular initiation of the innate immune system and leads to IR, impaired glucose tolerance (IGT), and T2DM [108-110]. WAT as lipids is the biological location of energy storage and is freshly documented for several important physiopathological activities [111-115]. Multiple studies reported that the WAT of overweight individuals is frequently penetrated by macrophages, which may act as a focal basis for the localized formation of pro-inflammatory cytokines [107,116-118]. WAT has generated a diverse spectrum of inflammatory particles, including TNF-α and interleukin-6 (IL-6), negatively impacted locally and systematically [110,119,120]. These pro-inflammatory cytokines originate IR and T2DM in fatty tissue, striated muscle, and the liver by impeding the insulin signal system, causing defective insulin signaling and glucose uptake [121-123]. Furthermore, cytokines (e.g., adipokines, hepatokines, inflammatory cytokines, myokines, and osteokines) also subsidize anomalous lipid metabolism [124-126].

Leptin is one of the adipokines produced by adipocytes; increasing adipose tissue mass elevates leptin concentration in plasma [127]. Again, IL-6 hinders the expression of insulin receptors and adiponectin. A recent study suggested that TNF-α is concerned with the inflammatory reactions that link centripetal adiposity by means of IR and inhibit the insulin-stimulated tyrosine kinase activity of the insulin receptor and substrate-1 (IRS-1), consequently decreasing insulin-dependent glucose transporter (GLUT-4) in the cells [128]. TNF-α also activates sphingomyelinase, thus stimulating ceramide production and accumulation in adipose tissue, inhibiting adiponectin secretion [129]. Hormone-sensitive lipase (HSL) acts as an intracellular neutral lipase that hydrolyzes several lipid esters, such as hydrolyzing diacylglycerol (DAG) into monoacylglycerol (MAG) or entirely with the let-out free fatty acid (FFA). The insulin is switched on principally by β-adrenergic catalyst force and rendered inoperative. However, it requires phosphorylation and translocation into lipid driblet to clarify its pursuit. Thus, the discharge of fatty acids is restricted in raised glucose concentrations [130], as insulin is unable to hinder HSL in an insulin-resistant state, causing an elevated FFA accumulation [131]. Additionally, outlying tissues started utilizing FFAs in β-oxidation as a power generation process or a substratum to produce additional lipids. Further lipid deposition in skeletal muscle and the liver accounts for the initiation of IR [132]. In T2DM, insulin sensitivity is declining. Throughout the aforementioned condition, the hormone becomes futile and is primarily opposed by hyperinsulinemia to continue glucose equanimity. Ultimately, insulin manufacturing declines progressively, and T2DM occurs. Researchers found that T2DM patients have more BMI with a higher body fat percentage, and increased adiposity in obese individuals tends to develop metabolic syndrome, T2DM, and cardiac morbidities [133]. This augmented adipose tissue mass encourages IR through many inflammatory processes, amplified FFA discharge, and adipokine dysregulation, resulting in T2DM.

A study showed that ingesting prepackaged edibles increases foodstuff-related chronic illnesses such as overweight, obesity, T2DM, and hypertension [134]. Excess weight and obesity result from additional consumption of sugar-sweetened beverages containing high calories and high phosphates [135]. Food additives and preservatives improve the taste, and the desire to take processed foodstuffs is greater, resulting in obesity [136]. Again, highly flavorful processed edibles stimulate the brain’s reward and motivation pathways, raising the possibility of seeking processed food and its consumption [137]. The peroxisome proliferator-activated receptor (PPAR) family is related to the energy-yielding metabolic process. The nuclear receptors PPARα, PPARδ, and PPARγ act as lipid sensors regulating the expression of several genes crucial for controlling energy metabolism [138]. PPARγ increased Klotho expression during the early period of adipocyte differentiation. α-Klotho is a humoral factor that overpowers growth factor

receptors such as insulin and insulin-like growth factor-1 (IGF-1) [139]. In addition, fetuin-A, a blood serum glycoprotein generated by the liver, can attach to the β subunit of the insulin receptor, jamming the metabolic arm of insulin action, thus hindering insulin-dependent activation of the receptor. This disruption of fetuin-A mediated insulin receptor control in defective glucose disposal, IR, and fatty liver [140].

*Food Additive and Preservative Adversaries on Vascular Physiology*

Factory-made food contains added sugar and fat and holds several additional molecules to rise deliciousness, adjust consistency, and extend durability. These supplementary goods are together termed foodstuff additives [141]. Foodstuff additives must comply with rigorous safety tests to determine their possible adverse impacts on human health, following national and international guiding principles [142,143]. Vascular pathology is often instigated using dyslipidemia and hyperphosphatemia [144-146]. Statins have been reported globally for their effective management of dyslipidemia [147-149], whereas there are still no appropriate therapeutic options for treating hyperphosphatemia [150,151].

In contrast, tangential colloidal nanoparticles consisting of crystalized fetuin-A attached with $Ca_3(PO_4)_2$ in the blood had been notified to be the originator of vascular injury and the formation of solidified clumps in soft tissues [152]. Hyperphosphatemia has been related to death, cardiac events, and vascular ossification in human studies for the last few years [153]. Adverse outcomes from increased phosphate are incompletely understood; until now, evidence recommends an immediate influence of $PO_4^{3-}$ on vascular ossification and FGF23 and calcitriol transition.

Inorganic phosphate has numerous physiological functions, for instance, skeletal development, bone mineralization, adenosine triphosphate (ATP) generation, plasma membrane probity conversion, cell signaling (control of subcellular procedures over protein phosphorylation of crucial enzymes), signal transduction, nucleotide metabolism, enzyme control system by nucleic acids, acid-base equilibrium preservation from end to end protecting effect in urine, and platelet accumulation [154]. Again, inorganic phosphate is mainly needed to keep up essential functions and is frequently obtained from foodstuffs containing organic phosphorus. Foodstuff preservers having inorganic phosphate are absorbed solely and readily (80%-100%) from our intestines [155]. Researchers revealed that persistent intake of mineral phosphate started accumulating in the different body systems, and high plasma concentration of phosphate can cause a mess with the hormonal regulation to maintain balanced phosphate echelons in physically fit people [156].

*Phosphate and Mitochondrial Dysfunction*

Mitochondria are membranous organelles that produce ATP by transforming glucose to provide cell nourishment [157]. Inside the mitochondrion of β-cells of islets of Langerhans of the pancreas, ATP formation controls insulin secretion, and membranous transportation of inorganic phosphate for ATP formation ensues by type III $Na^+$-dependent cotransporters PiT1/2 [158]. In vitro experimentations on cultured β-cell (INS-IE) and pancreatic islet cells have revealed that concentrations of inorganic phosphate outside the cells (1-5 mM) prompted mitochondrial malfunction; in addition to this, it was observed that depressed ATP synthesis and rise of ROS related to low insulin content decreased insulin release and increased endoplasmic reticulum (ER) stress [159]. Investigators found that the collection of higher concentration of $Ca_3(PO_4)_2$ inside the mitochondrion is similarly connected to the entrance of the mitochondrial permeability transition pore (mPTP), a protein complex involving the mitochondrial membranes, and space allows substances equal to 1500 Dalton size to pass in and leave the mitochondrial milieu [160]. This invasion can cause distension and disruption of the external mitochondrion membrane and discharge mitochondrial proapoptotic features, subsequent in necrotic or apoptotic cell death [161]. Again, free $Ca^{2+}$ hitched higher inorganic phosphate content and excessive calcium-phosphate product formation in serum [162].

*Vascular Calcification*

Vascular smooth muscle cells (VSMCs) are essential in the pathology of vascular ossification. VSMCs may turn into bone-forming and cartilage-forming cells in the progression of stress. Osteoblast-like cells that comprehend hydroxyapatite crystals look as if in the extracellular matrix in the course of vascular smooth muscle ossification (Figure *3*) [163].

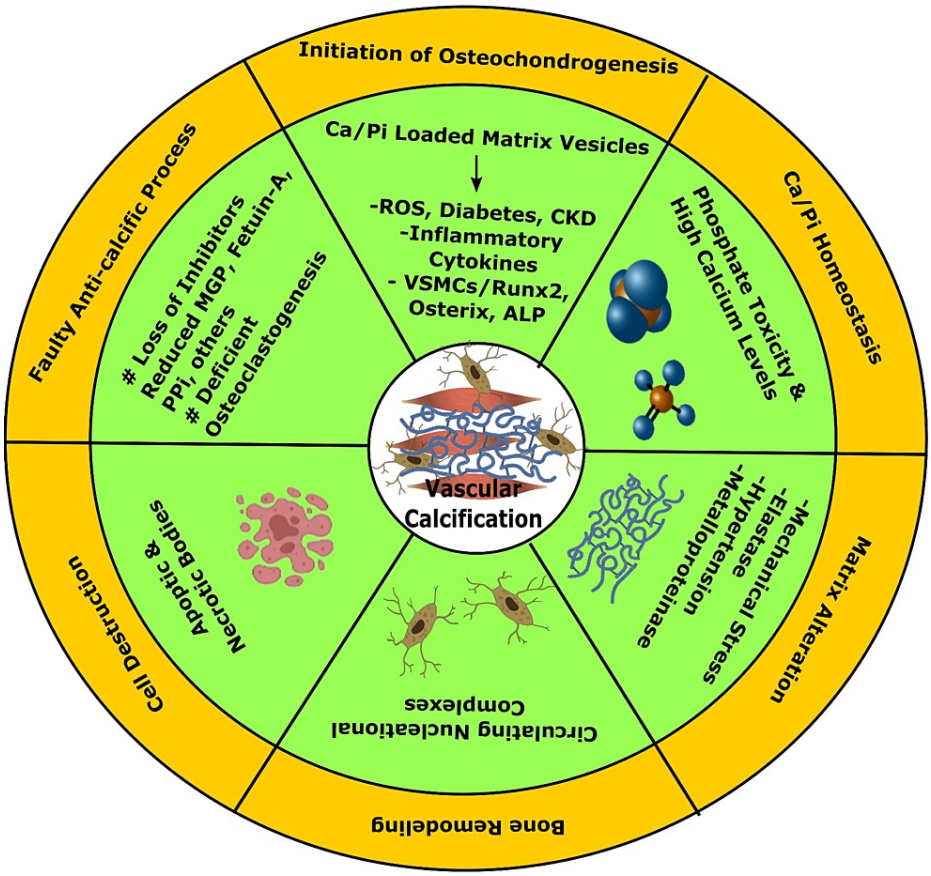


**FIGURE 3: Mechanisms for vascular calcification.**

(1) Faulty anti-calcific process due to lack of expressed mineralization inhibitors, (2) product of vesicular matrices act as a nest for $Ca_3(PO_4)_2$ deposition initiating the osteochondrogenic process, (3) necrotic debris from cellular death by apoptosis perform as nucleation of apatite, (4) irregular Ca/Pi balance sediments $Ca_3(PO_4)_2$ hydroxyapatite, (5) nucleational complexes help deranged mineralization, and (6) matrix alterations by biodegradable irritants are also engaged in vascular calcification.

MGP: matrix Gla protein; PPi: inorganic pyrophosphate; ROS: reactive oxygen species; CKD: chronic kidney disease; VSMCs: vascular smooth muscle cells; ALP: alkaline phosphatase

Image credit: Susmita Sinha

Vessel ossification is of two types: one is intimal calcification, and the other is medial calcification. Intimal calcification may be responsible for atherosclerosis and chronic inflammation, and VSMCs are converted to bone-forming cells. In addition, medial layer ossification might cause elastin degradation, extracellular matrix remodeling events, and increased phosphate in the blood, resulting in chronic kidney disease (CKD), hypertension, and T2DM [164]. The factors involved in facilitating and suppressing vessel ossification are listed in Table *1* [165]. The physiological calcification process begins with accumulating the cell derivative matrix vesicles into the extracellular matrix. Hydroxyapatite crystal deposits are observed in vivo in a human being, a vascular cell model (Figure *4*) [166].

| Facilitators | Suppressors |
|---|---|
| BMP2, BMP4, and BMP6 | MGP |
| Osteocalcin | Osteopontin |
| Alkaline phosphatase (SOX9) | Osteoprotegerin |
| | Vitamin K |
| Osterix | Magnesium |
| MMP2, MMP3, and MMP7 | BMP7 |
| Runx2 | Fetuin-A |
| $Ca^{2+}$ | Klotho |
| $PO_4^{3-}$ | PTH |
| $C_6H_{12}O_6$ | Pyrophosphate |
| Advanced glycation end products | Carbonic anhydrase |
| Oxidized low-density lipoproteins | |
| Collagen I | |
| RANKL | |

**TABLE 1: Chief facilitator and suppressor elements concerned in vessel ossification.**

BMP: bone morphogenetic protein; MGP: matrix Gla protein; MMP: matrix metalloproteinase; BMP7: bone morphogenetic protein 7; Runx2: runt-related transcription factor 2; PTH: parathyroid hormone; RANKL: receptor activator of nuclear factor-kappa B ligand; SOX9: sex-determining region Y-box 9

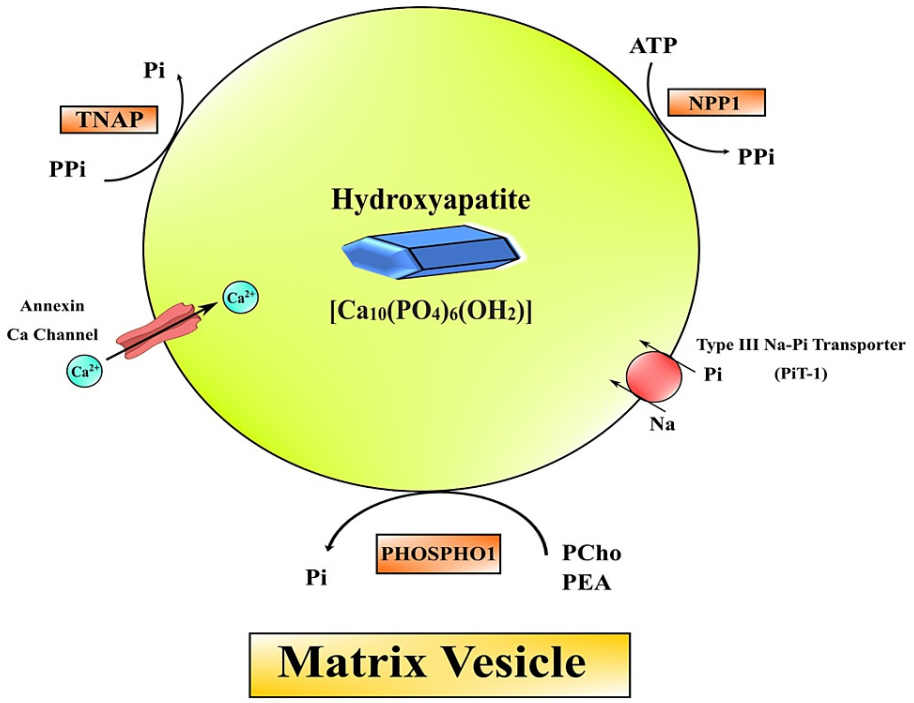


**FIGURE 4: Formation of hydroxyapatite crystal in matrix vesicle.**

TNAP: tissue-nonspecific alkaline phosphatase; NPP1: nucleotide pyrophosphatase/phosphodiesterase; PHOSPHO1: phosphoethanolamine/phosphocholine phosphatase 1; PEA: phosphoethanolamine; PCho: phosphocholine

Image credit: Susmita Sinha

*Phosphate Toxicity and Vascular Impediment*

The progression of the calcification procedure in vessels by persuading the formation of cells similar to bone-forming cells from VSMCs can result from hyperphosphatemia [167]. Elevated $PO_4^{3-}$ upregulates the expression of PiT in VSMCs [168]. Investigational studies specified that the activation of GK1/nuclear factor-kappa B (NF-κB), Wnt/β-catenin signaling, and upregulation of osteogenesis transcript factors Runx2, msh homeobox 2 (MSX2), sex-determining region Y-box 9 (SOX9), and osterix are usual processes of osteogenesis distinction of VSMCs, among which runt-related transcription factor 2 (Runx2) has an important part [169]. Again, cytokines that tend to cause inflammation are a group of endogenic peptides primarily formed by immune cells, as well as interleukin (IL)-1β, TNF-α, and IL-6. In vitro studies showed that IL-1β and TNF-α could excite the in-cell nuclear factor-kappa B (NF-κB) signaling, and IL-6 activates the BMP-2Wnt/β-catenin pathway to encourage the ossification of VSCMs [170]. This research has discovered that growth arrest-specific transcript 5 (GAS5)/miR-26-5p/phosphatase and tensin homolog (PTEN), FGFR1c-MEK/ERK-GALNT3 path, and alpha Klotho deficiency are important processes of vessel ossification. In addition to this, huge $PO_4^{3-}$ inducement downregulated the expressiveness of a long-chain noncoding RNA (lncRNA), growth-specific inhibitor, and growth arrest-specific transcript 5 (GAS5) in a person's aortic non-striated muscle cells, which deteriorated the hindrance of small nucleolar RNA miR-26b-5p and thus its subsequent focus protein phosphatase and tensin homolog (PTEN). PTEN is a protein/lipid phosphatase that encourages mesenchymal cells' osteogenesis by augmenting the expressiveness of runt-related transcription factor 2 (Runx2) [171,172]. Another study predicate that more $PO_4^{3-}$ bound to FGFR1c actuates the down-streaming of extracellular regulated protein kinase mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) phosphorylation and encourages the expressiveness of osteogenesis-associated proteins, such as BMP-2 and BMP-7 [173]. In high phosphate concentration, VSMCs process and push pyrophosphate extracellularly. Again, fetuin-A is a protein that can attach directly to Ca2+ or hydroxyapatite to hinder the progress of hydroxyapatite crystals [174]. In addition, tissue-nonspecific alkaline phosphatase (ALP) is amplified, resulting from the repress production of calcification inhibitions by high phosphate levels. ALP causes the deposition of microcalcification and the development of calcium phosphate crystals [175]. An extracellular matrix renovation in the tunica media occurs in response to phosphate toxicity. Accelerated generation of matrix metalloproteinases (MMPs) by VSMCs, such as MMP2 or MMP9, and additional deterioration of quite a few extracellular matrix proteins and elastin filaments make an available extra den for calcium phosphate precipitation [176-178].

A disproportionate quantity of the cysteine protease cathepsin S escorts to the breakup of elastin and the production of bioactive elastin peptides, which can perform straightly on VSMCs to hasten vascular calcification in phosphate excess [179]. Moreover, osteogenic/chondrogenic transdifferentiation of VSMCs induced by $PO_4^{3-}$ misplace the contractile constitution and acquire the same characteristics as osteoblasts and chondroblasts and exhibit osteogenic transcription factors, e.g., msh homeobox 2 (MSX2), core-binding factor α-1 (CBFA1) or osterix, and chondrogenic transcription factor with sex-determining region Y-box 9 (SOX9) [180].

*Phosphate Toxicity and Deranged Vascular Calcification in Obesity*

Phosphate toxicity is a notable consequence of impaired renal function. However, the pathological outcomes of hyperphosphatemia in obese individuals have no longer been explored in equal intensity (Table *2*). Investigators found that the prevalence of obesity-associated renal impairment is rising worldwide; along with this, experiments showed vast soft tissue and vessel ossification in the renal system, great vessels, lungs, and other organs in genetically modified hyperphosphatemic obese experimental animals [181]. Phosphate is an important constituent of our everyday foodstuffs and is primarily acquired from proteins. Over the last few years, $PO_4^{3-}$ has been abundantly utilized as an artificial food enhancer in treated edibles, carbonated drinks, cola, fast foods, precooked packaged foods, and processed meats [182]. Consuming high phosphate-containing foods in excess may cause various noncommunicable diseases, principally abdominal or central obesity (Table *2*), chronically raised blood pressure, dyslipidemia, IR/impaired insulin glucose metabolism, and steatohepatitis.

FGF23 is derived from osteocytes, and FGF23 is capable of reducing phosphate levels to normal by two processes. The first process is by lowering renal phosphate reabsorption by suppressing type II $Na^{+}$-$PO_4^{3-}$ symporters (NaPi-2a and NaPi-2c) in the proximal convoluted tubule and inhibiting the obstruction of 1-alpha-hydroxylase. The subsequent process involves the upregulation of 24-hydroxylases, which reduces 1,25-dihydroxycholecalciferol concentration, promotes intestinal phosphate uptake, and thus lowers serum $PO_4^{3-}$ concentration [183]. Researchers showed a strong relation linking high FGF23 and hypertrophic cardiac myopathy in obese young people without T2DM [184]. In another study, researchers evaluated that the levels of FGF23, alpha Klotho, and 1-25(OH)2D3 were remarkably reduced in obese subjects than in control [185].

*Phosphate Toxicity, T2DM, and Impaired Vascular Function*

More than phosphate toxicity, the Pi level plays an integral part in the progression of calcified vessels in T2DM [186]. $Ca_3(PO_4)_2$ deposits as hydroxyapatite, predominantly present in DM and CKD, resulting from plaque formations in tunica media and intima of the blood vessels [187]. Researchers observed that human VSMCs incubated in high $Ca^{2+}$ and $PO_4^{3-}$ concentrations instigated impairment to VSMC mitochondria, lessened mitochondrion action, augmented superoxide creation, and caused calcified vessels through altering VSMC metabolic processes [188]. The ossification of cultivated VSMCs persuaded under elevated $PO_4^{3-}$ conditions was related to the augmented inflammatory cytokine expressiveness of IL-1β, IL-6, and TNF-α, along with phosphorylation and triggering of the toll-like receptor-4 (TLR-4)/nuclear factor-kappa B (NF-κB) signaling pathway that is similarly linked to long-lasting inflammation [189].

Modification in bone metabolism leads to raised serum phosphate in T2DM, especially in CKD patients, and serum concentrations of osteocalcin decline in diabetic patients [190]. Researchers showed that serum alkaline phosphatase (ALP) action is upregulated in diabetic subjects, and ALP disintegrates inorganic pyrophosphate (PPi) [191]. Phosphate toxicity also represses the distinction of monocytes/macrophages into an osteoclast-like cell in vitro by downregulated RANKL-driven signaling. In contrast, diabetes-associated oxidative stress has a prohibitory influence on the segregation of osteoblasts and bone marrow cells (BMCs) [192]. Raised extracellular phosphate concentrations to enhance phosphate influx into VSMCs, initiating Runx2 and osteocalcin (Figure *5*) [193]. Atherosclerotic vascular calcification was also encouraged throughout the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) signaling pathway in trial animals with DM via Runx2 upregulating the transdifferentiation of VSMC into similar bone-forming cells [194]. In addition, when foods rich in $PO_4^{3-}$ are supplied to experimental animals, the phosphatidylinositol 3-kinase/Akt signaling pathway is initiated [195].

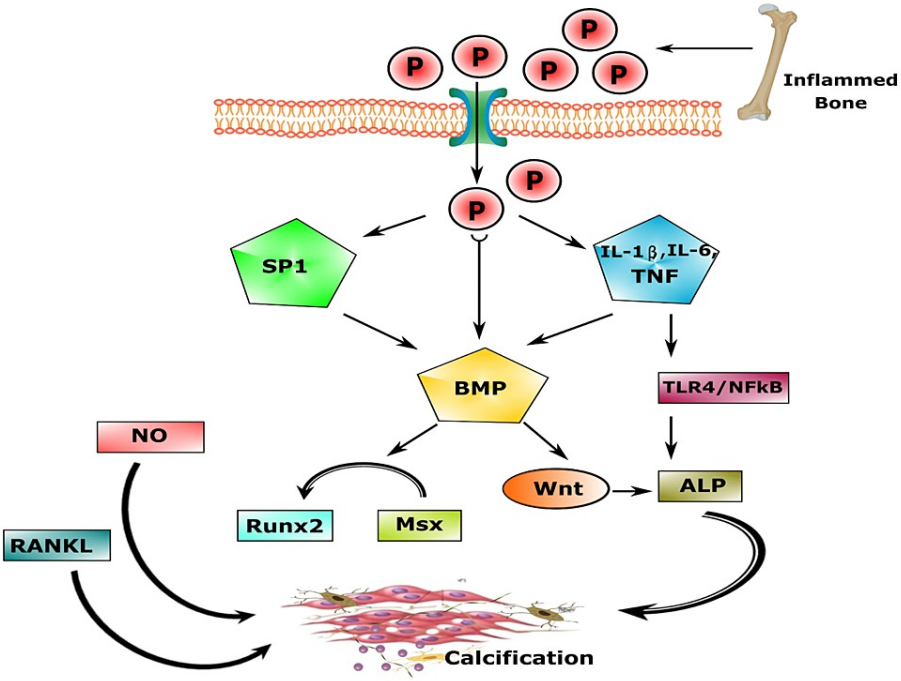


**FIGURE 5: Mechanism of the formation of vascular calcification in T2DM due to phosphate toxicity.**

TNF: tumor necrosis factor; IL: interleukins; BMP: bone morphogenic protein; Runx2: runt-related transcription factor 2; NF-κB: nuclear factor-kappa B; MSX: msh homeobox; ALP: alkaline phosphatase; RANKL: receptor activator of nuclear factor-kappa B ligand

Image credit: Susmita Sinha

Elevated serum $PO_4^{3-}$ concentrations cause liberation of FGF23 from bone to decrease serum $PO_4^{3-}$ by reducing renal $PO_4^{3-}$ reabsorption and rising urinary phosphate excretion [196]. Phosphate toxicity results in long-lasting renal disorder and end-stage renal disease and is also linked to diabetic nephropathy. Kidneys have abundant mitochondria in the proximal convoluted tubule; defects in mitochondria may cause reduced ATP synthesis and renal malfunction in diabetic kidney illness. Again, renal proximal convoluted tubular cells are found to be infiltrated with calcium phosphate precipitates after culturing in osteogenic environments [197].

Another experimental study showed that phosphate toxicity results in uremia in trial rats, and sediments of calcium phosphate were found in the basal ganglia. Furthermore, excess dietary intake of phosphate instigated malnutrition and inflammation, including vascular calcification in experimental rodents with uremia [198]. Lower vitamin D levels are frequently observed in T2DM, linked to pain in diabetic peripheral neuropathy, but the relationship is not established yet [199]. Phosphate toxicity causes decreased bioactive vitamin D synthesis and reduced intestinal absorption of $PO_4^{3-}$ and $Ca^{2+}$. Furthermore, it decreases renal $Ca^{2+}$ and $PO_4^{3-}$ reabsorption and causes impaired bone mineralization, thereby reducing serum $PO_4^{3-}$ levels. This could be an intervening reason to clarify the relationship of reduced vitamin D echelons in DM subjects with hurting diabetic peripheral neuropathy [200]. A recent study found that calcium phosphate deposition in mitochondria caused neuronal mitochondria defect and neurodegeneration [201].

*Phosphate Toxicity Affecting Renal Physiology*

There is a balance in $PO_4^{3-}$ concentration maintained by the kidneys during physiological conditions. After filtration, $PO_4^{3-}$ is taken up in the renal tubular epithelium via $Na^+$-Pi symporters [202]. Kidney bone derangements involve renal insufficiency, osteoporosis, and vascular calcification resulting from phosphate toxicity. Excessive phosphate consumption through foodstuffs causes disturbance in renal filtration, increasing phosphate retention and thus raising phosphate levels [203]. Renal proximal tubular epithelial cells accommodate three categories of Na/Pi symporters. The type 2 symporter group includes Na/Pi2a, and Napi2c are considered as much dynamic $PO_4^{3-}$ taken up in the kidney. Unlike the type 2 symporter, the type

1 symporter (NPT1) is primarily an anion carrier.

In contrast, the type 3 symporter system comprises two transporters, PiT1 and PiT2, and their role in $PO_4^{3-}$ transportation is a sphere of study [204]. In addition, alpha Klotho, the cofactor for FGF23 bioactivities, is available mainly in the distal tubule [205]; in addition to this, CKD patients show decreased levels of alpha Klotho, which causes FGF23 to be inoperative, thus limiting the kidneys' ability to eliminate phosphate [206].

Another in vivo study showed that phosphate toxicity in alpha Klotho-ablated mice accompanies the increased renal activity of Na/Pi2a; ensuing phosphate toxicity (Figure *6*) begins from an unbalanced accumulation of $PO_4^{3-}$ in the body [207]. Bone health and overall existence can be altered in the presence of more than normal $PO_4^{3-}$ levels related to foodstuffs; it can contribute to the progression of the human aging process [208]. Calciprotein particles (CPPs) are identified in the bloodstream, particularly in CKD patients, as a protagonist in phosphate-arbitrated renal tissue grievances [209]. The estimated prevalence of CKD worldwide is 8%-16% [210]. Edible $PO_4^{3-}$ excess may cause an increased $PO_4^{3-}$, a burden that results in renal tubular injury and interstitial fibrosis. There is a raised level of the possibility of evolving poor renal function with high serum phosphate [211]. Recent studies showed that treating human embryonic kidney cells (HEK-293) with increased concentrations of Pi for a short while persuades cytotoxicity. The investigators also found that phosphate in a dose-dependent phenomenon affects the cell division cycle and cell survival. In HEK-293 cells, an increase in Pi caused a notable rise in Akt phosphorylation, and a gradual rise in Pi concentrations caused an additional increase in Akt phosphorylation. Thus, Pi enhances Akt stimulation, resulting in cell cycle progression encouraged by the PI3K/Akt pathway. As processed foodstuffs (Table *2*) and drinks contain high phosphate concentrations, CKD patients should cut their consumption of these food products [212,213]. Multiple studies reported that high levels of phosphate preservatives are found in convenience food or ready-to-eat meal [77,214-229]. Additionally, high serum phosphorus is incorporated with the cardiac death toll in long-lasting kidney diseases [78,230-232].

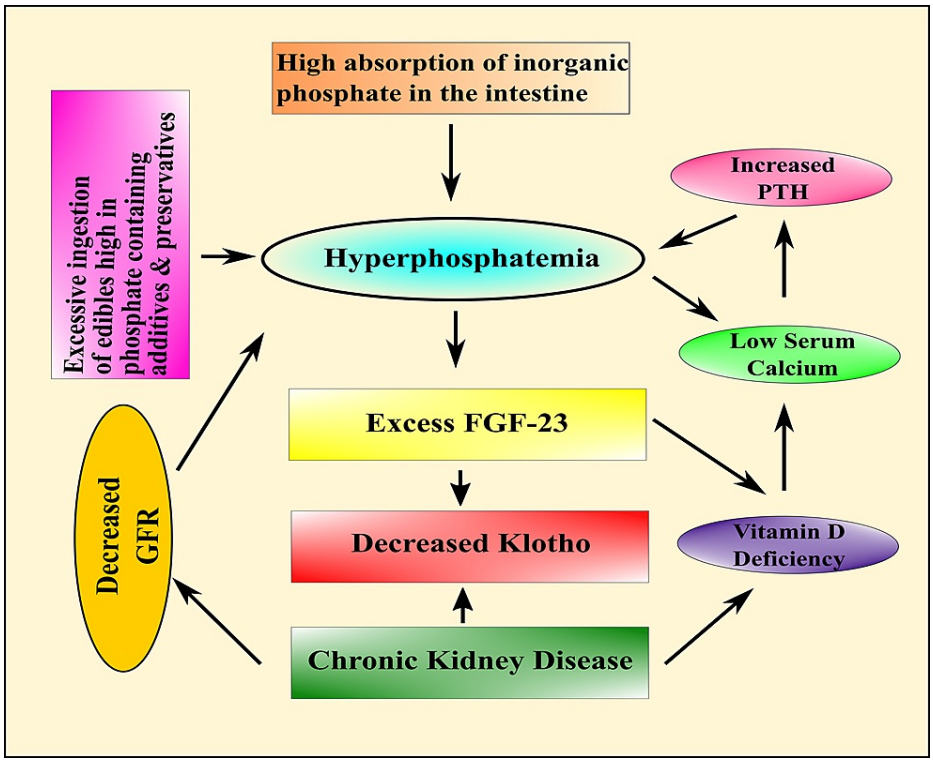


**FIGURE 6: Schematic presentation of the effects of phosphate toxicity on the renal system.**

PTH: parathyroid hormone; FGF23: fibroblast growth factor-23; GFR: growth factor receptor

Image credit: Susmita Sinha

| Reference | Country | Study | Study | Results |
|---|---|---|---|---|

| | involved | population | design | |
|---|---|---|---|---|
| Anyanwu et al. [214] | Indonesia | N = 31,160 | Cross-sectional study | The prevalence of overweight and obesity among the study population was 30.9% and 17.4%, respectively. Younger age and male gender significantly correlated with higher eating habits of processed foods. |
| Almandoz et al. [215] | USA | N = 404 | Cross-sectional study | Around 5% of the study population put on additional weight. These individuals were found to have more stressful life patterns, anxiety, and depression and were often less deprived of poor physical activity. They preferred to take less healthy meals such as more processed, ready-to-eat foods. They also frequently overindulge with binge eating disorder (BED). |
| Rey-García et al. [216] | Spain | N = 1,312 | Prospective cohort study | The consumption of processed food was statistically significantly (p = 0.026) correlated with declining renal physiology. Additionally, high consumption of ready-to-eat meals is sovereignly related to more than 50% possibility of jeopardizing renal physiology among the Spanish elderly community. |
| Sandoval-Insausti et al. [217] | Spain | N = 3,521 | Prospective cohort study | Higher convenience store food (fast food) ingestion was linked with central obesity among Spanish individuals aged 60 and over. |
| Beslay et al. [218] | France | N = 110,260 | Prospective study | French people consuming more ultra-processed food were positively related to weight gain in BMI and a greater risk of overweight and obesity. |
| Donat-Vargas et al. [219] | Spain | N = 1,082 | Prospective cohort study | Individuals who were principally dependent on ready-to-eat meals are frequently related to hypertriglyceridemia or low HDL cholesterol. |
| Llavero-Valero et al. [220] | Spain | N = 20,060 | Prospective cohort study | This study reported that those people who chiefly depend on processed food are independently associated with a higher risk for type 2 diabetes mellitus. |
| Montero-Salazar et al. [221] | Spain | N = 1,876 | Cross-sectional study | Among middle-aged persons, consuming processed food daily was related to coronary atherosclerosis. Additionally, it has been observed that the risk of cardiovascular issues doubles with consuming 500 g daily than 100 g daily. |
| Du et al. [222] | USA | N = 13,548 | Cross-sectional study | Greater ultra-processed food consumption was related to a higher risk of coronary artery disease among US adults who are 45-65 years. Additionally, it has been reported that linear relation was observed between packaged food consumption and the hazard of coronary artery disease. |
| Kurniawan et al. [223] | Taiwan | N = 41,128 | Cross-sectional study | Multivariate linear regression analysis revealed that high consumption of packed food, especially flesh and rice/flour products, and low intake of plant origin foods, e.g., fruit and dark-colored vegetables, frequently increases the possibility of cardiovascular disease and weakened renal function among individuals aged 40-95 years. |
| Kurniawan et al. [224] | Taiwan | N = 25,569 | Prospective study | This study revealed that eating habits were related to metabolic syndrome. |
| Vogelzangs et al. [225] | The Netherlands | N = 634 | Prospective cohort study | It has been reported that Dutch nondiabetic obese individuals possess both liver and muscle IR with high valine, isoleucine, oxoisovaleric acid, alanine, lactate, and triglycerides and lower levels of glycine. Additionally, the hepatic IR index was statistically significant and associated with amplified levels of leucine, hydroxyisobutyrate, tyrosine, proline, creatine, and n-acetyl and lower levels of acetoacetate and 3-OH-butyrate. |
| Wang et al. [226] | China | N = 94,952 | Prospective cohort study | IR had a robust relationship with the Chinese obese community. |
| Niu et al. [227] | China | N = 369 | Retrospective study | It has been reported that obesity remains the principal instigating factor for several noncommunicable disorders. These include IR, T2DM, hypertension, hyperuricemia, and metabolic syndrome. |
| Martins et al. [228] | Brazil | N = 153 | Cross-sectional study | This study revealed that the elderly community under hemodialysis frequently has an unhealthy diet than healthy elderly individuals. Additionally, it has been further spotted that these dialysis patients consume relatively worse processed food on non-dialysis days. |
| Watanabe | | | Cross-sectional | This study revealed that protein with phosphate-containing preservatives in |

| | | | | |
|---|---|---|---|---|
| et al. [44] | Brazil | N = 100 | descriptive-analytical study | prepackaged food was significantly higher ($p < 0.0001$) than in fresh foods, as well as the phosphate-to-protein ratio. |

**TABLE 2: Depicting processed food and its implication for obesity, renal impairment, and endocrine issues.**

HDL: high-density lipoprotein; IR: insulin resistance; T2DM: type 2 diabetes mellitus

## Professional annotation

Excessive, constant consumption of foods containing high phosphate levels has been linked to the amplified incidence of several long-term disorders and metabolic disorganization. Again, oxidative stress has a crucial role as an important influence relating obesity with its allied complexities. Obesity alone can persuade systemic oxidative stress via numerous biochemical processes, for instance, superoxide generation from nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, oxidative phosphorylation, glyceraldehyde auto-oxidation, protein kinase C activation, and hexosamine pathways [233]. Oxidative stress originated from reactive oxygen species (ROS), which adipokines can provoke yielded from adipocytes in obesity. Oxidative stress in obesity involves multiple processes, namely, mitochondrial and peroxisomal oxidation of fatty acids and excessive use of oxygen [234]. Obesity enhances oxidative stress and exhibits inflammation linked with insulin resistance and endothelial affliction [235]. Endothelial dysfunction is expressed as decreased biological availability of vasodilators such as nitric oxide (NO) and raised endothelium-derived contractile factors [236]. Inorganic phosphates (Pi) assimilate into the mitochondria, producing ROS, leading to ER stress and mitochondrial malfunction through the opening of the mitochondrial permeability transition pore (mPT). Increased blood glucose levels raised the requirement for insulin, which put a considerable load on the endoplasmic reticulum (ER). Proinsulin translation in response to increased blood glucose levels provokes extreme protein folding in ER, leading to ER stress. During ER stress, few β-cells pass away, and the remainder of β-cells intensify ER workload. In addition, if ER stress continues, β-cell numbers decrease, resulting in DM [237].

Furthermore, phosphate toxicity may result in inorganic phosphate excess instigating bone-producing cell distinction and vascular smooth muscle ossification facilitated by oxidative stress. For this reason, insulin-liberating cells are immensely susceptible to oxidation, and phosphate toxicity might be incredibly destructive to the pancreatic β-cells [238]. A study showed that ingesting prepackaged edibles increases foodstuff-related excess weight and obesity resulting from additional consumption of sugar-sweetened beverages containing high calories and high phosphates [239]. Moreover, researchers found that FGF23, vitamin D, and PTH mainly facilitate the endocrine control of phosphate balance. Disturbance of harmony among these factors, either solo or in alliance, may provoke phosphorus disproportion, and the inhibition of the FGF23 Klotho system can cause hyperphosphatemia with widespread tissue injury instigated by hyperphosphatemia [240]. Besides, researchers showed that without Klotho, elevated levels of FGF23 cannot control systemic phosphate homeostasis [241]. Hyperphosphatemia is one of the leading causes of decreased renal function [242]. In addition, another study acquired leptin-deficient obese experimental animals to see the effect of phosphate toxicity on obesity and discovered a wide range of nonskeletal tissue and calcified vessels in the kidneys, aorta, lungs, and other organs of these obese mice [243]. In particular, the biological activity of FGF23 depends upon alpha Klotho, available principally in the distal convoluted tubule. CKD patients showed diminished alpha Klotho levels, resulting in restricted urinary phosphate excretion. Phosphate toxicity results in chronic kidney and end-stage renal disease and is also linked to diabetic nephropathy [244]. Thus, diet-induced phosphate burden could impair kidney functions through tubular injury and interstitial fibrosis, increasing the risk of kidney disease.

# Conclusions

Collecting proof recommends that dietary elements, for instance, foodstuff flavorings and preservatives, contribute to the genesis of obesity and T2DM. With further research, the clinical intervention to reduce phosphate consumption and subsequent hyperphosphatemia has an enormous capability for upcoming advancements in the management and progression of T2DM and associated complications. There exist different types of biomolecular processes that have crucial influences on the pathophysiology of the ossification of blood vessels. In addition, conservative and alternate prevention processes, for example, preserving a well-balanced eating regimen and remedial strategies, are prospects to reduce the vascular calcification problem in T2DM due to hyperphosphatemia. It is becoming further noticeable from an observational study and human trials that phosphate toxicity characteristics may arise after consuming foodstuffs rich in $PO_4^{3-}$. Recent survey results highlight that people are unaware of the unseen supply of $PO_4^{3-}$ in their food and emphasize the necessity for awareness-raising activities of the hazard produced through foods with veiled $PO_4^{3-}$ constituents.

There are no convincing epidemiological connections between food additives and preservatives, obesity, and T2DM; clinical trials are a time-demanding issue for establishing an association. In addition, extensive and random testing with challenging endpoints is instantly needed. To lessen the $PO_4^{3-}$ problem, alertness of its nutritional origin is crucial. Suitable dietary instruction might improve phosphate control and help the whole community with regular renal performance. Information about $PO_4^{3-}$ additives, $PO_4^{3-}$ bioavailability, and the phosphate-to-protein ratio would be beneficial data for creating intervention strategies. Food-associated hyperphosphatemia is seemly an emerging international health concern. Without measures to modify ultimate dietary consumption, it will probably exert damaging outcomes on fitness and ailments. Future studies should look into alternate eating regimen concepts with lower glycemic index and safe levels of $PO_4^{3-}$ quantity.

The following are the highlights of the present article. First, ready-to-eat food consumption is associated with obesity and several noninfectious illnesses such as cardiovascular diseases, hypertension, diabetes mellitus, and tumors. Second, insulin-secreting cells are extremely susceptible to oxidative stress, and phosphate toxicity might be incredibly injurious to pancreatic β-cells. Third, atherosclerotic vascular calcification was also encouraged throughout the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) signaling pathway in trial animals with DM via Runx2, which upregulated the transdifferentiation of VSMCs into osteoblast-like cells. Lastly, phosphate toxicity results in chronic kidney diseases and end-stage renal disease and is also linked to diabetic nephropathy.

# Additional Information

## Disclosures

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