



Review

# Vitamin K as an Endocrine Modulator: Mechanistic Links to Glucose Metabolism and Beyond

Wojciech Matuszewski <sup>1,\*</sup>, Mikołaj Madeksza <sup>1</sup>, Michał Szklarz <sup>1</sup>, Aleksandra Rutkiewicz <sup>1</sup>,  
Joanna Rutkowska <sup>1</sup> and Joanna Maria Harazny <sup>2,3</sup>

<sup>1</sup> Clinic of Endocrinology and Metabolic Diseases, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, 10-957 Olsztyn, Poland

<sup>2</sup> Department of Human Physiology and Pathophysiology, School of Medicine, University of Warmia and Mazury in Olsztyn, 10-719 Olsztyn, Poland

<sup>3</sup> Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich Alexander University Erlangen Nuremberg (FAU), 91054 Erlangen, Germany

\* Correspondence: wmatuszewski82@wp.pl

## Abstract

Vitamin K (VK), traditionally recognized for its role in coagulation, is increasingly implicated in extrahepatic processes, including glucose metabolism and calcium regulation. A suboptimal VK status is common in the general population and may limit these functions, yet evidence linking VK to glucose metabolism and other endocrine axes remains heterogeneous and incompletely synthesized. This narrative review integrates mechanistic, observational, and interventional evidence to examine the role of VK across the endocrine system, with particular emphasis on glucose metabolism. Mechanistic studies indicate that VK supports pancreatic  $\beta$ -cell function, modulates peripheral insulin sensitivity, and facilitates proper calcium distribution. Observational studies consistently associate a higher VK status with a lower risk of type 2 diabetes, while interventional studies suggest that VK supplementation may improve glucose metabolism, primarily in metabolically impaired populations. In bone and mineral metabolism, VK acts synergistically with calcitriol, with combined supplementation showing more consistent benefits in skeletal outcomes than either vitamin alone. Evidence for VK involvement in other endocrine axes, including reproductive and inflammatory pathways, remains limited and largely mechanistic. Overall, the available evidence supports a context-dependent role for VK in glucose metabolism, influenced by baseline nutritional and metabolic status and outcome selection, as well as a synergistic interaction with calcitriol and parathormone in calcium regulation. Future clinical studies should incorporate baseline VK status stratification, dynamic measures of insulin sensitivity, and adequately powered designs to clarify the therapeutic relevance of VK across endocrine and metabolic outcomes.



Academic Editor: Pilar Aranda Ramírez

Received: 6 March 2026

Revised: 28 March 2026

Accepted: 2 April 2026

Published: 9 April 2026

**Copyright:** © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\) license](https://creativecommons.org/licenses/by/4.0/).

**Keywords:** vitamin K; glucose metabolism; type 2 diabetes; osteocalcin; calcium metabolism; endocrine system

## 1. Introduction

Vitamin K (VK) is best known for its essential role in blood coagulation but is increasingly recognized as a contributor to a range of extrahepatic processes, including glucose regulation and insulin sensitivity [1,2], bone and mineral metabolism [3,4], immune and inflammatory pathways [5,6], and vascular health [7,8]. While minimal intake is sufficient to maintain normal coagulation, many of these extrahepatic functions appear to require

a higher VK status [9–11]. Nevertheless, current dietary reference intakes and clinical practice remain focused on coagulation requirements [9,12], with supplementation recommendations largely limited to neonatal prophylaxis [13,14] and the use of menaquinone-4 in osteoporosis management in Japan [15]. Consequently, a substantial proportion of the population is thought to have a subclinical VK deficiency—a state in which coagulation is preserved but VK availability may be insufficient to support its broader physiological roles [9–12,16]. Accumulating evidence links this condition to impaired glucose [17–21] and calcium metabolism [4,7], highlighting the need to better define VK's roles within the endocrine regulatory pathways.

Several reviews have addressed VK and glucose metabolism; however, the most recent synthesis integrating mechanistic insights with human observational and interventional data was published in 2021 [2] and does not incorporate recent advances. Since then, new mechanistic insights have emerged regarding VK-dependent regulation of  $\beta$ -cell function [22,23], peripheral glucose metabolism [24], and antioxidant pathways [25], alongside a substantial increase in interventional studies published in the past five years [26–31]. In parallel, reported clinical findings remain heterogeneous, and prior reviews have largely summarized outcomes without systematically addressing key biological and methodological factors—such as baseline VK status, metabolic phenotype, VK form, and outcome selection—that may underlie inconsistent results across studies. Furthermore, the literature on VK and endocrine function remains fragmented, with most reviews focusing on individual domains—such as glucose metabolism, calcium homeostasis, or the proposed endocrine role of osteocalcin—rather than considering endocrine regulation as an integrated system [2,3,32–34].

In this narrative review, we integrate the current evidence on VK within the context of the endocrine system, with primary emphasis on glucose metabolism. We synthesize recent mechanistic findings with observational and interventional human data to examine how VK may influence pancreatic  $\beta$ -cell function, insulin secretion, and peripheral insulin sensitivity. We also provide a concise overview of the established and emerging roles of VK in other endocrine pathways and propose a framework for interpreting heterogeneous findings in light of key biological and methodological considerations.

## 2. Materials and Methods

This narrative review examines the endocrine and metabolic roles of VK. The review is based on original research articles, systematic reviews, and meta-analyses published in English. A literature search was conducted using PubMed and Google Scholar from the database's inception through January 2026. Initial broad searches were conducted to identify endocrine pathways potentially linked to VK, and search terms were subsequently refined based on the availability and relevance of mechanistic and clinical evidence. These included Medical Subject Headings and free-text keywords, such as “vitamin K”, “VK”, “phylloquinone”, “menaquinone”, “osteocalcin”, “OCN”, “endocrin\*”, “pancrea\*”, “insulin”, “glucose”, “diabetes”, “type 2 diabetes”, “calcitriol”, “vitamin D”, “bone”, “osteoporosis”, “calcium”, “inflammat\*”, “metaboli\*”, “thyroid”, “parathyroid”, “gonad\*”, “testi\*”, “ovar\*”, “PTH”, “testosterone”, “estrogen”, and “progesterone”, used alone or in combination. The reference lists of relevant articles were additionally screened to identify further studies.

The keywords listed above are illustrative rather than exhaustive and reflect the domains ultimately covered in the manuscript. Additional hormonal axes, including glucagon, cortisol, adipokines, myokines, ADH, oxytocin, adrenal hormones, and melatonin, were considered during the initial search but were not included in the final synthesis due to limited evidence linking these pathways to VK-dependent mechanisms.

We focused on studies examining VK status, intake, or supplementation in relation to endocrine or metabolic outcomes. Human studies were prioritized where available, particularly randomized controlled trials (RCTs) and meta-analyses, while animal and in vitro studies were included to describe mechanistic pathways and support biological plausibility. Evidence was synthesized qualitatively, and no formal risk-of-bias assessment or quantitative synthesis was performed. Where findings were inconsistent, studies were interpreted in the context of study design, population characteristics, and consistency across different lines of evidence. Studies primarily addressing coagulation, cardiovascular endpoints, advanced chronic kidney disease, cancer biology, or pharmacokinetics were not considered unless they directly informed endocrine or metabolic mechanisms.

### 3. Vitamin K Forms and Cellular Mechanisms of Action

#### 3.1. VK Vitamers: Sources, Metabolism, and Tissue Availability

VK comprises a group of fat-soluble vitamers sharing a 2-methyl-1,4-naphthoquinone (menadione) core, and is present in the diet as phyloquinone (vitamin K1, VK1) and menaquinones (VK2; MK-n, where n denotes the number of prenyl units in the side chain) [35,36]. VK1 is abundant in leafy green vegetables, whereas MKs are derived mainly from fermented foods and animal products, with MK-4 additionally synthesized endogenously from VK1 [36–39].

Although VK1 accounts for the majority of dietary intake [35,36], it is tightly bound to plant tissue and is less efficiently absorbed than MKs [35,37,40]. Following intestinal absorption, VK1 is transported predominantly in triacylglycerol-rich lipoproteins and is taken up by the liver, resulting in a short biological half-life [36,39,41]. In contrast, MKs preferentially associate with low-density lipoproteins, which limits hepatic uptake and confers longer circulation times and greater availability to extrahepatic tissues [35,36,39,41]. Consistent with these pharmacokinetic differences, MKs surpass VK1 levels in most peripheral tissues, and likely contribute disproportionately to VK's extrahepatic functions [37,39,41,42].

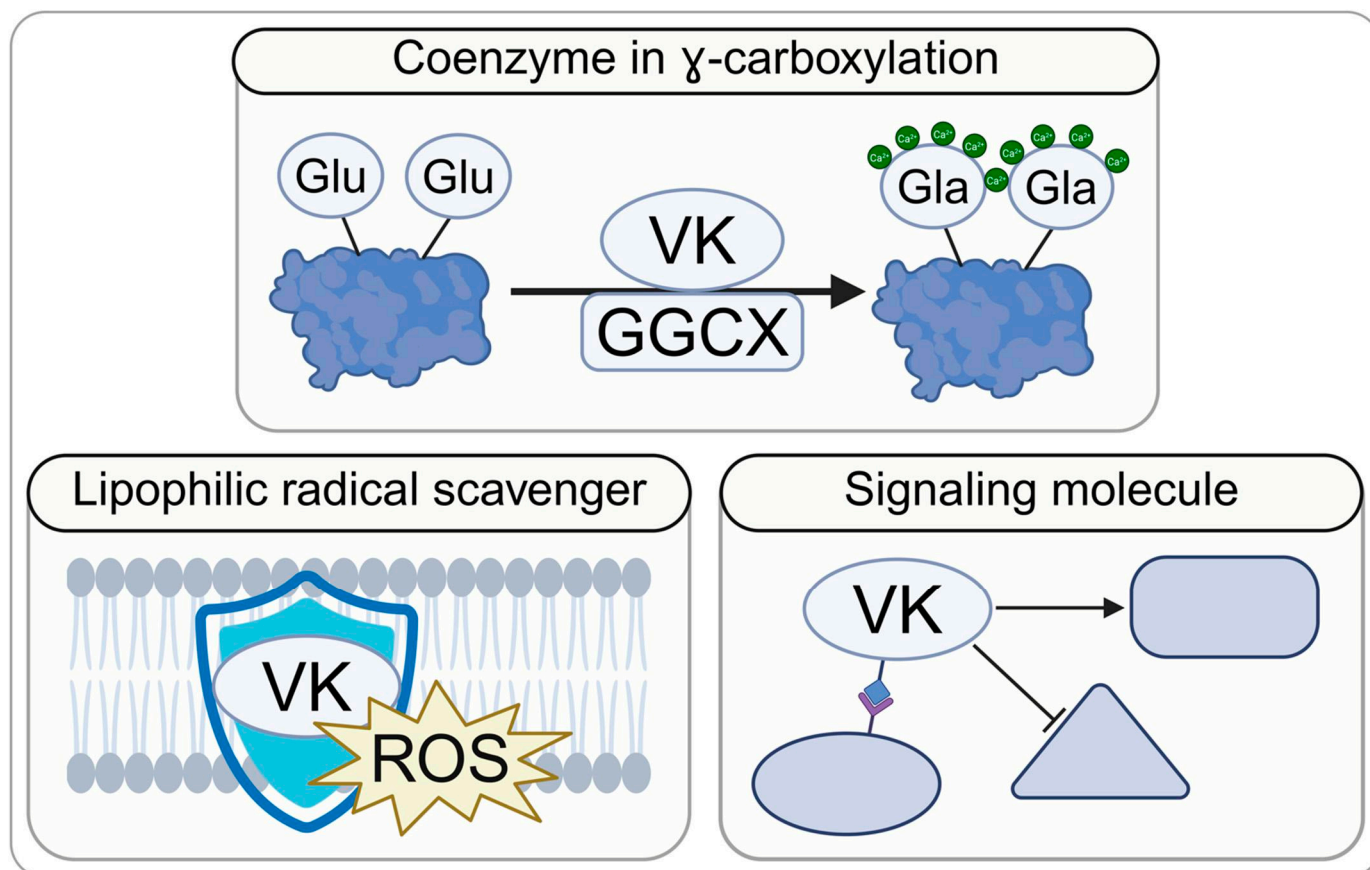
In addition to dietary forms, VK also includes hydrophilic precursors such as menadione (vitamin K3) and its derivatives (vitamin K4) [35]. Menadione serves as an intermediate in the conversion of VK1 to MK-4, while VK4 refers to synthetic menadione precursors [27,35,41]. Although these compounds can substitute for VK, their use in humans is limited by safety concerns at higher concentrations [11,35,43,44].

#### 3.2. Cellular Actions of VK: $\gamma$ -Carboxylation, Signaling, and Radical Scavenging

At the cellular level, VK acts through three principal mechanisms. First, it functions as a coenzyme for  $\gamma$ -glutamyl carboxylase (GGCX), enabling the post-translational conversion of glutamate (Glu) residues into  $\gamma$ -carboxylglutamyl (Gla) residues [35,39]. Approximately 20 proteins undergo this modification and are collectively termed VK-dependent proteins (VKDPs) [22,45–60]. The resulting Gla residues confer high-affinity calcium binding, which is essential for VKDP function.

Second, VK modulates several intracellular signaling pathways, including AMP-activated protein kinase (AMPK) [19,24], the cAMP-dependent exchange protein directly activated by cAMP 2 (Epac2), and protein kinase A (PKA) [61–65]. These pathways are directly relevant to endocrine function and are discussed in subsequent sections. VK has also been shown to influence several transcription factors [4,66–70] and cell-survival pathways [11,67,71–73]; however, the endocrine relevance of these actions remains unknown.

Finally, VK acts as a lipophilic radical-trapping antioxidant that inhibits (phospho)lipid peroxidation and suppresses ferroptosis, an iron-dependent form of cell death driven by lipid peroxidation [25,74,75]. Figure 1 provides a simplified overview of these mechanisms, while a more detailed representation is presented in Supplementary Figure S1.



**Figure 1.** The three modes of vitamin K action. Notes: A more detailed mechanistic overview is provided in Supplementary Figure S1. Created in BioRender. Madeksza, M. (2026) <https://BioRender.com/cjey5vz>. Abbreviations: GGCX,  $\gamma$ -glutamyl carboxylase; Gla,  $\gamma$ -carboxylglutamyl acid; Glu, glutamate; ROS, reactive oxygen species; VK, vitamin K.

## 4. Vitamin K Status and Its Measurement

### 4.1. VK Status Markers, Their Use, and Limitations

The assessment of VK nutritional status relies on two primary approaches: dietary questionnaires and biomarkers [76]. Dietary questionnaires are practical and cost-effective, making them common in large observational studies [77], but they are subject to recall bias and confounding by overall diet quality and lifestyle, as phylloquinone intake often reflects the consumption of leafy greens and other health-associated foods [78–80]. Although adjustment for dietary and lifestyle factors can mitigate this bias, it cannot fully eliminate it [78].

Biomarkers provide a more objective assessment of VK status and include circulating VK concentrations, functional measures of VKDP carboxylation, coagulation assays, and urinary metabolites [78]. Circulating VK1 reflects recent intake, peaking approximately 6–10 h postprandially, and is influenced by triglyceride levels due to transport on triacylglycerol-rich lipoproteins; accordingly, fasting samples and adjustment for triglycerides are recommended [78].

Undercarboxylated osteocalcin (ucOCN) and dephosphorylated-undercarboxylated matrix Gla protein (dp-ucMGP) are the most sensitive indicators of extrahepatic VK status [78,81]. Elevated levels of these proteins reflect low VK availability in tissues where they are predominantly active—primarily bone for ucOCN and vascular smooth muscle for dp-ucMGP. Expressing these measures relative to total protein concentrations (e.g., %ucOCN) improves interpretability, although they are not entirely VK-specific: their levels

are influenced by physiological factors such as bone turnover (ucOCN) [78,82–84] and age or vascular pathology (dp-ucMGP) [78,85]. Both %ucOCN and dp-ucMGP respond rapidly to changes in VK intake and therefore primarily reflect short-term VK status [82,86–88].

Other VKDP-based measures, including undercarboxylated prothrombin and coagulation assays, are less sensitive within physiological VK ranges, whereas urinary VK metabolites are impractical for large-scale studies [78]. Overall, no single gold-standard biomarker is currently available, and a combined assessment of circulating VK1 and a functional VKDP marker (%ucOCN or dp-ucMGP) offers the most comprehensive evaluation of VK status [78]. Supplementary Table S1 summarizes the available VK status markers and their key limitations.

#### 4.2. Genetic Determinants of VK Status

VK status markers show large interindividual variability compared with other fat-soluble vitamins. This variability is only partly explained by dietary intake and other nongenetic factors, and several single nucleotide polymorphisms (SNPs) have been associated with VK status (Table 1) [20,89,90]. These variants cluster in genes involved in VK metabolism (e.g., *CYP4F2*, *VKOR*, and *GGCX*) [91,92], lipoprotein-mediated transport (e.g., the *APOA1/C3/A4/A5* gene cluster) [41,90], as well as additional loci whose functional roles in VK biology remain unclear [89].

Consistent with a genetic contribution, a multi-ethnic cohort has identified race and ethnicity as significant predictors of circulating VK1 concentrations, with higher levels observed in Chinese American and African American populations compared with Caucasian and Hispanic populations [93]. These findings suggest that genetic background substantially influences VK status and responsiveness to VK intake, which may predispose certain individuals to low functional VK availability despite similar dietary exposure [86,89,90].

**Table 1.** Genetic polymorphisms associated with VK status.

Gene(s)	Encoded Protein(s)	SNP(s)	Effect on VK Status	Ref.
<i>CYP4F2</i>	CYP4F2 (VK1 oxidase)	rs2108622	↑ plasma VK1 and MK-4	[94]
<i>VKORC1</i>	VKOR	rs8050894	↑ plasma VK1	[95]
<i>GGCX</i>	GGCX	rs10187424, rs7568458	↑ %ucOCN	[95]
<i>APOA1/C3/A4/A5</i> cluster	apolipoproteins	rs964184	↑ plasma VK1	[90]
<i>CTNNA2</i>	α-2-catenin	rs2192574, rs4852146	↑ plasma VK1	[90]
<i>CDO1</i>	cysteine dioxidase 1	rs4122275, rs686207, rs6862909	↓ plasma VK1	[90]
<i>COL22A1</i>	collagen	rs2199565, rs4645543, rs7018214	↓ plasma VK1	[90]

Note: ↑ indicates an increase and ↓ indicates a decrease in the specified VK status biomarker associated with the given genetic polymorphism(s). Abbreviations: GGCX, γ-glutamyl carboxylase; SNP, single nucleotide polymorphism; VK1, vitamin K1 (phylloquinone); VKOR, vitamin K epoxide reductase; %ucOCN, % of undercarboxylated osteocalcin.

#### 4.3. Baseline VK Status and Responsiveness to Supplementation

As with many micronutrients [96–98], the biochemical and clinical effects of VK supplementation appear to be greatest in individuals with a low baseline status, while those with adequate VK levels show limited responses due to a ceiling effect [5,99–105]. Consequently, supplementation trials that do not account for baseline VK status may fail

to detect meaningful benefits confined to deficient subgroups. These and other factors complicating the interpretation of clinical VK research are further discussed in Section 8.4.

## 5. Vitamin K and Glucose Metabolism: Mechanistic Plausibility and Clinical Evidence from Human Studies

### 5.1. VK and $\beta$ -Cell Function: ER Calcium Handling, cAMP Signaling, and Inflammatory Stress

VK supports  $\beta$ -cell integrity and function through ER calcium handling, cAMP signaling, and anti-inflammatory effects. Endoplasmic reticulum Gla protein (ERGP) is a recently identified VKDP that restrains store-operated calcium entry (SOCE) and protects  $\beta$ -cells from dysregulated insulin secretion under metabolic stress [22]. The tight regulation of intracellular  $\text{Ca}^{2+}$  is essential for  $\beta$ -cell function, as  $\text{Ca}^{2+}$  influx triggers insulin granule exocytosis [106–108]. SOCE replenishes intracellular  $\text{Ca}^{2+}$  following the depletion of endoplasmic reticulum (ER)  $\text{Ca}^{2+}$  stores and supports  $\beta$ -cell integrity and glucose-stimulated insulin secretion (GSIS) [109,110]. However, chronic nutrient excess induces ER stress and ER  $\text{Ca}^{2+}$  depletion [108,111], which can lead to excessive SOCE activation [112], uncontrolled insulin secretion, and downstream insulin resistance [22,113,114]. ERGP counteracts this process in a glucose-dependent manner: rising intracellular glucose levels enhance ERGP  $\gamma$ -carboxylation, strengthening its inhibitory effect on SOCE and preventing  $\text{Ca}^{2+}$  overflow [22]. The physiological relevance of this mechanism is underscored by  $\beta$ -cell-specific *Ggcx*-knockout mice, which exhibit  $\beta$ -cell apoptosis and impaired GSIS, and develop insulin resistance with fasting hyperinsulinemia and hyperglycemia within one week of a high-fat diet [22]. These findings suggest that VK-dependent regulation of ER  $\text{Ca}^{2+}$  handling helps preserve  $\beta$ -cell function under conditions of metabolic stress.

Beyond ER calcium homeostasis, VK can also influence  $\beta$ -cell function through cAMP signaling. In isolated islets and INS-1 cells, MK-4 enhances GSIS via increased intracellular cAMP levels and the activation of the exchange protein directly activated by the cAMP 2 (Epac2) pathway [23]. Because the cAMP/Epac2 axis contributes to the incretin-dependent potentiation of GSIS without increasing basal insulin secretion [115–118], activation of this pathway by VK may help preserve incretin responsiveness, which is impaired in type 2 diabetes (T2D) [119,120].

In addition to these signaling mechanisms, VK participates in multiple anti-inflammatory and antioxidant pathways across diverse cell types, as detailed in the Supplementary Figure S1 [25,36,66,74,75,91,121–139]. In the pancreas, VK1 administration in a streptozotocin-induced diabetes model reduced oxidative stress, preserved islet morphology, and restored insulin secretion [140]. Although this model reflects toxin-induced  $\beta$ -cell injury rather than the pathophysiology of T2D, it provides direct evidence that VK can modulate inflammatory signaling within the endocrine pancreas. Collectively, these mechanisms support the plausibility that an adequate VK status contributes to  $\beta$ -cell integrity and adaptive insulin secretion during metabolic stress, consistent with the high concentrations of vitamin K observed in pancreatic tissue.

### 5.2. VK and Insulin Resistance: Direct and Indirect Links

Beyond its effects on  $\beta$ -cell function, VK has been shown to alleviate hepatic and peripheral insulin resistance through tissue-intrinsic metabolic mechanisms. In mouse models of T2D, VK1 supplementation improves impaired glucose metabolism through the activation of sirtuin 1 (SIRT1)-dependent pathways in the liver [19], while VK2 supplementation enhances insulin sensitivity, mitochondrial function, and oxidative fiber composition in skeletal muscle via the same signaling axis [24]. Notably, VK1—the predominant dietary form of VK—is preferentially taken up by the liver [9,42]; thus, hepatic VK actions (e.g., SIRT1 pathway activation) are supported across a broad range of intakes, whereas

VK-mediated mechanisms in peripheral tissues such as skeletal muscle may require higher intake and are therefore more sensitive to variations in VK status.

Furthermore, VK may indirectly influence glucose metabolism through modulation of the gut microbiome. Several gut commensal bacteria rely on VK as an electron carrier [141], and VK deficiency or warfarin exposure has been associated with microbial dysbiosis in rodent models [142,143]. Conversely, higher dietary VK1 intake has been linked to increased microbial production of butyrate [144]—a short-chain fatty acid associated with improved insulin sensitivity and metabolic health [145,146]. Given that butyrate production is reduced in T2D [147–150], microbiome-mediated effects may contribute to VK-associated metabolic improvements. Additionally, VK's involvement in multiple anti-inflammatory and antioxidant pathways (Supplementary Figure S1) may support insulin signaling in peripheral tissues, providing additional biological plausibility for VK-mediated improvements in insulin sensitivity. However, direct evidence for VK-dependent anti-inflammatory effects in insulin-responsive tissues is limited. These  $\beta$ -cell-intrinsic and peripheral actions of VK are summarized in Figure 2.

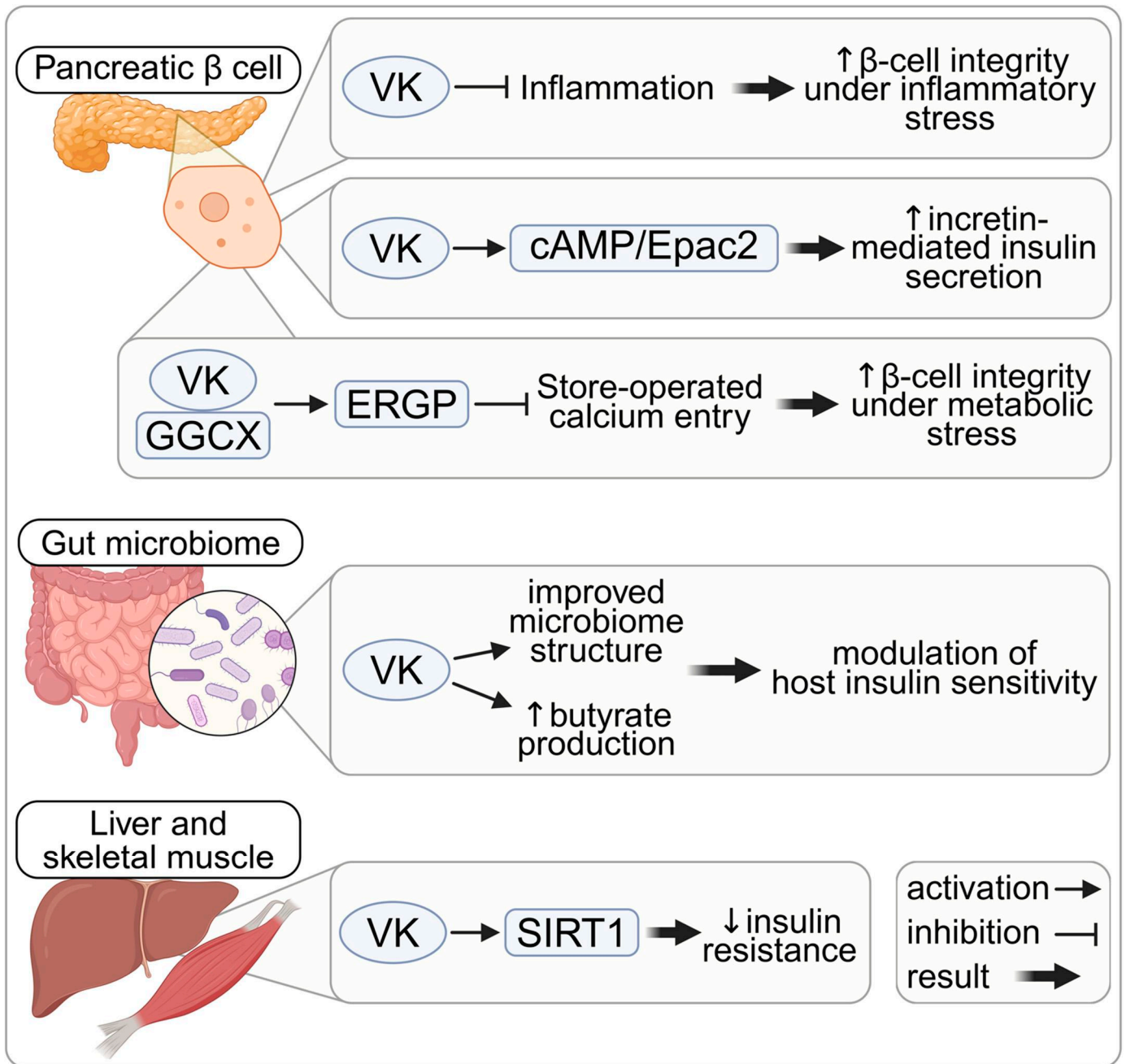
### 5.3. Osteocalcin and Glucose Metabolism: Mediator, Marker, or Confounder?

OCN is unique among other VKDPs because its undercarboxylated form circulates in blood, where it was proposed to act as a hormone; however, the nature and relevance of its endocrine role in humans remains incompletely defined [151,152]. Observational studies consistently associate higher circulating OCN levels with favorable metabolic outcomes, including a lower prevalence of T2D [153,154], obesity [154,155], and metabolic syndrome [153,154], as well as lower HbA1c, fasting and OGTT blood glucose [153,154], reduced HOMA-IR [153], improved  $\beta$ -cell function [154], and higher adiponectin levels [154]. Importantly, fewer than one-third of these studies distinguish between different OCN forms [82,154,155]. Among those that do, both total OCN and ucOCN generally correlate with metabolic outcomes [154–156], and a contribution from the carboxylated form cannot be excluded [157–164]. Moreover, circulating OCN levels are strongly influenced by bone remodeling activity [82,165], which itself is altered in metabolic disease [166,167], raising the possibility that OCN acts primarily as a biomarker or confounder rather than a direct endocrine mediator. Preclinical studies have not resolved this uncertainty [81].

In this context, the interpretation of VK's effects is further complicated by the fact that VK supplementation typically reduces %ucOCN without altering total OCN [81,168,169]. As long as the metabolically active OCN form(s) in humans remain undefined, it is therefore unclear whether changes in OCN carboxylation represent a mechanistic pathway linking VK to glucose metabolism or an epiphenomenon reflecting altered bone turnover [82].

### 5.4. VK Status and Risk of T2D: Observational Evidence

In line with the preclinical findings described above, a growing body of clinical research suggests an association between VK status and glucose metabolism, particularly under conditions of metabolic impairment. Three large observational studies, including one Mendelian randomization analysis, reported inverse associations between VK status and risk of T2D [18,20,170], while two additional studies found that warfarin use—unlike anticoagulants not targeting  $\gamma$ -carboxylation—was associated with a higher risk of T2D [171,172]. These results suggest the potential protective role of an adequate VK status in the development of T2D.



**Figure 2.** Mechanisms by which vitamin K may influence glucose metabolism and insulin sensitivity. Notes: ↑ indicates an increase and ↓ indicates a decrease in the indicated biological effect associated with VK action. Created in BioRender. Madeksza, M. (2026) <https://BioRender.com/kucipw1>. Abbreviations: Epac2, cAMP-dependent exchange protein directly activated by cAMP 2; ERGP, endoplasmic reticulum Gla protein; GGCX,  $\gamma$ -glutamyl carboxylase; SIRT1, sirtuin 1; VK, vitamin K.

5.5. VK and Glucose Metabolism: Effects Depend on Baseline Metabolic Status and Outcome Measures

Evidence from intervention and observational studies indicates that the effects of VK on glucose metabolism are heterogeneous and dependent on baseline metabolic status (Table 2). Across 20 identified studies (five observational, 15 interventional), benefits were consistently observed in individuals with impaired glucose metabolism but not in metabolically healthy populations. In line with a 2018 meta-analysis reporting no effect of VK supplementation in healthy individuals [173], studies conducted in normoglycemic participants generally failed to demonstrate improvements in glycemic control [16,174–176].

In contrast, all nine studies involving participants with (pre)diabetes or polycystic ovary syndrome (PCOS) reported significant improvements in two or more glucose metabolism parameters with a higher VK status or supplementation.

The apparent efficacy of VK also varies by outcome measure. Fasting plasma glucose was largely unaffected, while effects on fasting insulin and HOMA-IR were inconsistent, with roughly equal numbers of studies reporting reductions or null findings. This pattern is reflected in meta-analytic evidence: a 2017 meta-analysis limited to non-diabetic individuals found no significant effects of VK supplementation on fasting insulin or HOMA-IR [177], whereas two 2025 meta-analyses that included participants with (pre)diabetes and PCOS reported significant reductions in fasting insulin, HOMA-IR, and HbA1c [1,21].

More consistent improvements were observed for dynamic indices of insulin sensitivity: ISI(0,120) improved in all four studies assessing it [178–181], QUICKI improved in four of five studies [17,29,30,182,183], and OGTT plasma glucose improved in three of four studies [27,178,181,184]. The observation that ISI(0,120)—capturing both hepatic and peripheral glucose disposal—showed more consistent improvement than HOMA-IR, which primarily reflects hepatic insulin resistance, suggests that VK may preferentially enhance peripheral insulin sensitivity [181,185,186]. However, the limited number of studies and substantial heterogeneity in study design preclude definitive conclusions.

**Table 2.** A summary of human studies on the effect of VK on insulin sensitivity and/or glycemic status.

Study	Year	Subjects (N)	VK Dose/VK Status	Period	Outcome
(a) observational studies					
Santos et al. [17]	2020	Adult men (136) and women (192)	Usual dietary intake	Cross-sectional study	in women: (Higher VK intake) ↓ fasting PG, ↓ fasting PI, ↓ HOMA-IR, ↑ QUICKI; ↔ in men
Zwakenberg et al. [20]	2019	Pooled from: the EPIC cohort study, the DIAGRAM meta-analysis, and the UK Biobank cohort (total of 69,647 adults with T2D)	Usual dietary intake	EPIC cohort: 1997–2007; UK Biobank cohort: 2006–2010; DIAGRAM meta-analysis: data from 23 studies	(Higher genetically predicted circulating VK1) ↓ T2D risk
Dihingia et al. [19]	2018	Adult men and women with T2D (25) and healthy controls (20)	Usual dietary intake	Cross-sectional study	↓ circulating VK1 in T2D vs. controls (Higher circulating VK1) ↓ fasting PG, ↓ HOMA-IR among T2D patients

Table 2. Cont.

Study	Year	Subjects (N)	VK Dose/VK Status	Period	Outcome
Ibarrola-Jurado et al. [18]	2012	Elderly men (861) and women (1062) with high CV risk	Usual dietary intake	5.5 years (median follow-up)	(Higher VK1 intake) ↓ T2D risk
Beulens et al. [170]	2010	Adult men (9740) and women (28,354)	Usual dietary intake	10.3 years	(Higher VK intake) ↓ T2D risk
Pan and Jackson [16]	2009	Adult men (2867) and women (2933)	Usual dietary intake	Cross-sectional study	(Higher VK intake) ↔ fasting PG and fasting PI
Yoshida et al. [178]	2008	Adult men (1247) and women (1472)	Usual dietary intake	1 year	(Higher VK intake) ↓ OGTT PG, ↑ ISI(0,120) ↔ fasting PG, HbA1c, PI, and HOMA-IR
Sakamoto et al. [184]	1999	Healthy young men (16)	Usual dietary intake	1 week food checklist, acute insulin response	(Higher VK intake) ↓ OGTT PG, ↑ insulin response ↔ fasting PG
(b) interventional studies					
Zhang et al. [26]	2023	Adult men (29) and women (31) with T2D	With or without 90 µg/day MK-7	6 months	↓ fasting PG, ↓ fasting PI, ↓ HbA1c, ↓HOMA-IR
Ali et al. [27]	2023	Adult men (10) and women (80) with T2D	With or without 1000 µg/day K4	6 months	↓ fasting PI, ↓ HOMA-IR; ↓ treatment intensification, ↑ dose reduction of antidiabetic drugs; ↔ fasting PG and OGTT PG
Adeli et al. [28]	2023	Adult men and women with T2D (45)	With or without 200 µg/day MK-7	3 months	↓ fasting PG, ↓ fasting PI; ↓ plasma leptin
Rahimi Sakak et al. [29]	2021	Adult men and women with T2D (63)	With or without 360 µg/day MK-7	3 months	↓ fasting PG, ↓ HbA1c; ↔ fasting PI, HOMA-IR, QUICKI
Karamzad et al. [31]	2020	Adult men (31) and premenopausal women (14) with T2D	With or without 200 µg/day MK-7	3 months	↓ fasting PG and HbA1c; ↔ fasting PI, HOMA-IR

Table 2. Cont.

Study	Year	Subjects (N)	VK Dose/VK Status	Period	Outcome
Tarkesh et al. [30]	2020	Women with PCOS (79)	With or without 90 µg/day MK-7	2 months	↓ HOMA-IR, ↓ PI, ↑ QUICKI ↔ fasting PG
Karamali et al. [182]	2017	Women with PCOS (55)	With or without 180 µg MK-7, 10 µg vitamin D and 1 g Ca/day	2 months	↓ PI, ↓ HOMA-IR, ↑ QUICKI ↔ fasting PG
Asemi et al. [183]	2016	Adult men (35) and women (31) with T2D and coronary heart disease	With or without 180 µg MK-7, 10 µg vitamin D and 1 g Ca/day	3 months	↓ PI, ↓ HOMA-IR, ↑ QUICKI ↔ fasting PG
Knapen et al. [176]	2015	Healthy postmenopausal women (244)	With or without 180 µg/day MK-7	3 years	↔ fasting PG
Centi et al. [174]	2015	Healthy adult men and women (42)	500 µg/day VK1	1 month	↔ on HOMA-IR
Rasekhi et al. [181]	2015	Premenopausal prediabetic women (82)	With or without 1000 µg/day VK1	1 month	↓ OGTT PG, ↓ OGTT plasma insulin, ↑ ISI(0,120); ↔ on fasting PG, fasting PI, and HOMA-IR
Choi et al. [179]	2011	Healthy young men (33)	With or without 30,000 µg/day MK-4	1 month	↑ ISI(0,120); ↔ on fasting PG
Kumar et al. [175]	2010	Healthy postmenopausal women (42)	With or without 1000 µg/day VK1	1 year	↔ fasting PG, fasting PI, and HOMA-IR
Yoshida et al. [178]	2008	Elderly nondiabetic men (124) and women (165)	With or without 500 µg/day VK1	3 years	↓ fasting PI and ↓ HOMA-IR in men; ↔ in women; ↔ fasting PG in both sexes
Sakamoto et al. [180]	2000	Healthy young men with low (4) medium (4) and high (4) DP levels	90,000 µg/day MK-4	1 week	↑ ISI(0,120) in men with high DP levels; ↔ on ISI in other subjects; ↔ on all other measured parameters

↓—VK supplementation (or higher serum concentration) resulted in a significant decrease in a parameter; ↑—it resulted in a significant increase in a parameter; ↔—it had no significant effect on a parameter. Abbreviations: CV, cardiovascular; DP, decarboxylated prothrombin; DIAGRAM, Diabetes Genetics Replication and Meta-analysis; EPIC, European Prospective Investigation into Cancer and Nutrition; OGTT, oral glucose tolerance test; PG, plasma glucose; PI, plasma insulin; ISI, insulin sensitivity index; HOMA-IR, homeostatic model assessment for insulin resistance; T2D, type 2 diabetes; PCOS, polycystic ovary syndrome.

### 5.6. Other Cardiometabolic Domains Linked to VK Status

Beyond glycemic control, VK status has been associated with several cardiometabolic domains relevant to T2D, although evidence in these areas is largely observational or derived from preclinical models. Cross-sectional studies consistently report inverse associations between VK status and measures of adiposity [163,187–189], circulating inflammatory markers [5,16,170,190–194], and a more favorable lipid profile [16,170,189,195]. Experimental and cellular studies also suggest vasoprotective effects, including improved NO-dependent endothelial function [196–198], anti-senescence effects on endothelial and vascular smooth muscle cells, and the inhibition of glucose-induced endothelial inflammation [121,198]. However, RCTs have generally failed to demonstrate corresponding effects of VK supplementation [21,27,29,31,177,199,200]. Collectively, these findings suggest that VK may influence multiple cardiometabolic pathways relevant to T2D, but current evidence does not support a clear causal effect of VK supplementation on these outcomes. The implications and limitations of this evidence are considered in greater detail in Section 8.3.

## 6. Vitamin K Collaborates with PTH and Calcitriol to Ensure Proper Calcium Distribution

### 6.1. VK Facilitates Safe Calcium Mobilization by Parathormone and Calcitriol

Parathormone (PTH) and calcitriol are the principal regulators of systemic calcium balance, acting on bone, the kidney, and the intestine to increase circulating calcium levels [201–204]. Both hormones also induce the expression of OCN and MGP [122,205–210], creating a functional dependence on adequate VK availability.

VK-dependent  $\gamma$ -carboxylation converts OCN and MGP into their biologically active forms, thereby directing the fate of mobilized calcium. Carboxylated OCN binds hydroxyapatite crystals in bone, regulating their shape, size, and alignment with collagen to support optimal bone strength and architecture [3,211,212], whereas phosphorylated-carboxylated MGP inhibits calcium-phosphate crystal growth in soft tissues and the vasculature [122–124]. Thus, by increasing the proportion of active OCN and MGP, a sufficient VK status ensures that calcium mobilized by PTH and calcitriol is deposited in bone rather than ectopically.

### 6.2. VK Amplifies Skeletal Responses to Calcitriol and Parathormone

VK influences bone remodeling by promoting osteoblast activity, suppressing osteoclastogenesis, and reducing %ucOCN [3,168,213,214]. However, RCTs of VK supplementation alone have reported inconsistent effects on bone mineral density (BMD) or fracture risk [169,215,216]. Similarly, calcitriol modestly improves BMD, while its effects on fracture prevention are limited [217–220].

In contrast, multiple trials indicate that combined VK and calcitriol supplementation produces greater improvements in BMD and fracture outcomes than either vitamin alone [221,222]. Comparable synergistic effects have also been observed when VK is administered alongside recombinant parathormone [223–225]. These findings suggest that VK enhances the skeletal efficacy of calcium-regulating hormones, likely by increasing cOCN levels within bone.

## 7. Vitamin K and Other Endocrine Axes

### 7.1. Reproductive Axes: Evidence for Testosterone Synthesis and Limited Data on Estrogen

Beyond glucose and calcium metabolism, experimental evidence also supports a role for VK in androgen synthesis. In Leydig cells, MK-4 enhances testosterone production via activation of the cAMP/PKA pathway, which stimulates steroidogenic acute regulatory protein (StAR)-mediated cholesterol transport and upregulates steroidogenic enzyme ex-

pression via transcription factors such as CREB and SF-1 [226,227]. Consistent with this mechanism, VK supplementation increases plasma and intratesticular testosterone levels in rats [63,228,229], and attenuates inflammation-induced suppression of steroidogenesis [230]. Human data remain sparse and inconsistent; few studies have assessed VK status alongside testosterone, reporting both inverse [231] and positive [232] associations with %ucOCN. A related observational study also linked higher VK intake to greater muscle mass in men but not women [233].

Furthermore, total OCN levels correlate positively with testosterone across populations [234–238], and OCN has been proposed as a regulator of male gonadal function [239,240]. However, similarly to what was noted in Section 5.3, few studies distinguished between OCN forms, limiting the interpretation of VK's role in this potential regulatory axis.

Some evidence also suggests that VK may be involved in female reproductive endocrinology. Ovaries contain high VK concentrations and express VK-cycling enzymes [42,241], and PKA-dependent steroidogenic pathways—upregulated by VK in other tissues [61–64,209]—are central to ovarian hormone synthesis [242–244]. Observationally, lower circulating ucOCN has been associated with higher estrogen levels in women [245–248], though this relationship may reflect estrogen-mediated suppression of bone turnover rather than direct VK action. Additionally, *in vitro*, MK-4 upregulates 17 $\beta$ -hydroxysteroid dehydrogenase type 4, favoring estradiol-to-estrone conversion and reduced estrogen receptor activation [249], but the relevance of this mechanism remains unclear. In all, VK may contribute to gonadal steroidogenesis, particularly testosterone synthesis in men, but the evidence remains preliminary.

## 7.2. Thyroid Hormones and Other Endocrine Axes: Indirect and Uncertain Interactions with VK

VK is not known to directly influence the synthesis, metabolism, or action of most hormones. Although OCN has been implicated in the regulation of other endocrine axes, including GLP-1 and neuroendocrine pathways [50,250], the extent to which VK-dependent  $\gamma$ -carboxylation modulates these actions is unclear.

Separately, thyroid axis hormones have been shown to influence the activity of VK-dependent coagulation pathways. In rats, the administration of TRH, TSH, T3, and T4 reduces the activity of VK-dependent clotting factors II, VII, IX, and X [251,252]. This interaction has clinical implications, as thyroid status alters sensitivity to VK antagonists; hyperthyroidism or the initiation of L-thyroxine therapy generally necessitates warfarin dose reduction, whereas hypothyroidism or antithyroid therapy typically requires dose escalation [253–256].

## 8. Discussion

### 8.1. Key Findings

At the cellular level, VK acts as a coenzyme for  $\gamma$ -carboxylation of VKDPs, a signaling molecule, and a free-radical scavenger. Mechanistic studies demonstrate the VK-dependent regulation of pancreatic  $\beta$ -cell function, as well as effects on insulin sensitivity in peripheral tissues. In observational studies, a higher VK status is consistently associated with a lower risk of T2D, while interventional trials report heterogeneous effects of VK supplementation on glucose metabolism, with benefits observed primarily in metabolically impaired populations. In calcium and bone metabolism, VK interacts with PTH and calcitriol through  $\gamma$ -carboxylation of OCN and MGP, with combined supplementation studies reporting more consistent effects on skeletal outcomes than either intervention alone. Experimental data also suggest VK-dependent modulation of testicular steroidogenesis and inflammatory pathways, but human evidence in these areas is sparse and inconsistent.

### 8.2. Unresolved Mechanistic Questions

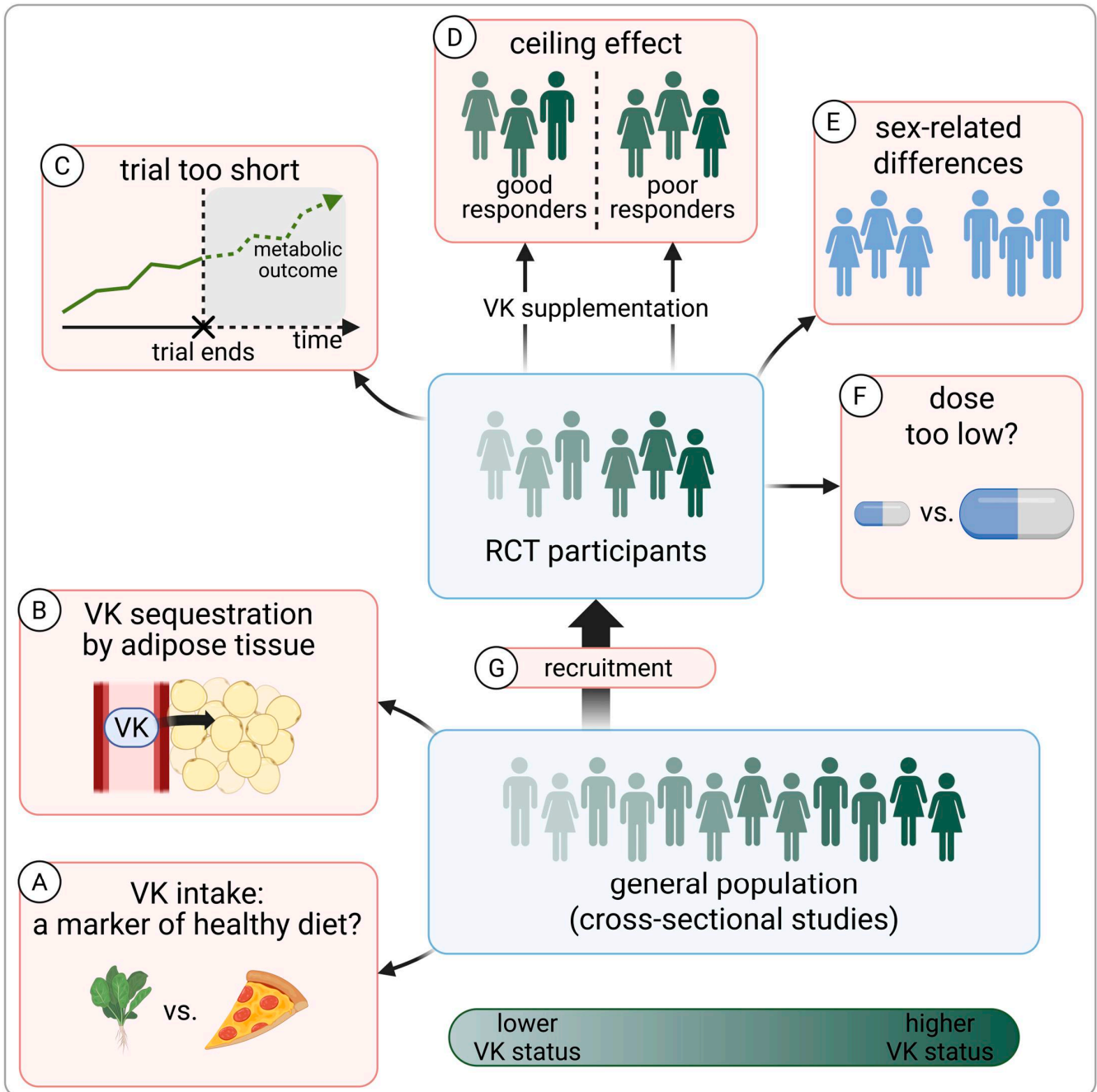
Several mechanistic uncertainties remain. The most prominent concerns the proposed endocrine role of OCN. Early mouse models suggested that OCN deficiency leads to hyperglycemia, reduced insulin production, increased visceral fat, and hypogonadism, supporting its classification as a bone-derived hormone [257]. However, more recent *Ocn* knockout lines failed to reproduce these phenotypes [212,258]. Moreover, while ucOCN is considered the active form in mice [259–262], VK supplementation—which increases OCN carboxylation—has nonetheless been reported to improve glucose metabolism [19,24,26,263] and male reproductive function [264]. Interpretation is further complicated by the fact that circulating OCN reflects bone remodeling activity [82,165], which is reduced in individuals with diabetes [166,167]. Consequently, associations between OCN and metabolic outcomes may be confounded by altered bone turnover rather than reflecting direct endocrine signaling [82]. To resolve these discrepancies, future clinical studies should distinguish between total and undercarboxylated OCN and incorporate additional markers of bone remodeling. Combined with emerging in vitro and omics-based approaches [151], this will help clarify the endocrine relevance of specific OCN forms in humans.

Another uncertainty concerns the role of VK's anti-inflammatory actions in endocrine signaling. While it remains unclear whether VK supplementation can reduce systemic inflammation [177,179,200], its involvement in multiple anti-inflammatory and antioxidant pathways (Supplementary Figure S1) may plausibly improve endocrine signaling by limiting inflammation within endocrine and effector tissues. For example, VK attenuates LPS-induced inflammation and preserves testosterone synthesis in rat testes [230], and in the pancreas, it reduces streptozotocin-induced oxidative stress, preserves islet morphology, and restores insulin secretion [140]. Comparable studies in other endocrine tissues are lacking, representing a notable gap, given that inflammation commonly affects endocrine organs, including the ovaries in PCOS [265,266], and the thyroid gland in autoimmune thyroid disease [267,268].

Finally, while VK's insulin-sensitizing effects have been established in the liver and skeletal muscle [19,24], its actions within white adipose tissue (WAT) remain largely unexplored [269]. Importantly, WAT is an adipokine-secreting endocrine organ whose dysfunction plays a central role in the metabolic inflammation associated with obesity and insulin resistance [270]. Given VK's anti-inflammatory properties and its ability to activate AMPK, VK may plausibly improve both insulin sensitivity and adipokine secretion in WAT, representing a priority for future research.

### 8.3. Quality and Interpretation of Clinical Evidence

While mechanistic studies provide important biological context, the clinical relevance of vitamin K supplementation in humans must ultimately be based on clinical evidence. Within clinical data, a recurring challenge is the discrepancy between cross-sectional findings and RCTs. Observational studies consistently associate a higher VK status with better bone health [271], a lower risk of T2D (Table 2) and cardiovascular disease [272], lower inflammatory markers [5,16,170,190–194], and lower adiposity [163,187–189,273], whereas RCTs often fail to demonstrate comparable effects of VK supplementation. Null RCT findings are frequently interpreted as evidence against a causal role of VK, while observational associations are commonly attributed to residual confounding, under the assumption that VK-rich diets reflect healthier lifestyle patterns [2,20,273]. However, this interpretation is overly simplistic and overlooks several additional factors, summarized in Figure 3.



**Figure 3.** Factors complicating clinical research on vitamin K. Notes: Points (A–F) are covered in more detail in Section 8.4. (A)—VK intake is often assumed to reflect healthier dietary patterns; however, mixed meals and convenience foods are major contributors to VK1 intake due to vegetable oil content, while VK2 is derived primarily from cheese, other dairy products, and meat. (B)—VK can be sequestered in adipose tissue, potentially reducing its bioavailability in individuals with a higher body fat percentage. (C)—Metabolic changes occur gradually, and many trials may have been too short to detect meaningful effects. (D)—The biochemical and clinical effects of VK supplementation depend on baseline VK status; a ceiling effect in individuals with an adequate status may obscure benefits associated with correcting a suboptimal VK status. (E)—The available RCT evidence includes an underrepresentation of men, in whom VK may act through distinct mechanisms and for whom supplementation effects may differ from those observed in women. (F)—The dose and form of VK used in some trials may have been insufficient to elicit extrahepatic effects. (G)—Trial participants are often health-conscious volunteers and therefore less likely to have low nutrient intakes, increasing the proportion of individuals susceptible to ceiling effects [98]. Created in BioRender. Madeksza, M. (2026) <https://BioRender.com/xsnia3i>. Abbreviations: VK, vitamin K.

First, population-based dietary surveys challenge the notion that VK intake is a reliable marker of health-conscious behavior. In NHANES 2011–2012, mixed meals and convenience foods were major contributors to phyloquinone intake, presumably due to vegetable oil content [274,275]. Among individuals with low vegetable intake—representing approximately three-quarters of the cohort—VK1 intake from mixed meals, fats, oils, and snacks exceeded that from vegetables. Similarly, in Western diets, menaquinones are derived predominantly from cheese, other dairy products, and meat, which are not typically associated with overall healthier dietary patterns [36,170]. These findings weaken the assumption that VK intake simply proxies diet quality.

On the other hand, VK's lipophilic nature may help explain some cross-sectional associations without implying causality. Like other fat-soluble vitamins, VK can be sequestered in adipose tissue, potentially reducing its bioavailability in individuals with a higher body fat percentage [187]; this may partly account for inverse associations between VK status markers and adiposity [163,187–189], as well as downstream associations with insulin resistance, inflammation, and cardiometabolic risk.

Furthermore, several methodological limitations of existing RCTs likely reduce their ability to detect the benefits of VK supplementation. Many trials may be too short to capture changes in outcomes that evolve gradually, such as body composition, inflammation, or insulin sensitivity. Notably, although most trials assessing anthropometric outcomes reported null findings [15,26–30,103,163,181,276–279], the few studies with longer follow-up durations (3 years) did demonstrate significant effects [103,163].

Another key issue is the baseline VK status. The biochemical and clinical effects of VK supplementation appear to be greatest in individuals with a low baseline status, while those with adequate VK levels show limited responses due to a ceiling effect [5,99–105]. Despite this, few trials in endocrine and cardiometabolic research have stratified participants by baseline VK status or conducted responder analyses [103,180], raising the possibility that overall null results obscure clinically meaningful effects confined to deficient subgroups.

An additional limitation may be sex imbalance. As shown in Table 2, the available RCT evidence on VK and glucose metabolism is characterized by a predominance of female participants, and similar patterns have been reported across other areas of VK research [21,280]. As discussed earlier, sex-related differences in VK metabolism and actions are likely, and the current interventional data may therefore insufficiently capture VK-related mechanisms that are more relevant in men, including potential effects on testosterone synthesis and muscle metabolism.

Finally, the dose and form of VK used in several trials may have been suboptimal for eliciting extrahepatic effects. Current dietary reference intakes for VK1—90 µg/day for women and 120 µg/day for men—are based solely on coagulation requirements, reflecting VK action in the liver [9]. Because VK1 is preferentially taken up by the liver, substantially higher intakes may be necessary to support extrahepatic tissues [36,39,41], and even the dose of 500 µg/day of VK1 used in some trials [174,276,281,282] may not have been optimal. In contrast, menaquinones are more readily distributed to peripheral tissues [35,39,41], suggesting that lower doses may be sufficient to engage extrahepatic mechanisms.

Taken together, the discrepancy between observational studies and RCTs in VK research should not be interpreted as evidence against biological relevance, but rather as a reflection of complex nutritional physiology combined with suboptimal trial design. Addressing baseline VK status, treatment duration, sex-specific effects, and the dose and form of supplementation will be essential to further determine whether VK plays a causal role in endocrine and cardiometabolic health.

#### 8.4. Practical Implications and Future Directions

The findings presented here highlight several priorities for future research. As responses to VK supplementation appear to depend on baseline status, clinical studies should account for baseline VK status or preferentially target populations in whom extrahepatic VK insufficiency is most likely. Trials should also employ supplementation durations and doses sufficient to engage extrahepatic VK pathways. In studies on glucose metabolism, dynamic indices of insulin sensitivity should be incorporated to better characterize VK's effects on peripheral insulin resistance. In addition, VK-dependent regulation of testicular testosterone synthesis is well supported experimentally but remains poorly defined in humans, representing an important research gap—particularly given the increasing prevalence of male hypogonadism associated with aging and obesity [283–285].

Beyond clinical trials, these findings also point to the potential public health relevance of VK insufficiency. Current dietary reference intakes for VK are based solely on coagulation outcomes and do not necessarily reflect requirements for the extrahepatic pathways involved in glucose and calcium metabolism. Furthermore, VK status shows marked interindividual variability that is only partly explained by dietary intake [86]. Apparent dietary adequacy may therefore coexist with functional insufficiency, and this state likely affects a substantial proportion of the population [9–12,16]. Together, these considerations highlight the plausible population-level relevance of functional VK status as a potentially modifiable factor in health conditions associated with impaired insulin sensitivity, skeletal fragility, and vascular calcification, all of which are increasingly prevalent worldwide [286–288].

#### 8.5. Strengths and Limitations

The main limitation of this work is its narrative design. Unlike systematic reviews, it does not rely on a predefined search strategy or formal quality assessment, and selection bias cannot be excluded. In addition, the emphasis placed on individual studies may not fully reflect their methodological quality or statistical power. To address these limitations, this review distinguishes between study types, interpreting findings in light of their methodological context. Where available, greater emphasis is placed on meta-analyses and RCTs, while observational and mechanistic studies are used primarily to support biological plausibility and generate hypotheses. Accordingly, the interpretations presented should be viewed as context-dependent and hypothesis-generating rather than as definitive assessments.

Notwithstanding this limitation, this review has several strengths. First, it integrates mechanistic, observational, and interventional evidence to provide a comprehensive and up-to-date synthesis of VK's effects on glucose metabolism—a field that has expanded rapidly in recent years. Second, it explicitly addresses key biological and methodological factors that complicate the interpretation of clinical evidence, including baseline VK status and ceiling effect, outcome selection, and heterogeneity in study populations. By doing so, the review goes beyond a descriptive summary of reported findings and offers a conceptual framework for understanding inconsistencies in the literature and for informing the design of future studies better suited to test VK-dependent mechanisms. Finally, by adopting a broad endocrine perspective, this review integrates evidence across multiple hormonal axes, and highlights emerging data supporting a plausible role for VK in male reproductive endocrinology.

## 9. Conclusions

Beyond coagulation, VK is increasingly recognized as a contributor to metabolic and endocrine processes. The mechanistic and clinical evidence reviewed here supports roles for

VK in glucose metabolism and calcium homeostasis. In these domains, VK interacts with key hormonal pathways, including insulin signaling, PTH, and calcitriol. Clinically, VK supplementation has been associated with improvements in glucose metabolism, primarily in metabolically impaired populations, and appears to act synergistically with calcitriol, with combined interventions showing more consistent benefits in skeletal outcomes than either vitamin alone. The evidence for VK involvement in other endocrine axes remains preliminary and largely mechanistic. Together, these findings highlight the need for further well-designed studies that link mechanistic hypotheses to relevant clinical outcomes in order to clarify the endocrine significance of VK.

**Supplementary Materials:** The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/nu18081183/s1>, Supplementary Figure S1: The vitamin K cycle and vitamin K-mediated regulation of oxidative stress and inflammation; and Supplementary Table S1: Characteristics, interpretive value, and limitations of commonly used vitamin K status measures. References [25,36,66,74,75,91,121–139] are cited in the Supplementary Materials.

**Author Contributions:** M.M., A.R. and M.S.: performance of the literature search, creation of all figures, and drafting the manuscript; J.R.: editing the manuscript; W.M. and J.M.H.: conceptualization, data curation, and validation. All authors contributed to the review and editing. All authors have read and agreed to the published version of the manuscript.

**Funding:** The authors report no external funding sources.

**Data Availability Statement:** Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

## References

1. Khatapoush, S.; Mohit, M.; Mansouri Shirazi, F.; Moazen, M.; Ebrahimzadeh, A.; Hejazi, N. The Effect of Vitamin K Supplementation on Glycemic Indices in Adults: A Systematic Review and Meta—Analysis of Clinical Trials. *Int. J. Nutr. Sci.* **2025**, *10*, 186–198. [CrossRef]
2. Varsamis, N.A.; Christou, G.A.; Kiortsis, D.N. A Critical Review of the Effects of Vitamin K on Glucose and Lipid Homeostasis: Its Potential Role in the Prevention and Management of Type 2 Diabetes. *Hormones* **2021**, *20*, 415–422. [CrossRef]
3. Akbari, S.; Rasouli-Ghahroudi, A.A. Vitamin K and Bone Metabolism: A Review of the Latest Evidence in Preclinical Studies. *BioMed Res. Int.* **2018**, *2018*, 4629383. [CrossRef] [PubMed]
4. Fusaro, M.; Cianciolo, G.; Brandi, M.L.; Ferrari, S.; Nickolas, T.L.; Tripepi, G.; Plebani, M.; Zaninotto, M.; Iervasi, G.; La Manna, G.; et al. Vitamin K and Osteoporosis. *Nutrients* **2020**, *12*, 3625. [CrossRef]
5. Luo, W.; Ye, D.; Zhao, K.; Zhou, L.; Wu, Y.; Ge, Q. Associations between Vitamin K and Systemic Immune and Inflammation Biomarkers: A Population-Based Study from the NHANES (2007–2020). *Front. Nutr.* **2025**, *12*, 1625209. [CrossRef] [PubMed]
6. Xie, Y.; Li, S.; Wu, D.; Wang, Y.; Chen, J.; Duan, L.; Li, S.; Li, Y. Vitamin K: Infection, Inflammation, and Auto-Immunity. *J. Inflamm. Res.* **2024**, *17*, 1147–1160. [CrossRef] [PubMed]
7. Shioi, A.; Morioka, T.; Shoji, T.; Emoto, M. The Inhibitory Roles of Vitamin K in Progression of Vascular Calcification. *Nutrients* **2020**, *12*, 583. [CrossRef]
8. Lees, J.S.; Chapman, F.A.; Witham, M.D.; Jardine, A.G.; Mark, P.B. Vitamin K Status, Supplementation and Vascular Disease: A Systematic Review and Meta-Analysis. *Heart* **2019**, *105*, 938–945. [CrossRef]
9. McCann, J.C.; Ames, B.N. Vitamin K, an Example of Triage Theory: Is Micronutrient Inadequacy Linked to Diseases of Aging? *Am. J. Clin. Nutr.* **2009**, *90*, 889–907. [CrossRef]
10. Vermeer, C.V. Vitamin K: The Effect on Health beyond Coagulation – an Overview. *Food Nutr. Res.* **2012**, *56*, 5329. [CrossRef]
11. Kaźmierczak-Barańska, J.; Karwowski, B.T. Vitamin K Contribution to DNA Damage—Advantage or Disadvantage? A Human Health Response. *Nutrients* **2022**, *14*, 4219. [CrossRef]
12. Lee, S.E.; Schulze, K.J.; Cole, R.N.; Wu, L.S.F.; Yager, J.D.; Groopman, J.; Christian, P.; West, K.P. Biological Systems of Vitamin K: A Plasma Nutriproteomics Study of Subclinical Vitamin K Deficiency in 500 Nepalese Children. *OMICS* **2016**, *20*, 214–223. [CrossRef]
13. Ng, E.; Loewy, A.D. Guidelines for Vitamin K Prophylaxis in Newborns. *Paediatr. Child Health* **2018**, *23*, 394–397. [CrossRef]

14. Sankar, M.J.; Chandrasekaran, A.; Kumar, P.; Thukral, A.; Agarwal, R.; Paul, V.K. Vitamin K Prophylaxis for Prevention of Vitamin K Deficiency Bleeding: A Systematic Review. *J. Perinatol.* **2016**, *36*, S29–S35. [[CrossRef](#)] [[PubMed](#)]
15. Koitaya, N.; Sekiguchi, M.; Tousen, Y.; Nishide, Y.; Morita, A.; Yamauchi, J.; Gando, Y.; Miyachi, M.; Aoki, M.; Komatsu, M.; et al. Low-Dose Vitamin K2 (MK-4) Supplementation for 12 Months Improves Bone Metabolism and Prevents Forearm Bone Loss in Postmenopausal Japanese Women. *J. BONE Miner. Metab.* **2014**, *32*, 142–150. [[CrossRef](#)]
16. Pan, Y.; Jackson, R.T. Dietary Phylloquinone Intakes and Metabolic Syndrome in US Young Adults. *J. Am. Coll. Nutr.* **2009**, *28*, 369–379. [[CrossRef](#)]
17. Santos, E.A.D.; Giudici, K.V.; França, N.A.G.D.; Peters, B.S.E.; Fisberg, R.M.; Martini, L.A. Correlations among Vitamin K Intake, Body Fat, Lipid Profile and Glucose Homeostasis in Adults and the Elderly. *Arch. Endocrinol. Metab.* **2020**, *64*, 436–444. [[CrossRef](#)] [[PubMed](#)]
18. Ibarrola-Jurado, N.; Salas-Salvadó, J.; Martínez-González, M.A.; Bulló, M. Dietary Phylloquinone Intake and Risk of Type 2 Diabetes in Elderly Subjects at High Risk of Cardiovascular Disease. *Am. J. Clin. Nutr.* **2012**, *96*, 1113–1118. [[CrossRef](#)] [[PubMed](#)]
19. Dihingia, A.; Ozah, D.; Ghosh, S.; Sarkar, A.; Baruah, P.K.; Kalita, J.; Sil, P.C.; Manna, P. Vitamin K1 Inversely Correlates with Glycemia and Insulin Resistance in Patients with Type 2 Diabetes (T2D) and Positively Regulates SIRT1/AMPK Pathway of Glucose Metabolism in Liver of T2D Mice and Hepatocytes Cultured in High Glucose. *J. Nutr. Biochem.* **2018**, *52*, 103–114. [[CrossRef](#)]
20. Zwakenberg, S.R.; Rimmelzwaal, S.; Beulens, J.W.J.; Booth, S.L.; Burgess, S.; Dashti, H.S.; Imamura, F.; Feskens, E.J.M.; Van Der Schouw, Y.T.; Sluijs, I. Circulating Phylloquinone Concentrations and Risk of Type 2 Diabetes: A Mendelian Randomization Study. *Diabetes* **2019**, *68*, 220–225. [[CrossRef](#)]
21. Nikpayam, O.; Jafari, A.; Faghfour, A.; Pasand, M.; Noura, P.; Najafi, M.; Sohrab, G. Effect of Menaquinone-7 (MK-7) Supplementation on Anthropometric Measurements, Glycemic Indices, and Lipid Profiles: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Prostaglandins Other Lipid Mediat.* **2025**, *177*, 106970. [[CrossRef](#)]
22. Lacombe, J.; Guo, K.; Bonneau, J.; Faubert, D.; Gioanni, F.; Vivoli, A.; Muir, S.M.; Hezzaz, S.; Poitout, V.; Ferron, M. Vitamin K-Dependent Carboxylation Regulates Ca<sup>2+</sup> Flux and Adaptation to Metabolic Stress in  $\beta$  Cells. *Cell Rep.* **2023**, *42*, 112500. [[CrossRef](#)] [[PubMed](#)]
23. Ho, H.-J.; Shirakawa, H.; Hirahara, K.; Sone, H.; Kamiyama, S.; Komai, M. Menaquinone-4 Amplified Glucose-Stimulated Insulin Secretion in Isolated Mouse Pancreatic Islets and INS-1 Rat Insulinoma Cells. *Int. J. Mol. Sci.* **2019**, *20*, 1995. [[CrossRef](#)] [[PubMed](#)]
24. Su, X.; Wang, W.; Fang, C.; Ni, C.; Zhou, J.; Wang, X.; Zhang, L.; Xu, X.; Cao, R.; Lang, H.; et al. Vitamin K2 Alleviates Insulin Resistance in Skeletal Muscle by Improving Mitochondrial Function via SIRT1 Signaling. *Antioxid. Redox Signal.* **2021**, *34*, 99–117. [[CrossRef](#)]
25. Mishima, E.; Ito, J.; Wu, Z.; Nakamura, T.; Wahida, A.; Doll, S.; Tonnus, W.; Nepachalovich, P.; Eggenhofer, E.; Aldrovandi, M.; et al. A Non-Canonical Vitamin K Cycle Is a Potent Ferroptosis Suppressor. *Nature* **2022**, *608*, 778–783. [[CrossRef](#)] [[PubMed](#)]
26. Zhang, Y.; Liu, L.; Wei, C.; Wang, X.; Li, R.; Xu, X.; Zhang, Y.; Geng, G.; Dang, K.; Ming, Z.; et al. Vitamin K2 Supplementation Improves Impaired Glycemic Homeostasis and Insulin Sensitivity for Type 2 Diabetes through Gut Microbiome and Fecal Metabolites. *BMC Med.* **2023**, *21*, 174. [[CrossRef](#)]
27. Ali, A.M.; Abbassi, M.M.; Sabry, N.A.; Fawzi, M.; Mousa, S. The Effect of Vitamin K4 Supplementation on Insulin Resistance in Individuals with Type 2 Diabetes: A Double-Blind Randomised Placebo-Controlled Clinical Trial. *Eur. J. Nutr.* **2023**, *62*, 3241–3249. [[CrossRef](#)]
28. Adeli, S.; Pourghassem Gargari, B.; Karamzad, N. The Effects of Vitamin K2 (Menaquinone-7) on the Leptin and Adiponectin Levels in Overweight/Obese Type 2 Diabetes Patients: A Randomized Clinical Trial. *Pharm. Sci.* **2023**, *29*, 346–354. [[CrossRef](#)]
29. Rahimi Sakak, F.; Moslehi, N.; Niroomand, M.; Mirmiran, P. Glycemic Control Improvement in Individuals with Type 2 Diabetes with Vitamin K2 Supplementation: A Randomized Controlled Trial. *Eur. J. Nutr.* **2021**, *60*, 2495–2506. [[CrossRef](#)]
30. Tarkesh, F.; Namavar Jahromi, B.; Hejazi, N.; Tabatabaee, H. Beneficial Health Effects of Menaquinone-7 on Body Composition, Glycemic Indices, Lipid Profile, and Endocrine Markers in Polycystic Ovary Syndrome Patients. *Food Sci. Nutr.* **2020**, *8*, 5612–5621. [[CrossRef](#)]
31. Karamzad, N.; Faraji, E.; Adeli, S.; Carson-Chahhoud, K.; Azizi, S.; Pourghassem Gargari, B. Effects of MK-7 Supplementation on Glycemic Status, Anthropometric Indices and Lipid Profile in Patients with Type 2 Diabetes: A Randomized Controlled Trial. *Diabetes Metab. Syndr. Obes. Targets Ther.* **2020**, *13*, 2239–2249. [[CrossRef](#)]
32. Manna, P.; Kalita, J. Beneficial Role of Vitamin K Supplementation on Insulin Sensitivity, Glucose Metabolism, and the Reduced Risk of Type 2 Diabetes: A Review. *Nutrition* **2016**, *32*, 732–739. [[CrossRef](#)]
33. Ho, H.-J.; Komai, M.; Shirakawa, H. Beneficial Effects of Vitamin K Status on Glycemic Regulation and Diabetes Mellitus: A Mini-Review. *Nutrients* **2020**, *12*, 2485. [[CrossRef](#)]
34. Aaseth, J.O.; Finnes, T.E.; Askim, M.; Alexander, J. The Importance of Vitamin K and the Combination of Vitamins K and D for Calcium Metabolism and Bone Health: A Review. *Nutrients* **2024**, *16*, 2420. [[CrossRef](#)] [[PubMed](#)]

35. Mladěnka, P.; Macáková, K.; Kujovská Krčmová, L.; Javorská, L.; Mrštná, K.; Carazo, A.; Protti, M.; Remião, F.; Nováková, L. the OEMONOM researchers and collaborators. Vitamin K—Sources, Physiological Role, Kinetics, Deficiency, Detection, Therapeutic Use, and Toxicity. *Nutr. Rev.* **2022**, *80*, 677–698. [[CrossRef](#)] [[PubMed](#)]
36. Halder, M.; Petsophonsakul, P.; Akbulut, A.C.; Pavlic, A.; Bohan, F.; Anderson, E.; Maresz, K.; Kramann, R.; Schurgers, L. Vitamin K: Double Bonds beyond Coagulation Insights into Differences between Vitamin K1 and K2 in Health and Disease. *Int. J. Mol. Sci.* **2019**, *20*, 896. [[CrossRef](#)] [[PubMed](#)]
37. Akbulut, A.C.; Pavlic, A.; Petsophonsakul, P.; Halder, M.; Maresz, K.; Kramann, R.; Schurgers, L. Vitamin K2 Needs an RDI Separate from Vitamin K1. *Nutrients* **2020**, *12*, 1852. [[CrossRef](#)]
38. Shea, M.K.; Berkner, K.L.; Ferland, G.; Fu, X.; Holden, R.M.; Booth, S.L. Perspective: Evidence before Enthusiasm—A Critical Review of the Potential Cardiovascular Benefits of Vitamin K. *Adv. Nutr.* **2021**, *12*, 632–646. [[CrossRef](#)]
39. Simes, D.C.; Viegas, C.S.B.; Araújo, N.; Marreiros, C. Vitamin K as a Diet Supplement with Impact in Human Health: Current Evidence in Age-Related Diseases. *Nutrients* **2020**, *12*, 138. [[CrossRef](#)]
40. Schurgers, L.J.; Vermeer, C. Determination of Phylloquinone and Menaquinones in Food. *Pathophysiol. Haemost. Thromb.* **2000**, *30*, 298–307. [[CrossRef](#)]
41. Shearer, M.J.; Newman, P. Metabolism and Cell Biology of Vitamin K. *Thromb. Haemost.* **2008**, *100*, 530–547.
42. Ferland, G.; Doucet, I.; Mainville, D. Phylloquinone and Menaquinone-4 Tissue Distribution at Different Life Stages in Male and Female Sprague–Dawley Rats Fed Different VK Levels Since Weaning or Subjected to a 40% Calorie Restriction since Adulthood. *Nutrients* **2016**, *8*, 141. [[CrossRef](#)] [[PubMed](#)]
43. Loor, G.; Kondapalli, J.; Schriewer, J.M.; Chandel, N.S.; Vanden Hoek, T.L.; Schumacker, P.T. Menadione Triggers Cell Death through ROS-Dependent Mechanisms Involving PARP Activation without Requiring Apoptosis. *Free Radic. Biol. Med.* **2010**, *49*, 1925–1936. [[CrossRef](#)]
44. Munday, R.; Smith, B.L.; Munday, C.M. Toxicity of 2,3-Dialkyl-1,4-Naphthoquinones in Rats: Comparison with Cytotoxicity in Vitro. *Free Radic. Biol. Med.* **1995**, *19*, 759–765. [[CrossRef](#)]
45. Girolami, A.; Ferrari, S.; Cosi, E.; Santarossa, C.; Randi, M.L. Vitamin K-Dependent Coagulation Factors That May Be Responsible for Both Bleeding and Thrombosis (FII, FVII, and FIX). *Clin. Appl. Thromb.* **2018**, *24*, 42S–47S. [[CrossRef](#)]
46. Muller, M.P.; Wang, Y.; Morrissey, J.H.; Tajkhorshid, E. Lipid Specificity of the Membrane Binding Domain of Coagulation Factor X. *J. Thromb. Haemost.* **2017**, *15*, 2005–2016. [[CrossRef](#)] [[PubMed](#)]
47. Ten Kate, M.K.; Van Der Meer, J. Protein S Deficiency: A Clinical Perspective. *Haemophilia* **2008**, *14*, 1222–1228. [[CrossRef](#)] [[PubMed](#)]
48. Esmon, C.T. The Protein C Pathway. *Chest* **2003**, *124*, 26S–32S. [[CrossRef](#)]
49. Broze, G. Protein Z-Dependent Regulation of Coagulation. *Thromb. Haemost.* **2001**, *86*, 08–13. [[CrossRef](#)]
50. Karsenty, G. Osteocalcin: A Multifaceted Bone-Derived Hormone. *Annu. Rev. Nutr.* **2023**, *43*, 55–71. [[CrossRef](#)]
51. Zhu, S.; Barbe, M.F.; Liu, C.; Hadjiargyrou, M.; Popoff, S.N.; Rani, S.; Safadi, F.F.; Litvin, J. Periostin-like-factor in Osteogenesis. *J. Cell. Physiol.* **2009**, *218*, 584–592. [[CrossRef](#)]
52. Duchamp De Lageneste, O.; Julien, A.; Abou-Khalil, R.; Frangi, G.; Carvalho, C.; Cagnard, N.; Cordier, C.; Conway, S.J.; Colnot, C. Periosteum Contains Skeletal Stem Cells with High Bone Regenerative Potential Controlled by Periostin. *Nat. Commun.* **2018**, *9*, 773. [[CrossRef](#)] [[PubMed](#)]
53. Chang, L.-C.; Lin, H.-S.; Chen, W.-C. The Reappraisal of Nephrocalcin—Its Role in the Inhibition of Calcium Oxalate Crystal Growth and Interaction with Divalent Metal Ions. *Urol. Res.* **2001**, *29*, 89–93. [[CrossRef](#)] [[PubMed](#)]
54. El Asmar, M.; Naoum, J.; Arbid, E. Vitamin K Dependent Proteins and the Role of Vitamin K2 in the Modulation of Vascular Calcification: A Review. *Oman Med. J.* **2014**, *29*, 172–177. [[CrossRef](#)]
55. Viegas, C.S.; Simes, D.C. Gla-Rich Protein (GRP): A New Player In The Burden Of Vascular Calcification. *J. Cardiovasc. Dis. Diagn.* **2016**, *4*, 2. [[CrossRef](#)]
56. Zhuo, L.; Kimata, K. Structure and Function of Inter- $\alpha$ -Trypsin Inhibitor Heavy Chains. *Connect. Tissue Res.* **2008**, *49*, 311–320. [[CrossRef](#)] [[PubMed](#)]
57. Qiu, C.; Zheng, H.; Tao, H.; Yu, W.; Jiang, X.; Li, A.; Jin, H.; Lv, A.; Li, H. Vitamin K2 Inhibits Rat Vascular Smooth Muscle Cell Calcification by Restoring the Gas6/Axl/Akt Anti-Apoptotic Pathway. *Mol. Cell. Biochem.* **2017**, *433*, 149–159. [[CrossRef](#)]
58. Kulman, J.D.; Harris, J.E.; Xie, L.; Davie, E.W. Proline-Rich Gla Protein 2 Is a Cell-Surface Vitamin K-Dependent Protein That Binds to the Transcriptional Coactivator Yes-Associated Protein. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 8767–8772. [[CrossRef](#)]
59. Kulman, J.D.; Harris, J.E.; Haldeman, B.A.; Davie, E.W. Primary Structure and Tissue Distribution of Two Novel Proline-Rich  $\gamma$ -Carboxyglutamic Acid Proteins. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 9058–9062. [[CrossRef](#)]
60. Kulman, J.D.; Harris, J.E.; Xie, L.; Davie, E.W. Identification of Two Novel Transmembrane  $\gamma$ -Carboxyglutamic Acid Proteins Expressed Broadly in Fetal and Adult Tissues. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 1370–1375. [[CrossRef](#)]

61. Ho, H.-J.; Shirakawa, H.; Komai, M. Menaquinone-4 Enhances Steroidogenesis in Testis Derived Tumor Cells Via the Elevation of cAMP Level. In *Vitamin K2—Vital for Health and Wellbeing*; Gordeladze, J.O., Ed.; InTech: London, UK, 2017. Available online: <http://www.intechopen.com/books/vitamin-k2-vital-for-health-and-wellbeing/menaquinone-4-enhances-steroidogenesis-in-testis-derived-tumor-cells-via-the-elevation-of-camp-level> (accessed on 2 July 2025).
62. Ichikawa, T.; Horie-Inoue, K.; Ikeda, K.; Blumberg, B.; Inoue, S. Vitamin K2 Induces Phosphorylation of Protein Kinase A and Expression of Novel Target Genes in Osteoblastic Cells. *J. Mol. Endocrinol.* **2007**, *39*, 239–247. [[CrossRef](#)]
63. Ito, A.; Shirakawa, H.; Takumi, N.; Minegishi, Y.; Ohashi, A.; Howlader, Z.H.; Ohsaki, Y.; Sato, T.; Goto, T.; Komai, M. Menaquinone-4 Enhances Testosterone Production in Rats and Testis-Derived Tumor Cells. *Lipids Health Dis.* **2011**, *10*, 158. [[CrossRef](#)] [[PubMed](#)]
64. Otsuka, M.; Kato, N.; Shao, R.-X.; Hoshida, Y.; Ijichi, H.; Koike, Y.; Taniguchi, H.; Moriyama, M.; Shiratori, Y.; Kawabe, T.; et al. Vitamin K2 Inhibits the Growth and Invasiveness of Hepatocellular Carcinoma Cells via Protein Kinase A Activation. *Hepatology* **2004**, *40*, 243–251. [[CrossRef](#)]
65. Tsang, C.K.; Kamei, Y. Novel Effect of Vitamin K1 (Phylloquinone) and Vitamin K2 (Menaquinone) on Promoting Nerve Growth Factor-Mediated Neurite Outgrowth from PC12D Cells. *Neurosci. Lett.* **2002**, *323*, 9–12. [[CrossRef](#)]
66. Staudinger, J.L.; Mahroke, A.; Patel, G.; Dattel, C.; Reddy, S. Pregnane X Receptor Signaling Pathway and Vitamin K: Molecular Mechanisms and Clinical Relevance in Human Health. *Cells* **2024**, *13*, 681. [[CrossRef](#)]
67. Azuma, K.; Inoue, S. Multiple Modes of Vitamin K Actions in Aging-Related Musculoskeletal Disorders. *Int. J. Mol. Sci.* **2019**, *20*, 2844. [[CrossRef](#)]
68. Welsh, J.; Bak, M.J.; Narvaez, C.J. New Insights into Vitamin K Biology with Relevance to Cancer. *Trends Mol. Med.* **2022**, *28*, 864–881. [[CrossRef](#)]
69. Maniwa, Y.; Kasukabe, T.; Kumakura, S. Vitamin K2 and Cotylenin A Synergistically Induce Monocytic Differentiation and Growth Arrest along with the Suppression of C-MYC Expression and Induction of Cyclin G2 Expression in Human Leukemia HL-60 Cells. *Int. J. Oncol.* **2015**, *47*, 473–480. [[CrossRef](#)]
70. Yamamoto, T.; Nakamura, H.; Liu, W.; Cao, K.; Yoshikawa, S.; Enomoto, H.; Iwata, Y.; Koh, N.; Saito, M.; Imanishi, H.; et al. Involvement of Hepatoma-Derived Growth Factor in the Growth Inhibition of Hepatocellular Carcinoma Cells by Vitamin K(2). *J. Gastroenterol.* **2009**, *44*, 228–235. [[CrossRef](#)]
71. Duan, F.; Yu, Y.; Guan, R.; Xu, Z.; Liang, H.; Hong, L. Vitamin K2 Induces Mitochondria-Related Apoptosis in Human Bladder Cancer Cells via ROS and JNK/P38 MAPK Signal Pathways. *PLoS ONE* **2016**, *11*, e0161886. [[CrossRef](#)]
72. Popa, D.-S.; Bigman, G.; Rusu, M.E. The Role of Vitamin K in Humans: Implication in Aging and Age-Associated Diseases. *Antioxidants* **2021**, *10*, 566. [[CrossRef](#)]
73. Xv, F.; Chen, J.; Duan, L.; Li, S. Research Progress on the Anticancer Effects of Vitamin K2 (Review). *Oncol. Lett.* **2018**, *15*, 8926–8934. Available online: <http://www.spandidos-publications.com/10.3892/ol.2018.8502> (accessed on 28 July 2025). [[CrossRef](#)]
74. Wu, J.; Shi, Y.; Zhou, M.; Chen, M.; Ji, S.; Liu, X.; Zhou, M.; Xia, R.; Zheng, X.; Wang, W. Nutrient Vitamins Enabled Metabolic Regulation of Ferroptosis via Reactive Oxygen Species Biology. *Front. Pharmacol.* **2024**, *15*, 1434088. [[CrossRef](#)]
75. Kolbrink, B.; Von Samson-Himmelstjerna, F.A.; Messtorff, M.L.; Riebeling, T.; Nische, R.; Schmitz, J.; Bräsen, J.H.; Kunzendorf, U.; Krautwald, S. Vitamin K1 Inhibits Ferroptosis and Counteracts a Detrimental Effect of Phenprocoumon in Experimental Acute Kidney Injury. *Cell. Mol. Life Sci.* **2022**, *79*, 387. [[CrossRef](#)]
76. Tsugawa, N.; Shiraki, M. Vitamin K Nutrition and Bone Health. *Nutrients* **2020**, *12*, 1909. [[CrossRef](#)]
77. Willett, W.C. *Nutritional Epidemiology*, 3rd ed.; Monographs in Epidemiology and Biostatistics; Oxford University Press: Oxford, UK, 2013; 1p.
78. Shea, M.; Booth, S. Concepts and Controversies in Evaluating Vitamin K Status in Population-Based Studies. *Nutrients* **2016**, *8*, 8. [[CrossRef](#)] [[PubMed](#)]
79. Braam, L.; McKeown, N.; Jacques, P.; Lichtenstein, A.; Vermeer, C.; Wilson, P.; Booth, S. Dietary Phylloquinone Intake as a Potential Marker for a Heart-Healthy Dietary Pattern in the Framingham Offspring Cohort. *J. Am. Diet. Assoc.* **2004**, *104*, 1410–1414. [[CrossRef](#)] [[PubMed](#)]
80. Westerterp, K.R.; Goris, A.H.C. Validity of the Assessment of Dietary Intake: Problems of Misreporting. *Curr. Opin. Clin. Nutr. Metab. Care* **2002**, *5*, 489–493. [[CrossRef](#)]
81. Gundberg, C.M.; Lian, J.B.; Booth, S.L. Vitamin K-Dependent Carboxylation of Osteocalcin: Friend or Foe? *Adv. Nutr.* **2012**, *3*, 149–157. [[CrossRef](#)] [[PubMed](#)]
82. Booth, S.L.; Centi, A.; Smith, S.R.; Gundberg, C. The Role of Osteocalcin in Human Glucose Metabolism: Marker or Mediator? *Nat. Rev. Endocrinol.* **2013**, *9*, 43–55. [[CrossRef](#)]
83. Bernhard, M.; Okorie, O.; Tseng, W.-J.; Chen, M.; Danon, J.; Cui, M.; Lashbrooks, E.; Yang, Y.; Wang, B. Metabolic Shifts in Ratio of ucOcn to cOcn toward Bone Resorption Contribute to Age-Dependent Bone Loss in Male Mice. *Am. J. Physiol.-Endocrinol. Metab.* **2024**, *327*, E711–E722. [[CrossRef](#)]
84. Nowicki, J.K.; Jakubowska-Pietkiewicz, E. Osteocalcin: Beyond Bones. *Endocrinol. Metab.* **2024**, *39*, 399–406. [[CrossRef](#)]

85. O'Donnell, C.J.; Shea, M.K.; Price, P.A.; Gagnon, D.R.; Wilson, P.W.F.; Larson, M.G.; Kiel, D.P.; Hoffmann, U.; Ferencik, M.; Clouse, M.E.; et al. Matrix Gla Protein Is Associated With Risk Factors for Atherosclerosis but Not With Coronary Artery Calcification. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 2769–2774. [CrossRef]
86. Booth, S.L.; Rajabi, A.A. Determinants of Vitamin K Status in Humans. In *Vitamins & Hormones*; Elsevier: Amsterdam, The Netherlands, 2008; pp. 1–22. Available online: <https://linkinghub.elsevier.com/retrieve/pii/S0083672907000015> (accessed on 8 August 2025).
87. Delanaye, P.; Dubois, B.E.; Lukas, P.; Peters, P.; Krzesinski, J.-M.; Pottel, H.; Cavalier, E. Impact of Stopping Vitamin K Antagonist Therapy on Concentrations of Dephospho-Uncarboxylated Matrix Gla Protein. *Clin. Chem. Lab. Med.* **2015**, *53*, e191–e193. [CrossRef]
88. Truong, J.T.; Fu, X.; Saltzman, E.; Al Rajabi, A.; Dallal, G.E.; Gundberg, C.M.; Booth, S.L. Age Group and Sex Do Not Influence Responses of Vitamin K Biomarkers to Changes in Dietary Vitamin K. *J. Nutr.* **2012**, *142*, 936–941. [CrossRef] [PubMed]
89. Dupuy, M.; Bondonno, N.P.; Pokharel, P.; Linneberg, A.; Levinger, I.; Schultz, C.; Hodgson, J.M.; Sim, M. Vitamin K: Metabolism, Genetic Influences, and Chronic Disease Outcomes. *Food Sci. Nutr.* **2025**, *13*, e70431. [CrossRef] [PubMed]
90. Dashti, H.S.; Shea, M.K.; Smith, C.E.; Tanaka, T.; Hruby, A.; Richardson, K.; Wang, T.J.; Nalls, M.A.; Guo, X.; Liu, Y.; et al. Meta-Analysis of Genome-Wide Association Studies for Circulating Phylloquinone Concentrations. *Am. J. Clin. Nutr.* **2014**, *100*, 1462–1469. [CrossRef]
91. Tie, J.K.; Stafford, D.W. Structural and Functional Insights into Enzymes of the Vitamin K Cycle. *J. Thromb. Haemost.* **2016**, *14*, 236–247. [CrossRef]
92. Edson, K.Z.; Prasad, B.; Unadkat, J.D.; Suhara, Y.; Okano, T.; Guengerich, F.P.; Rettie, A.E. Cytochrome P450-Dependent Catabolism of Vitamin K:  $\omega$ -Hydroxylation Catalyzed by Human CYP4F2 and CYP4F11. *Biochemistry* **2013**, *52*, 8276–8285. [CrossRef] [PubMed]
93. Shea, M.K.; Booth, S.L.; Nettleton, J.A.; Burke, G.L.; Chen, H.; Kritchevsky, S.B. Circulating Phylloquinone Concentrations of Adults in the United States Differ According to Race and Ethnicity. *J. Nutr.* **2012**, *142*, 1060–1066. [CrossRef]
94. Hirai, K.; Yamada, Y.; Hayashi, H.; Tanaka, M.; Izumiya, K.; Suzuki, M.; Yoshizawa, M.; Moriwaki, H.; Akimoto, T.; Tsuji, D.; et al. Plasma Vitamin K Concentrations Depend on CYP4F2 Polymorphism and Influence on Anticoagulation in Japanese Patients with Warfarin Therapy. *Thromb. Res.* **2015**, *135*, 861–866. [CrossRef]
95. Crosier, M.D.; Peter, I.; Booth, S.L.; Bennett, G.; Dawson-Hughes, B.; Ordovas, J.M. Association of Sequence Variations in Vitamin K Epoxide Reductase and  $\gamma$ -Glutamyl Carboxylase Genes with Biochemical Measures of Vitamin K Status. *J. Nutr. Sci. Vitaminol.* **2009**, *55*, 112–119. [CrossRef] [PubMed]
96. Zhou, Z.; Zhang, N.; Lin, T.; Song, Y.; Liu, L.; Wang, Z.; Wei, Y.; Li, J.; Zhang, Y.; Huo, Y.; et al. Plasma 25-Hydroxyvitamin D3 Concentrations and Incident Risk of Ischemic Stroke in Rural Chinese Adults: New Insight on Ceiling Effect. *Nutrition* **2022**, *99–100*, 111627. [CrossRef]
97. Bouillon, R.; Manousaki, D.; Rosen, C.; Trajanoska, K.; Rivadeneira, F.; Richards, J.B. The Health Effects of Vitamin D Supplementation: Evidence from Human Studies. *Nat. Rev. Endocrinol.* **2022**, *18*, 96–110. [CrossRef] [PubMed]
98. Morris, M.C.; Tangney, C.C. A Potential Design Flaw of Randomized Trials of Vitamin Supplements. *JAMA* **2011**, *305*, 1348. [CrossRef] [PubMed]
99. Levy-Schousboe, K.; Frimodt-Møller, M.; Hansen, D.; Peters, C.D.; Kjærgaard, K.D.; Jensen, J.D.; Strandhave, C.; Elming, H.; Larsen, C.T.; Sandstrøm, H.; et al. Vitamin K Supplementation and Arterial Calcification in Dialysis: Results of the Double-Blind, Randomized, Placebo-Controlled RenaKvit Trial. *Clin. Kidney J.* **2021**, *14*, 2114–2123. [CrossRef]
100. Aoun, M.; Makki, M.; Azar, H.; Matta, H.; Chelala, D.N. High Dephosphorylated-Uncarboxylated MGP in Hemodialysis Patients: Risk Factors and Response to Vitamin K2, A Pre-Post Intervention Clinical Trial. *BMC Nephrol.* **2017**, *18*, 191. [CrossRef]
101. O'Connor, E.M.; Greal, G.; McCarthy, J.; Desmond, A.; Craig, O.; Shanahan, F.; Cashman, K.D. Effect of Phylloquinone (Vitamin K<sub>1</sub>) Supplementation for 12 Months on the Indices of Vitamin K Status and Bone Health in Adult Patients with Crohn's Disease. *Br. J. Nutr.* **2014**, *112*, 1163–1174. [CrossRef]
102. Vermeer, C.; Vik, H. Effect of Menaquinone-7 (Vitamin K2) on Vascular Elasticity in Healthy Subjects: Results from a One-Year Study. *Vasc. Dis. Ther.* **2020**, *5*, 1–4. Available online: <https://www.oatext.com/effect-of-menaquinone-7-vitamin-k2-on-vascular-elasticity-in-healthy-subjects-results-from-a-one-year-study.php> (accessed on 14 August 2025). [CrossRef]
103. Knapen, M.H.J.; Jardon, K.M.; Vermeer, C. Vitamin K-Induced Effects on Body Fat and Weight: Results from a 3-Year Vitamin K2 Intervention Study. *Eur. J. Clin. Nutr.* **2017**, *72*, 136–141. [CrossRef] [PubMed]
104. Neogi, T.; Felson, D.T.; Sarno, R.; Booth, S.L. Vitamin K in Hand Osteoarthritis: Results from a Randomised Clinical Trial. *Ann. Rheum. Dis.* **2008**, *67*, 1570–1573. [CrossRef] [PubMed]
105. Ikari, Y.; Torii, S.; Shioi, A.; Okano, T. Impact of Menaquinone-4 Supplementation on Coronary Artery Calcification and Arterial Stiffness: An Open Label Single Arm Study. *Nutr. J.* **2015**, *15*, 53. [CrossRef]
106. Sabatini, P.V.; Speckmann, T.; Lynn, F.C. Friend and Foe:  $\beta$ -Cell Ca<sup>2+</sup> Signaling and the Development of Diabetes. *Mol. Metab.* **2019**, *21*, 1–12. [CrossRef]

107. Gilon, P.; Chae, H.-Y.; Rutter, G.A.; Ravier, M.A. Calcium Signaling in Pancreatic  $\beta$ -Cells in Health and in Type 2 Diabetes. *Cell Calcium* **2014**, *56*, 340–361. [[CrossRef](#)] [[PubMed](#)]
108. Zhang, I.X.; Raghavan, M.; Satin, L.S. The Endoplasmic Reticulum and Calcium Homeostasis in Pancreatic Beta Cells. *Endocrinology* **2020**, *161*, bqz028. [[CrossRef](#)]
109. Kono, T.; Tong, X.; Taleb, S.; Bone, R.N.; Iida, H.; Lee, C.-C.; Sohn, P.; Gilon, P.; Roe, M.W.; Evans-Molina, C. Impaired Store-Operated Calcium Entry and STIM1 Loss Lead to Reduced Insulin Secretion and Increased Endoplasmic Reticulum Stress in the Diabetic  $\beta$ -Cell. *Diabetes* **2018**, *67*, 2293–2304. [[CrossRef](#)] [[PubMed](#)]
110. Sabourin, J.; Le Gal, L.; Saurwein, L.; Haeffliger, J.-A.; Raddatz, E.; Allagnat, F. Store-Operated  $\text{Ca}^{2+}$  Entry Mediated by Orai1 and TRPC1 Participates to Insulin Secretion in Rat  $\beta$ -Cells. *J. Biol. Chem.* **2015**, *290*, 30530–30539. [[CrossRef](#)]
111. Marmugi, A.; Parnis, J.; Chen, X.; Carmichael, L.; Hardy, J.; Mannan, N.; Marchetti, P.; Piemonti, L.; Bosco, D.; Johnson, P.; et al. Sorcin Links Pancreatic  $\beta$ -Cell Lipotoxicity to ER  $\text{Ca}^{2+}$  Stores. *Diabetes* **2016**, *65*, 1009–1021. [[CrossRef](#)] [[PubMed](#)]
112. Zhang, I.X.; Ren, J.; Vadrevu, S.; Raghavan, M.; Satin, L.S. ER Stress Increases Store-Operated  $\text{Ca}^{2+}$  Entry (SOCE) and Augments Basal Insulin Secretion in Pancreatic Beta Cells. *J. Biol. Chem.* **2020**, *295*, 5685–5700. [[CrossRef](#)]
113. Mittendorfer, B.; Patterson, B.W.; Smith, G.I.; Yoshino, M.; Klein, S.  $\beta$  Cell Function and Plasma Insulin Clearance in People with Obesity and Different Glycemic Status. *J. Clin. Invest.* **2022**, *132*, e154068. [[CrossRef](#)] [[PubMed](#)]
114. Hudish, L.I.; Reusch, J.E.B.; Sussel, L.  $\beta$  Cell Dysfunction during Progression of Metabolic Syndrome to Type 2 Diabetes. *J. Clin. Investig.* **2019**, *129*, 4001–4008. [[CrossRef](#)]
115. Stožer, A.; Paradiž Leitgeb, E.; Pohorec, V.; Dolenšek, J.; Križančič Bombek, L.; Gosak, M.; Skelin Klemen, M. The Role of cAMP in Beta Cell Stimulus–Secretion and Intercellular Coupling. *Cells* **2021**, *10*, 1658. [[CrossRef](#)]
116. Song, W.-J.; Mondal, P.; Li, Y.; Lee, S.E.; Hussain, M.A. Pancreatic  $\beta$ -Cell Response to Increased Metabolic Demand and to Pharmacologic Secretagogues Requires EPAC2A. *Diabetes* **2013**, *62*, 2796–2807. [[CrossRef](#)]
117. Holz, G.G. Epac: A New cAMP-Binding Protein in Support of Glucagon-like Peptide-1 Receptor-Mediated Signal Transduction in the Pancreatic Beta-Cell. *Diabetes* **2004**, *53*, 5–13. [[CrossRef](#)]
118. Kashima, Y.; Miki, T.; Shibasaki, T.; Ozaki, N.; Miyazaki, M.; Yano, H.; Seino, S. Critical Role of cAMP-GEFII-Rim2 Complex in Incretin-Potentiated Insulin Secretion. *J. Biol. Chem.* **2001**, *276*, 46046–46053. [[CrossRef](#)] [[PubMed](#)]
119. Nauck, M.A.; Meier, J.J. The Incretin Effect in Healthy Individuals and Those with Type 2 Diabetes: Physiology, Pathophysiology, and Response to Therapeutic Interventions. *Lancet Diabetes Endocrinol.* **2016**, *4*, 525–536. [[CrossRef](#)] [[PubMed](#)]
120. Bagger, J.I.; Knop, F.K.; Lund, A.; Vestergaard, H.; Holst, J.J.; Vilsbøll, T. Impaired Regulation of the Incretin Effect in Patients with Type 2 Diabetes. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 737–745. [[CrossRef](#)]
121. Dihingia, A.; Ozah, D.; Baruah, P.K.; Kalita, J.; Manna, P. Prophylactic Role of Vitamin K Supplementation on Vascular Inflammation in Type 2 Diabetes by Regulating the NF- $\kappa$ B/Nrf2 Pathway via Activating Gla Proteins. *Food Funct.* **2018**, *9*, 450–462. [[CrossRef](#)]
122. Garbuzova, V.Y.; Ataman, A.V. Matrix Gla-Protein and Its Role in Vascular Calcification. *Int. J. Physiol. Pathophysiol.* **2012**, *3*, 79–99. [[CrossRef](#)]
123. Bjørklund, G.; Svanberg, E.; Dadar, M.; Card, D.J.; Chirumbolo, S.; Harrington, D.J.; Aaseth, J. The Role of Matrix Gla Protein (MGP) in Vascular Calcification. *Curr. Med. Chem.* **2020**, *27*, 1647–1660. [[CrossRef](#)]
124. Evrard, S.; Delanaye, P.; Kamel, S.; Cristol, J.-P.; Cavalier, E.; Arnaud, J.; Zaoui, P.; Carlier, M.C.; Laville, M.; Fouque, D.; et al. Vascular Calcification: From Pathophysiology to Biomarkers. *Clin. Chim. Acta* **2015**, *438*, 401–414. [[CrossRef](#)]
125. Barrett, H.; O’Keeffe, M.; Kavanagh, E.; Walsh, M.; O’Connor, E. Is Matrix Gla Protein Associated with Vascular Calcification? A Systematic Review. *Nutrients* **2018**, *10*, 415. [[CrossRef](#)] [[PubMed](#)]
126. Shearer, M.J.; Okano, T. Key Pathways and Regulators of Vitamin K Function and Intermediary Metabolism. *Annu. Rev. Nutr.* **2018**, *38*, 127–151. [[CrossRef](#)] [[PubMed](#)]
127. Rothlin, C.V.; Carrera-Silva, E.A.; Bosurgi, L.; Ghosh, S. TAM Receptor Signaling in Immune Homeostasis. *Annu. Rev. Immunol.* **2015**, *33*, 355–391. [[CrossRef](#)]
128. Van Der Meer, J.H.M.; Van Der Poll, T.; Van ’T Veer, C. TAM Receptors, Gas6, and Protein S: Roles in Inflammation and Hemostasis. *Blood* **2014**, *123*, 2460–2469. [[CrossRef](#)]
129. Mukherjee, S.K.; Wilhelm, A.; Antoniadis, C.G. TAM Receptor Tyrosine Kinase Function and the Immunopathology of Liver Disease. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **2016**, *310*, G899–G905. [[CrossRef](#)]
130. Gilchrist, S.E.; Goudarzi, S.; Hafizi, S. Gas6 Inhibits Toll-Like Receptor-Mediated Inflammatory Pathways in Mouse Microglia via Axl and Mer. *Front. Cell. Neurosci.* **2020**, *14*, 576650. Available online: <https://www.frontiersin.org/article/10.3389/fncel.2020.576650/full> (accessed on 14 July 2025). [[CrossRef](#)] [[PubMed](#)]
131. Rizzi, M.; Tonello, S.; D’Onghia, D.; Sainaghi, P.P. Gas6/TAM Axis Involvement in Modulating Inflammation and Fibrosis in COVID-19 Patients. *Int. J. Mol. Sci.* **2023**, *24*, 951. [[CrossRef](#)]

132. Nassar, M.; Tabib, Y.; Capucha, T.; Mizraji, G.; Nir, T.; Saba, F.; Salameh, R.; Eli-Berchoer, L.; Wilensky, A.; Burstyn-Cohen, T.; et al. Multiple Regulatory Levels of Growth Arrest-Specific 6 in Mucosal Immunity Against an Oral Pathogen. *Front. Immunol.* **2018**, *9*, 1374. Available online: <https://www.frontiersin.org/article/10.3389/fimmu.2018.01374/full> (accessed on 14 July 2025). [CrossRef]
133. Ohsaki, Y.; Shirakawa, H.; Miura, A.; Giriwono, P.E.; Sato, S.; Ohashi, A.; Iribe, M.; Goto, T.; Komai, M. Vitamin K Suppresses the Lipopolysaccharide-Induced Expression of Inflammatory Cytokines in Cultured Macrophage-like Cells via the Inhibition of the Activation of Nuclear Factor  $\kappa$ B through the Repression of IKK $\alpha$ / $\beta$  Phosphorylation. *J. Nutr. Biochem.* **2010**, *21*, 1120–1126. [CrossRef]
134. Ozaki, I.; Zhang, H.; Mizuta, T.; Ide, Y.; Eguchi, Y.; Yasutake, T.; Sakamaki, T.; Pestell, R.G.; Yamamoto, K. Menatetrenone, a Vitamin K2 Analogue, Inhibits Hepatocellular Carcinoma Cell Growth by Suppressing Cyclin D1 Expression through Inhibition of Nuclear Factor  $\kappa$ B Activation. *Clin. Cancer Res.* **2007**, *13*, 2236–2245. [CrossRef]
135. Kieronska-Rudek, A.; Kij, A.; Kaczara, P.; Tworzydło, A.; Napiorkowski, M.; Sidoryk, K.; Chłopicki, S. Exogenous Vitamins K Exert Anti-Inflammatory Effects Dissociated from Their Role as Substrates for Synthesis of Endogenous MK-4 in Murine Macrophages Cell Line. *Cells* **2021**, *10*, 1571. [CrossRef]
136. Li, J.; Wang, H.; Rosenberg, P.A. Vitamin K Prevents Oxidative Cell Death by Inhibiting Activation of 12-lipoxygenase in Developing Oligodendrocytes. *J. Neurosci. Res.* **2009**, *87*, 1997–2005. [CrossRef]
137. El-Sherbiny, M.; Atef, H.; Helal, G.M.; Al-Serwi, R.H.; Elkattawy, H.A.; Shaker, G.A.; Said, E.; Abulfaraj, M.; Albalawi, M.A.; Elsherbiny, N.M. Vitamin K2 (MK-7) Intercepts Keap-1/Nrf-2/HO-1 Pathway and Hinders Inflammatory/Apoptotic Signaling and Liver Aging in Naturally Aging Rat. *Antioxidants* **2022**, *11*, 2150. [CrossRef]
138. Aloufi, A.M.; Aldobikhi, Y.A.; Binhudayb, N.A.; AlTorkai, R.H.A.; El-Sherbiny, M.; Elkattawy, H.A.; Eladl, M.A.; El-Shafey, M.; Hadhod, S.; Elsherbiny, N. Vitamin K2 (MK-7) Modulated Nrf2/NLRP3/Caspase-1 Axis to Protect against Age-related Structural and Cognitive Deterioration in Naturally Aged Rats. *FASEB J.* **2022**, *36*. Available online: <https://faseb.onlinelibrary.wiley.com/doi/10.1096/fasebj.2022.36.S1.R3319> (accessed on 23 July 2025). [CrossRef]
139. Zheng, X.; Hou, Y.; He, H.; Chen, Y.; Zhou, R.; Wang, X.; Gong, T.; Jiang, W. Synthetic Vitamin K Analogs Inhibit Inflammation by Targeting the NLRP3 Inflammasome. *Cell. Mol. Immunol.* **2021**, *18*, 2422–2430. [CrossRef]
140. Varsha, M.K.N.S.; Thiagarajan, R.; Manikandan, R.; Dhanasekaran, G. Vitamin K1 Alleviates Streptozotocin-Induced Type 1 Diabetes by Mitigating Free Radical Stress, as Well as Inhibiting NF- $\kappa$ B Activation and iNOS Expression in Rat Pancreas. *Nutrition* **2015**, *31*, 214–222. [CrossRef] [PubMed]
141. Lai, Y.; Masatoshi, H.; Ma, Y.; Guo, Y.; Zhang, B. Role of Vitamin K in Intestinal Health. *Front. Immunol.* **2022**, *12*, 791565. [CrossRef] [PubMed]
142. Quarta, G.; Kim, S.; Cho, I.; Blaser, M. Mo1817 Warfarin Induces Intestinal Dysbiosis Involving Vitamin K-Expressing Bacteria. *Gastroenterology* **2015**, *148*, S-718. [CrossRef]
143. Ellis, J.L.; Karl, J.P.; Oliverio, A.M.; Fu, X.; Soares, J.W.; Wolfe, B.E.; Hernandez, C.J.; Mason, J.B.; Booth, S.L. Dietary Vitamin K Is Remodeled by Gut Microbiota and Influences Community Composition. *Gut Microbes* **2021**, *13*, 1887721. [CrossRef]
144. Mathers, J.C.; Fernandez, F.; Hill, M.J.; McCarthy, P.T.; Shearer, M.J.; Oxley, A. Dietary Modification of Potential Vitamin K Supply from Enteric Bacterial Menaquinones in Rats. *Br. J. Nutr.* **1990**, *63*, 639–652. [CrossRef]
145. Cui, J.; Ramesh, G.; Wu, M.; Jensen, E.T.; Crago, O.; Bertoni, A.G.; Gao, C.; Hoffman, K.L.; Sheridan, P.A.; Wong, K.E.; et al. Butyrate-Producing Bacteria and Insulin Homeostasis: The Microbiome and Insulin Longitudinal Evaluation Study (MILES). *Diabetes* **2022**, *71*, 2438–2446. [CrossRef] [PubMed]
146. Zhang, L.; Liu, C.; Jiang, Q.; Yin, Y. Butyrate in Energy Metabolism: There Is Still More to Learn. *Trends Endocrinol. Metab.* **2021**, *32*, 159–169. [CrossRef] [PubMed]
147. Bielka, W.; Przekaz, A.; Pawlik, A. The Role of the Gut Microbiota in the Pathogenesis of Diabetes. *Int. J. Mol. Sci.* **2022**, *23*, 480. [CrossRef]
148. Portincasa, P.; Bonfrate, L.; Vacca, M.; De Angelis, M.; Farella, I.; Lanza, E.; Khalil, M.; Wang, D.Q.-H.; Sperandio, M.; Di Ciaula, A. Gut Microbiota and Short Chain Fatty Acids: Implications in Glucose Homeostasis. *Int. J. Mol. Sci.* **2022**, *23*, 1105. [CrossRef]
149. Arora, T.; Tremaroli, V. Therapeutic Potential of Butyrate for Treatment of Type 2 Diabetes. *Front. Endocrinol.* **2021**, *12*, 761834. [CrossRef]
150. Qin, J.; Li, Y.; Cai, Z.; Li, S.; Zhu, J.; Zhang, F.; Liang, S.; Zhang, W.; Guan, Y.; Shen, D.; et al. A Metagenome-Wide Association Study of Gut Microbiota in Type 2 Diabetes. *Nature* **2012**, *490*, 55–60. [CrossRef]
151. Moser, S.C.; Van Der Eerden, B.C.J. Osteocalcin—A Versatile Bone-Derived Hormone. *Front. Endocrinol.* **2019**, *9*, 794. [CrossRef]
152. Kanazawa, I. Osteocalcin as a Hormone Regulating Glucose Metabolism. *World J. Diabetes* **2015**, *6*, 1345. [CrossRef] [PubMed]
153. Kunutsor, S.K.; Apekey, T.A.; Laukkanen, J.A. Association of Serum Total Osteocalcin with Type 2 Diabetes and Intermediate Metabolic Phenotypes: Systematic Review and Meta-Analysis of Observational Evidence. *Eur. J. Epidemiol.* **2015**, *30*, 599–614. [CrossRef]

154. Ferron, M.; Lacombe, J. Regulation of Energy Metabolism by the Skeleton: Osteocalcin and Beyond. *Arch. Biochem. Biophys.* **2014**, *561*, 137–146. [[CrossRef](#)] [[PubMed](#)]
155. Liu, X.; Liu, Y.; Mathers, J.; Cameron, M.; Levinger, I.; Yeap, B.B.; Lewis, J.R.; Brock, K.E.; Brennan-Speranza, T.C. Osteocalcin and Measures of Adiposity: A Systematic Review and Meta-Analysis of Observational Studies. *Arch. Osteoporos.* **2020**, *15*, 145. [[CrossRef](#)] [[PubMed](#)]
156. Liu, D.-M.; Guo, X.-Z.; Tong, H.-J.; Tao, B.; Sun, L.-H.; Zhao, H.-Y.; Ning, G.; Liu, J.-M. Association between Osteocalcin and Glucose Metabolism: A Meta-Analysis. *Osteoporos. Int.* **2015**, *26*, 2823–2833. [[CrossRef](#)]
157. Shea, M.K.; Gundberg, C.M.; Meigs, J.B.; Dallal, G.E.; Saltzman, E.; Yoshida, M.; Jacques, P.F.; Booth, S.L.  $\gamma$ -Carboxylation of Osteocalcin and Insulin Resistance in Older Men and Women. *Am. J. Clin. Nutr.* **2009**, *90*, 1230–1235. [[CrossRef](#)] [[PubMed](#)]
158. Hwang, Y.; Jeong, I.; Ahn, K.J.; Chung, H.Y. The Uncarboxylated Form of Osteocalcin Is Associated with Improved Glucose Tolerance and Enhanced B-cell Function in Middle-aged Male Subjects. *Diabetes Metab. Res. Rev.* **2009**, *25*, 768–772. [[CrossRef](#)]
159. Diamanti-Kandarakis, E.; Livadas, S.; Katsikis, I.; Piperi, C.; Aimplia, M.; Papavassiliou, A.G.; Panidis, D. Serum Concentrations of Carboxylated Osteocalcin Are Increased and Associated with Several Components of the Polycystic Ovarian Syndrome. *J. Bone Miner. Metab.* **2011**, *29*, 201–206. [[CrossRef](#)]
160. Díaz-López, A.; Bulló, M.; Juanola-Falgarona, M.; Martínez-González, M.A.; Estruch, R.; Covas, M.-I.; Arós, F.; Salas-Salvadó, J. Reduced Serum Concentrations of Carboxylated and Undercarboxylated Osteocalcin Are Associated With Risk of Developing Type 2 Diabetes Mellitus in a High Cardiovascular Risk Population: A Nested Case-Control Study. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 4524–4531. [[CrossRef](#)]
161. Schwetz, V.; Lerchbaum, E.; Schweighofer, N.; Hacker, N.; Trummer, O.; Borel, O.; Pieber, T.R.; Chapurlat, R.; Obermayer-Pietsch, B. Osteocalcin Levels on Oral Glucose Load in Women Being Investigated for Polycystic Ovary Syndrome. *Endocr. Pract.* **2014**, *20*, 5–14. [[CrossRef](#)]
162. Pollock, N.K.; Bernard, P.J.; Gower, B.A.; Gundberg, C.M.; Wenger, K.; Misra, S.; Bassali, R.W.; Davis, C.L. Lower Uncarboxylated Osteocalcin Concentrations in Children with Prediabetes Is Associated with  $\beta$ -Cell Function. *J. Clin. Endocrinol. Metab.* **2011**, *96*, E1092–E1099. [[CrossRef](#)]
163. Knapen, M.H.J.; Schurgers, L.J.; Shearer, M.J.; Newman, P.; Theuvsissen, E.; Vermeer, C. Association of Vitamin K Status with Adiponectin and Body Composition in Healthy Subjects: Uncarboxylated Osteocalcin Is Not Associated with Fat Mass and Body Weight. *Br. J. Nutr.* **2012**, *108*, 1017–1024. [[CrossRef](#)]
164. Polgreen, L.E.; Jacobs, D.R.; Nathan, B.M.; Steinberger, J.; Moran, A.; Sinaiko, A.R. Association of Osteocalcin With Obesity, Insulin Resistance, and Cardiovascular Risk Factors in Young Adults. *Obesity* **2012**, *20*, 2194–2201. [[CrossRef](#)] [[PubMed](#)]
165. Martiniakova, M.; Biro, R.; Kovacova, V.; Babikova, M.; Zemanova, N.; Mondockova, V.; Omelka, R. Current Knowledge of Bone-Derived Factor Osteocalcin: Its Role in the Management and Treatment of Diabetes Mellitus, Osteoporosis, Osteopetrosis and Inflammatory Joint Diseases. *J. Mol. Med.* **2024**, *102*, 435–452. [[CrossRef](#)]
166. Napoli, N.; Chandran, M.; Pierroz, D.D.; Abrahamsen, B.; Schwartz, A.V.; Ferrari, S.L.; On behalf of the IOF Bone and Diabetes Working Group. Mechanisms of Diabetes Mellitus-Induced Bone Fragility. *Nat. Rev. Endocrinol.* **2017**, *13*, 208–219. [[CrossRef](#)] [[PubMed](#)]
167. Hygum, K.; Starup-Linde, J.; Harsløf, T.; Vestergaard, P.; Langdahl, B.L. Mechanisms in Endocrinology: Diabetes Mellitus, a State of Low Bone Turnover—A Systematic Review and Meta-Analysis. *Eur. J. Endocrinol.* **2017**, *176*, R137–R157. [[CrossRef](#)]
168. O'Connor, E.M.; Durack, E. Osteocalcin: The Extra-Skeletal Role of a Vitamin K-Dependent Protein in Glucose Metabolism. *J. Nutr. Intermed. Metab.* **2017**, *7*, 8–13. [[CrossRef](#)]
169. Xie, C.; Gong, J.; Zheng, C.; Zhang, J.; Gao, J.; Tian, C.; Guo, X.; Dai, S.; Gao, T. Effects of Vitamin K Supplementation on Bone Mineral Density at Different Sites and Bone Metabolism in the Middle-Aged and Elderly Population. *Bone Jt. Res.* **2024**, *13*, 750–763. [[CrossRef](#)]
170. Beulens, J.W.J.; Van Der A, D.L.; Grobbee, D.E.; Sluijs, I.; Spijkerman, A.M.W.; Van Der Schouw, Y.T. Dietary Phylloquinone and Menaquinones Intakes and Risk of Type 2 Diabetes. *Diabetes Care* **2010**, *33*, 1699–1705. [[CrossRef](#)]
171. Cheung, C.-L.; Sing, C.-W.; Lau, W.C.Y.; Li, G.H.Y.; Lip, G.Y.H.; Tan, K.C.B.; Cheung, B.M.Y.; Chan, E.W.Y.; Wong, I.C.K. Treatment with Direct Oral Anticoagulants or Warfarin and the Risk for Incident Diabetes among Patients with Atrial Fibrillation: A Population-based Cohort Study. *Cardiovasc. Diabetol.* **2021**, *20*, 71. [[CrossRef](#)]
172. Liu, X.; Feng, S.; Chen, Z.; Zhou, Y.; Yin, K.; Xue, Z.; Zhu, W. Is the Risk of Diabetes Lower in Patients With Atrial Fibrillation Treated With Direct Oral Anticoagulant Compared to Warfarin? *Front. Cardiovasc. Med.* **2022**, *9*, 874795. [[CrossRef](#)]
173. Shahdadian, F.; Mohammadi, H.; Rouhani, M. Effect of Vitamin K Supplementation on Glycemic Control: A Systematic Review and Meta-Analysis of Clinical Trials. *Horm. Metab. Res.* **2018**, *50*, 227–235. [[CrossRef](#)] [[PubMed](#)]
174. Centi, A.J. Association of Vitamin K with Insulin Resistance and Body Composition. Ph.D. Thesis, Tufts University, Medford, MA, USA, 2015.
175. Kumar, R.; Binkley, N.; Vella, A. Effect of Phylloquinone Supplementation on Glucose Homeostasis in Humans. *Am. J. Clin. Nutr.* **2010**, *92*, 1528–1532. [[CrossRef](#)] [[PubMed](#)]

176. Knapen, M.H.J.; Braam, L.A.J.L.M.; Drummen, N.E.; Bekers, O.; Hoeks, A.P.G.; Vermeer, C. Menaquinone-7 Supplementation Improves Arterial Stiffness in Healthy Postmenopausal Women: A Double-Blind Randomised Clinical Trial. *Thromb. Haemost.* **2015**, *113*, 1135–1144. [CrossRef]
177. Suksomboon, N.; Poolsup, N.; Darli Ko Ko, H. Effect of Vitamin K Supplementation on Insulin Sensitivity: A Meta-Analysis. *Diabetes Metab. Syndr. Obes. Targets Ther.* **2017**, *10*, 169–177. [CrossRef]
178. Yoshida, M.; Booth, S.L.; Meigs, J.B.; Saltzman, E.; Jacques, P.F. Phylloquinone Intake, Insulin Sensitivity, and Glycemic Status in Men and Women. *Am. J. Clin. Nutr.* **2008**, *88*, 210–215. [CrossRef]
179. Choi, H.J.; Yu, J.; Choi, H.; An, J.H.; Kim, S.W.; Park, K.S.; Jang, H.C.; Kim, S.Y.; Shin, C.S. Vitamin K2 Supplementation Improves Insulin Sensitivity via Osteocalcin Metabolism: A Placebo-Controlled Trial. *Diabetes Care* **2011**, *34*, e147. [CrossRef]
180. Sakamoto, N.; Nishiike, T.; Iguchi, H.; Sakamoto, K. Possible Effects of One Week Vitamin K (Menaquinone-4) Tablets Intake on Glucose Tolerance in Healthy Young Male Volunteers with Different Descarboxy Prothrombin Levels. *Clin. Nutr.* **2000**, *19*, 259–263. [CrossRef]
181. Rasekhi, H.; Karandish, M.; Jalali, M.T.; Mohammad-shahi, M.; Zarei, M.; Saki, A.; Shahbazian, H. The Effect of Vitamin K1 Supplementation on Sensitivity and Insulin Resistance via Osteocalcin in Prediabetic Women: A Double-Blind Randomized Controlled Clinical Trial. *Eur. J. Clin. Nutr.* **2015**, *69*, 891–895. [CrossRef]
182. Karamali, M.; Ashrafi, M.; Razavi, M.; Jamilian, M.; Akbari, M.; Asemi, Z. The Effects of Calcium, Vitamins D and K Co-Supplementation on Markers of Insulin Metabolism and Lipid Profiles in Vitamin D-Deficient Women with Polycystic Ovary Syndrome. *Exp. Clin. Endocrinol. Diabetes* **2017**, *125*, 316–321. [CrossRef]
183. Asemi, Z.; Raygan, F.; Bahmani, F.; Rezavandi, Z.; Talari, H.R.; Rafiee, M.; Poladchang, S.; Darooghegi Mofrad, M.; Taheri, S.; Mohammadi, A.A.; et al. The Effects of Vitamin D, K and Calcium Co-Supplementation on Carotid Intima-Media Thickness and Metabolic Status in Overweight Type 2 Diabetic Patients with CHD. *Br. J. Nutr.* **2016**, *116*, 286–293. [CrossRef] [PubMed]
184. Sakamoto, N.; Nishiike, T.; Iguchi, H.; Sakamoto, K. Relationship between Acute Insulin Response and Vitamin K Intake in Healthy Young Male Volunteers. *Diabetes Nutr. Metab.* **1999**, *12*, 37–41. [PubMed]
185. Gutch, M.; Kumar, S.; Razi, S.; Gupta, K.; Gupta, A. Assessment of Insulin Sensitivity/Resistance. *Indian J. Endocrinol. Metab.* **2015**, *19*, 160. [CrossRef]
186. Rutter, M.K.; Meigs, J.B.; Sullivan, L.M.; D’Agostino, R.B.; Wilson, P.W. Insulin Resistance, the Metabolic Syndrome, and Incident Cardiovascular Events in the Framingham Offspring Study. *Diabetes* **2005**, *54*, 3252–3257. [CrossRef]
187. Shea, M.K.; Booth, S.L.; Gundberg, C.M.; Peterson, J.W.; Waddell, C.; Dawson-Hughes, B.; Saltzman, E. Adulthood Obesity Is Positively Associated with Adipose Tissue Concentrations of Vitamin K and Inversely Associated with Circulating Indicators of Vitamin K Status in Men and Women. *J. Nutr.* **2010**, *140*, 1029–1034. [CrossRef]
188. Ravera, M.; Nickolas, T.; Plebani, M.; Iervasi, G.; Aghi, A.; Khairallah, P.; Gallieni, M.; Mereu, M.C.; Giannini, S.; Sella, S.; et al. Overweight-Obesity Is Associated with Decreased Vitamin K2 Levels in Hemodialysis Patients. *Clin. Chem. Lab. Med.* **2021**, *59*, 581–589. [CrossRef]
189. Dam, V.; Dalmeijer, G.W.; Vermeer, C.; Drummen, N.E.; Knapen, M.H.; Van Der Schouw, Y.T.; Beulens, J.W. Association Between Vitamin K and the Metabolic Syndrome: A 10-Year Follow-Up Study in Adults. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 2472–2479. [CrossRef] [PubMed]
190. Shea, M.K.; Booth, S.L.; Massaro, J.M.; Jacques, P.F.; D’Agostino, R.B.; Dawson-Hughes, B.; Ordovas, J.M.; O’Donnell, C.J.; Kathiresan, S.; Keaney, J.F.; et al. Vitamin K and Vitamin D Status: Associations with Inflammatory Markers in the Framingham Offspring Study. *Am. J. Epidemiol.* **2008**, *167*, 313–320. [CrossRef] [PubMed]
191. Shea, S.; O’Donnell, H.J.; Vermeer, C.; Magdeleyns, E.J.P.; Crosier, M.D.; Gundberg, C.M.; Ordovas, J.M.; Kritchevsky, S.B.; Booth, B. Circulating Uncarboxylated Matrix Gla Protein Is Associated with Vitamin K Nutritional Status, but Not Coronary Artery Calcium, in Older Adults. *J. Nutr.* **2011**, *141*, 1529–1534. [CrossRef] [PubMed]
192. Brnic, D.; Martinovic, D.; Zivkovic, P.M.; Tokic, D.; Vilovic, M.; Rusic, D.; Hadjina, I.T.; Libers, C.; Glumac, S.; Supe-Domic, D.; et al. Inactive Matrix Gla Protein Is Elevated in Patients with Inflammatory Bowel Disease. *World J. Gastroenterol.* **2020**, *26*, 4866–4877. [CrossRef]
193. Roumeliotis, S.; Roumeliotis, A.; Stamou, A.; Leivaditis, K.; Kantartzi, K.; Panagoutsos, S.; Liakopoulos, V. The Association of Dp-ucMGP with Cardiovascular Morbidity and Decreased Renal Function in Diabetic Chronic Kidney Disease. *Int. J. Mol. Sci.* **2020**, *21*, 6035. [CrossRef]
194. Schweighofer, N.; Colantonio, C.; Haudum, C.W.; Hutz, B.; Kolesnik, E.; Schmidt, A.; Zirlik, A.; Pieber, T.R.; Verheyen, N.; Obermayer-Pietsch, B. Is MGP an Inflammatory Marker? In *Endocrine Abstracts*; Bioscientifica: Bristol, UK, 2022. Available online: <http://www.endocrine-abstracts.org/ea/0081/ea0081EP368.htm> (accessed on 25 July 2025).
195. Wang, F.; Sun, M.; Guo, R.; Wu, Z.; Wang, X.; Yang, Y.; Liu, Y.; Dong, Y.; Wang, S.; Yan, S.; et al. The Association between Vitamin K Intake and Dyslipidemia in US Adults: The Mediating Effect of Insulin Resistance. *Food Funct.* **2024**, *15*, 2974–2981. [CrossRef]

196. Bar, A.; Kus, K.; Manterys, A.; Proniewski, B.; Sternak, M.; Przyborowski, K.; Moorlag, M.; Sitek, B.; Marczyk, B.; Jaształ, A.; et al. Vitamin K2-MK-7 Improves Nitric Oxide-Dependent Endothelial Function in ApoE/LDLR<sup>-/-</sup> Mice. *Vascul. Pharmacol.* **2019**, *122–123*, 106581. [[CrossRef](#)]
197. Kij, A.; Kieronska-Rudek, A.; Bar, A.; Czyzyska-Cichon, I.; Strus, M.; Koziem, L.; Wiecek, G.; Zeber-Lubecka, N.; Kulecka, M.; Kwiatkowski, G.; et al. Low Phylloquinone Intake Deteriorates Endothelial Function in Normolipidemic and Dyslipidaemic Mice. *J. Nutr. Biochem.* **2025**, *140*, 109867. [[CrossRef](#)]
198. Kieronska-Rudek, A.; Kij, A.; Bar, A.; Kurpinska, A.; Mohaissen, T.; Grosicki, M.; Stojak, M.; Sternak, M.; Buczek, E.; Proniewski, B.; et al. Phylloquinone Improves Endothelial Function, Inhibits Cellular Senescence, and Vascular Inflammation. *GeroScience* **2024**, *46*, 4909–4935. [[CrossRef](#)]
199. Jamka, M.; Walach, H.; Hołubiec, M.; Wasiewicz, M.; Walkowiak, J. Effect of Vitamin K Supplementation on Anthropometric Parameters and Adipokine Levels – a Systematic Review: Vitamin K and Anthropometric Parameters. *J. Med. Sci.* **2019**, *88*, 244–255. [[CrossRef](#)]
200. Karamzad, N.; Faraji, E.; Adeli, S.; Sullman, M.J.M.; Pourghassem Gargari, B. The Effect of Menaquinone-7 Supplementation on Dp-ucMGP, PIVKAI, Inflammatory Markers, and Body Composition in Type 2 Diabetes Patients: A Randomized Clinical Trial. *Nutr. Diabetes* **2022**, *12*, 15. [[CrossRef](#)]
201. Goltzman, D. Physiology of Parathyroid Hormone. *Endocrinol. Metab. Clin. N. Am.* **2018**, *47*, 743–758. [[CrossRef](#)]
202. Bikle, D.D. Vitamin D and Bone. *Curr. Osteoporos. Rep.* **2012**, *10*, 151–159. [[CrossRef](#)] [[PubMed](#)]
203. Carlberg, C. Vitamin D and Its Target Genes. *Nutrients* **2022**, *14*, 1354. [[CrossRef](#)] [[PubMed](#)]
204. Goltzman, D.; Mannstadt, M.; Marcocci, C. Physiology of the Calcium-Parathyroid Hormone-Vitamin D Axis. In *Frontiers of Hormone Research*; Giustina, A., Bilezikian, J.P., Eds.; S. Karger AG: Basel, Switzerland, 2018; pp. 1–13. [[CrossRef](#)]
205. Farzaneh-Far, A.; Weissberg, P.L.; Proudfoot, D.; Shanahan, C.M. Transcriptional Regulation of Matrix Gla Protein. *Z. Für Kardiol.* **2001**, *90*, 38–42. [[CrossRef](#)] [[PubMed](#)]
206. Ozono, K.; Liao, J.; Kerner, S.A.; Scott, R.A.; Pike, J.W. The Vitamin D-Responsive Element in the Human Osteocalcin Gene. Association with a Nuclear Proto-Oncogene Enhancer. *J. Biol. Chem.* **1990**, *265*, 21881–21888. [[CrossRef](#)]
207. van de Peppel, J.; van Leeuwen, J.P. Vitamin D and Gene Networks in Human Osteoblasts. *Front. Physiol.* **2014**, *5*, 137. [[CrossRef](#)]
208. Suttamanatwong, S.; Jensen, E.D.; Shilling, J.; Franceschi, R.T.; Carlson, A.E.; Mansky, K.C.; Gopalakrishnan, R. SP Proteins and RUNX2 Mediate Regulation of Matrix Gla Protein (MGP) Expression by Parathyroid Hormone. *J. Cell. Biochem.* **2009**, *107*, 284–292. [[CrossRef](#)] [[PubMed](#)]
209. Suttamanatwong, S.; Franceschi, R.T.; Carlson, A.E.; Gopalakrishnan, R. Regulation of Matrix Gla Protein by Parathyroid Hormone in MC3T3-E1 Osteoblast-like Cells Involves Protein Kinase A and Extracellular Signal-regulated Kinase Pathways. *J. Cell. Biochem.* **2007**, *102*, 496–505. [[CrossRef](#)] [[PubMed](#)]
210. Yu, S.; Franceschi, R.T.; Luo, M.; Zhang, X.; Jiang, D.; Lai, Y.; Jiang, Y.; Zhang, J.; Xiao, G. Parathyroid Hormone Increases Activating Transcription Factor 4 Expression and Activity in Osteoblasts: Requirement for Osteocalcin Gene Expression. *Endocrinology* **2008**, *149*, 1960–1968. [[CrossRef](#)] [[PubMed](#)]
211. Komori, T. What Is the Function of Osteocalcin? *J. Oral Biosci.* **2020**, *62*, 223–227. [[CrossRef](#)]
212. Moriishi, T.; Ozasa, R.; Ishimoto, T.; Nakano, T.; Hasegawa, T.; Miyazaki, T.; Liu, W.; Fukuyama, R.; Wang, Y.; Komori, H.; et al. Osteocalcin Is Necessary for the Alignment of Apatite Crystallites, but Not Glucose Metabolism, Testosterone Synthesis, or Muscle Mass. *PLoS Genet.* **2020**, *16*, e1008586. [[CrossRef](#)]
213. Koshihara, Y.; Hoshi, K.; Okawara, R.; Ishibashi, H.; Yamamoto, S. Vitamin K Stimulates Osteoblastogenesis and Inhibits Osteoclastogenesis in Human Bone Marrow Cell Culture. *J. Endocrinol.* **2003**, *176*, 339–348. [[CrossRef](#)]
214. Muszyńska, M.; Ambrożewicz, E.; Gegotek, A.; Gryniewicz, G.; Skrzydlewska, E. Protective Effects of Vitamin K Compounds on the Proteomic Profile of Osteoblasts under Oxidative Stress Conditions. *Molecules* **2020**, *25*, 1990. [[CrossRef](#)]
215. Mott, A.; Bradley, T.; Wright, K.; Cockayne, E.S.; Shearer, M.J.; Adamson, J.; Lanham-New, S.A.; Torgerson, D.J. Effect of Vitamin K on Bone Mineral Density and Fractures in Adults: An Updated Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Osteoporos. Int.* **2019**, *30*, 1543–1559. [[CrossRef](#)]
216. Booth, S.L.; Tucker, K.L.; Chen, H.; Hannan, M.T.; Gagnon, D.R.; Cupples, L.A.; Wilson, P.W.; Ordovas, J.; Schaefer, E.J.; Dawson-Hughes, B.; et al. Dietary Vitamin K Intakes Are Associated with Hip Fracture but Not with Bone Mineral Density in Elderly Men and Women. *Am. J. Clin. Nutr.* **2000**, *71*, 1201–1208. [[CrossRef](#)]
217. Yao, P.; Bennett, D.; Mafham, M.; Lin, X.; Chen, Z.; Armitage, J.; Clarke, R. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-Analysis. *JAMA Netw. Open* **2019**, *2*, e1917789. [[CrossRef](#)]
218. Kazemian, E.; Pourali, A.; Sedaghat, F.; Karimi, M.; Basirat, V.; Sajadi Hezaveh, Z.; Davoodi, S.H.; Holick, M.F. Effect of Supplemental Vitamin D3 on Bone Mineral Density: A Systematic Review and Meta-Analysis. *Nutr. Rev.* **2023**, *81*, 511–530. [[CrossRef](#)]
219. Burt, L.A.; Billington, E.O.; Rose, M.S.; Raymond, D.A.; Hanley, D.A.; Boyd, S.K. Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. *JAMA* **2019**, *322*, 736. [[CrossRef](#)]

220. Kong, S.H.; Jang, H.N.; Kim, J.H.; Kim, S.W.; Shin, C.S. Effect of Vitamin D Supplementation on Risk of Fractures and Falls According to Dosage and Interval: A Meta-Analysis. *Endocrinol. Metab.* **2022**, *37*, 344–358. [[CrossRef](#)]
221. Kuang, X.; Liu, C.; Guo, X.; Li, K.; Deng, Q.; Li, D. The Combination Effect of Vitamin K and Vitamin D on Human Bone Quality: A Meta-Analysis of Randomized Controlled Trials. *Food Funct.* **2020**, *11*, 3280–3297. [[CrossRef](#)]
222. Rusu, M.E.; Bigman, G.; Ryan, A.S.; Popa, D.-S. Investigating the Effects and Mechanisms of Combined Vitamin D and K Supplementation in Postmenopausal Women: An Up-to-Date Comprehensive Review of Clinical Studies. *Nutrients* **2024**, *16*, 2356. [[CrossRef](#)]
223. Zhang, Z.; Xia, K.; Gong, W.; Mai, R.; Liu, P.; Lu, Z. Efficacy of Recombinant Human Parathyroid Hormone 1–34 and Vitamin K2 Combination Therapy in Postmenopausal Osteoporosis. *Horm. Metab. Res.* **2025**, *57*, 33–38. [[CrossRef](#)] [[PubMed](#)]
224. Shimizu, T.; Takahata, M.; Kameda, Y.; Hamano, H.; Ito, T.; Kimura-Suda, H.; Todoh, M.; Tadano, S.; Iwasaki, N. Vitamin K-Dependent Carboxylation of Osteocalcin Affects the Efficacy of Teriparatide (PTH1–34) for Skeletal Repair. *Bone* **2014**, *64*, 95–101. [[CrossRef](#)] [[PubMed](#)]
225. Nagura, N.; Komatsu, J.; Iwase, H.; Hosoda, H.; Ohbayashi, O.; Nagaoka, I.; Kaneko, K. Effects of the Combination of Vitamin K and Teriparatide on the Bone Metabolism in Ovariectomized Rats. *Biomed. Rep.* **2015**, *3*, 295–300. [[CrossRef](#)] [[PubMed](#)]
226. Lei, T.; Yang, Y.; Yang, W.-X. Luteinizing Hormone Regulates Testosterone Production, Leydig Cell Proliferation, Differentiation, and Circadian Rhythm During Spermatogenesis. *Int. J. Mol. Sci.* **2025**, *26*, 3548. [[CrossRef](#)]
227. Stocco, D.M.; Wang, X.; Jo, Y.; Manna, P.R. Multiple Signaling Pathways Regulating Steroidogenesis and Steroidogenic Acute Regulatory Protein Expression: More Complicated than We Thought. *Mol. Endocrinol.* **2005**, *19*, 2647–2659. [[CrossRef](#)]
228. Shirakawa, H.; Ohsaki, Y.; Minegishi, Y.; Takumi, N.; Ohinata, K.; Furukawa, Y.; Mizutani, T.; Komai, M. Vitamin K Deficiency Reduces Testosterone Production in the Testis through Down-Regulation of the Cyp11a a Cholesterol Side Chain Cleavage Enzyme in Rats. *Biochim. Biophys. Acta—Gen. Subj.* **2006**, *1760*, 1482–1488. [[CrossRef](#)]
229. Murakami, R.; Ohsaki, Y.; Ito, H.; Ho, H.-J.; Agista, A.Z.; Chiang, Y.-F.; Chen, Y.-L.; Maekawa, M.; Hirose, T.; Hara, K.; et al. Effect of Vitamin K Supplementation on Testosterone Production in a Rat Model of Late-Onset Hypogonadism. *Foods* **2026**, *15*, 1070. [[CrossRef](#)]
230. Takumi, N.; Shirakawa, H.; Ohsaki, Y.; Ito, A.; Watanabe, T.; Giriwono, P.E.; Sato, T.; Komai, M. Dietary Vitamin K Alleviates the Reduction in Testosterone Production Induced by Lipopolysaccharide Administration in Rat Testis. *Food Funct.* **2011**, *2*, 406. [[CrossRef](#)] [[PubMed](#)]
231. Schwetz, V.; Gumpold, R.; Graupp, M.; Hacker, N.; Schweighofer, N.; Trummer, O.; Pieber, T.R.; Ballon, M.; Lerchbaum, E.; Obermayer-Pietsch, B. Osteocalcin Is Not a Strong Determinant of Serum Testosterone and Sperm Count in Men from Infertile Couples. *Andrology* **2013**, *1*, 590–594. [[CrossRef](#)] [[PubMed](#)]
232. Kanazawa, I.; Tanaka, K.; Ogawa, N.; Yamauchi, M.; Yamaguchi, T.; Sugimoto, T. Undercarboxylated Osteocalcin Is Positively Associated with Free Testosterone in Male Patients with Type 2 Diabetes Mellitus. *Osteoporos. Int.* **2013**, *24*, 1115–1119. [[CrossRef](#)] [[PubMed](#)]
233. Wang, Q.; Chen, P.; Guo, J.; Wang, S.; Bao, Y.; Zhang, Y.; Yu, K. Dietary Vitamin K Intake in Relation to Skeletal Muscle Mass and Strength among Adults: A Cross-Sectional Study Based on NHANES. *Front. Nutr.* **2024**, *11*, 1378853. [[CrossRef](#)]
234. Buday, B.; Pach, F.P.; Literati-Nagy, B.; Vitai, M.; Vecsei, Z.; Koranyi, L. Serum Osteocalcin Is Associated with Improved Metabolic State via Adiponectin in Females versus Testosterone in Males. Gender Specific Nature of the Bone–Energy Homeostasis Axis. *Bone* **2013**, *57*, 98–104. [[CrossRef](#)]
235. Liao, M.; Guo, X.; Yu, X.; Pang, G.; Zhang, S.; Li, J.; Tan, A.; Gao, Y.; Yang, X.; Zhang, H.; et al. Role of Metabolic Factors in the Association Between Osteocalcin and Testosterone in Chinese Men. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 3463–3469. [[CrossRef](#)]
236. Zhong, N.; Xu, B.; Cui, R.; Xu, M.; Su, J.; Zhang, Z.; Liu, Y.; Li, L.; Sheng, C.; Sheng, H.; et al. Positive Correlation between Serum Osteocalcin and Testosterone in Male Hyperthyroidism Patients with High Bone Turnover. *Exp. Clin. Endocrinol. Diabetes* **2016**, *124*, 452–456. [[CrossRef](#)]
237. Hannemann, A.; Breer, S.; Wallaschofski, H.; Nauck, M.; Baumeister, S.E.; Barvencik, F.; Amling, M.; Schinke, T.; Haring, R.; Keller, J. Osteocalcin Is Associated with Testosterone in the General Population and Selected Patients with Bone Disorders. *Andrology* **2013**, *1*, 469–474. [[CrossRef](#)] [[PubMed](#)]
238. Cui, R.; Su, B.; Sheng, C.; Cheng, X.; Yang, P.; Bu, L.; Li, H.; Wang, J.; Sheng, H.; Qu, S. Total Osteocalcin in Serum Predicts Testosterone Level in Male Type 2 Diabetes Mellitus. *Int. J. Clin. Exp. Med.* **2014**, *7*, 1145–1149.
239. Oury, F.; Sumara, G.; Sumara, O.; Ferron, M.; Chang, H.; Smith, C.E.; Hermo, L.; Suarez, S.; Roth, B.L.; Ducy, P.; et al. Endocrine Regulation of Male Fertility by the Skeleton. *Cell* **2011**, *144*, 796–809. [[CrossRef](#)]
240. Coskun, G.; Sencar, L.; Tuli, A.; Saker, D.; Alparslan, M.M.; Polat, S. Effects of Osteocalcin on Synthesis of Testosterone and INSL3 during Adult Leydig Cell Differentiation. *Int. J. Endocrinol.* **2019**, *2019*, 1041760. [[CrossRef](#)]
241. Caspers, M.; Czogalla, K.J.; Liphardt, K.; Müller, J.; Westhofen, P.; Watzka, M.; Oldenburg, J. Two Enzymes Catalyze Vitamin K 2,3-Epoxy Reductase Activity in Mouse: VKORC1 Is Highly Expressed in Exocrine Tissues While VKORC1L1 Is Highly Expressed in Brain. *Thromb. Res.* **2015**, *135*, 977–983. [[CrossRef](#)] [[PubMed](#)]

242. Rodriguez Esquivel, M.; Hayes, E.; Lakomy, O.; Hassan, M.; Foretz, M.; Stocco, C. Salt-Inducible Kinases Regulate Androgen Synthesis in Theca Cells by Enhancing CREB Signaling. *Mol. Cell. Endocrinol.* **2023**, *577*, 112030. [[CrossRef](#)]
243. Hunzicker-Dunn, M.E.; Lopez-Biladeau, B.; Law, N.C.; Fiedler, S.E.; Carr, D.W.; Maizels, E.T. PKA and GAB2 Play Central Roles in the FSH Signaling Pathway to PI3K and AKT in Ovarian Granulosa Cells. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, E2979–E2988. [[CrossRef](#)]
244. Przygodzka, E.; Hou, X.; Zhang, P.; Plewes, M.R.; Franco, R.; Davis, J.S. PKA and AMPK Signaling Pathways Differentially Regulate Luteal Steroidogenesis. *Endocrinology* **2021**, *162*, bqab015. [[CrossRef](#)]
245. Yasui, T.; Uemura, H.; Tomita, J.; Miyatani, Y.; Yamada, M.; Miura, M.; Irahara, M. Association of Serum Undercarboxylated Osteocalcin with Serum Estradiol in Pre-, Peri- and Early Post-Menopausal Women. *J. Endocrinol. Investig.* **2006**, *29*, 913–918. [[CrossRef](#)] [[PubMed](#)]
246. Booth, S.L.; Broe, K.E.; Peterson, J.W.; Cheng, D.M.; Dawson-Hughes, B.; Gundberg, C.M.; Cupples, L.A.; Wilson, P.W.F.; Kiel, D.P. Associations between Vitamin K Biochemical Measures and Bone Mineral Density in Men and Women. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 4904–4909. [[CrossRef](#)]
247. Lukacs, J.L.; Reame, N.E. Concentrations of Follicle-Stimulating Hormone Correlate with Alkaline Phosphatase and a Marker for Vitamin K Status in the Perimenopause. *J. Womens Health Gend. Based Med.* **2000**, *9*, 731–739. [[CrossRef](#)]
248. Yasui, T.; Uemura, H.; Umino, Y.; Yamada, M.; Kuwahara, A.; Matsuzaki, T.; Maegawa, M.; Furumoto, H.; Miura, M.; Irahara, M. Undercarboxylated Osteocalcin Concentration in Postmenopausal Women Receiving Hormone Therapy Daily and on Alternate Days. *Menopause* **2006**, *13*, 314–322. [[CrossRef](#)]
249. Otsuka, M.; Kato, N.; Ichimura, T.; Abe, S.; Tanaka, Y.; Taniguchi, H.; Hoshida, Y.; Moriyama, M.; Wang, Y.; Shao, R.-X.; et al. Vitamin K2 Binds 17 $\beta$ -Hydroxysteroid Dehydrogenase 4 and Modulates Estrogen Metabolism. *Life Sci.* **2005**, *76*, 2473–2482. [[CrossRef](#)]
250. Mizokami, A.; Mukai, S.; Gao, J.; Kawakubo-Yasukochi, T.; Otani, T.; Takeuchi, H.; Jimi, E.; Hirata, M. GLP-1 Signaling Is Required for Improvement of Glucose Tolerance by Osteocalcin. *J. Endocrinol.* **2020**, *244*, 285–296. [[CrossRef](#)]
251. Negrev, N.; Tashev, R.; Radev, R.; Anogeianaki, A.; Ivanova, M. Hormones of Hypothalamic-Pituitary-Thyroid Axis Are Significant Regulators of Synthesis and Secretion of Vitamin K-Dependent Plasma Coagulation Factors. *J. Biol. Regul. Homeost. Agents* **2011**, *25*, 21–26.
252. Negrev, N.N.; Radev, R.Z.; Velikova, M.S.; Anogeianaki, A. Effects of the Hormones of the Thyroid Axis on the Vitamin K-Dependent Plasma Factors of Blood Coagulation (II, VII, IX and X). *Int. J. Immunopathol. Pharmacol.* **2008**, *21*, 221–226. [[CrossRef](#)] [[PubMed](#)]
253. Kellett, H.A.; Sawers, J.S.; Boulton, F.E.; Cholerton, S.; Park, B.K.; Toft, A.D. Problems of Anticoagulation with Warfarin in Hyperthyroidism. *Q. J. Med.* **1986**, *58*, 43–51.
254. Ansell, J.; Hirsh, J.; Hylek, E.; Jacobson, A.; Crowther, M.; Palareti, G. Pharmacology and Management of the Vitamin K Antagonists. *Chest* **2008**, *133*, 160S–198S. [[CrossRef](#)]
255. Stephens, M.A.; Self, T.H.; Lancaster, D.; Nash, T. Hypothyroidism: Effect on Warfarin Anticoagulation. *S. Med. J.* **1989**, *82*, 1585–1586. [[CrossRef](#)]
256. Howard-Thompson, A.; Luckey, A.; George, C.; Choby, B.A.; Self, T.H. Graves' Disease and Treatment Effects on Warfarin Anticoagulation. *Case Rep. Med.* **2014**, *2014*, 292468. [[CrossRef](#)] [[PubMed](#)]
257. Ducy, P.; Desbois, C.; Boyce, B.; Pinero, G.; Story, B.; Dunstan, C.; Smith, E.; Bonadio, J.; Goldstein, S.; Gundberg, C.; et al. Increased Bone Formation in Osteocalcin-Deficient Mice. *Nature* **1996**, *382*, 448–452. [[CrossRef](#)] [[PubMed](#)]
258. Diegel, C.R.; Hann, S.; Ayturk, U.M.; Hu, J.C.W.; Lim, K.; Droscha, C.J.; Madaj, Z.B.; Foxa, G.E.; Izaguirre, I.; Transgenics Core, V.V.A.; et al. An Osteocalcin-Deficient Mouse Strain without Endocrine Abnormalities. *PLoS Genet.* **2020**, *16*, e1008361. [[CrossRef](#)]
259. Mera, P.; Ferron, M.; Mosialou, I. Regulation of Energy Metabolism by Bone-Derived Hormones. *Cold Spring Harb. Perspect. Med.* **2018**, *8*, a031666. [[CrossRef](#)]
260. Lee, N.K.; Sowa, H.; Hinoi, E.; Ferron, M.; Ahn, J.D.; Confavreux, C.; Dacquin, R.; Mee, P.J.; McKee, M.D.; Jung, D.Y.; et al. Endocrine Regulation of Energy Metabolism by the Skeleton. *Cell* **2007**, *130*, 456–469. [[CrossRef](#)] [[PubMed](#)]
261. Ferron, M.; Lacombe, J.; Germain, A.; Oury, F.; Karsenty, G. GGCX and VKORC1 Inhibit Osteocalcin Endocrine Functions. *J. Cell Biol.* **2015**, *208*, 761–776. [[CrossRef](#)] [[PubMed](#)]
262. Ferron, M.; Hinoi, E.; Karsenty, G.; Ducy, P. Osteocalcin Differentially Regulates  $\beta$  Cell and Adipocyte Gene Expression and Affects the Development of Metabolic Diseases in Wild-Type Mice. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 5266–5270. [[CrossRef](#)] [[PubMed](#)]
263. Dihingia, A.; Ozah, D.; Borah, T.; Kalita, J.; Manna, P. Gamma-Glutamyl-Carboxylated Gas6 Mediates Positive Role of Vitamin K on Lowering Hyperglycemia in Type 2 Diabetes. *Ann. N. Y. Acad. Sci.* **2020**, *1462*, 104–117. [[CrossRef](#)]
264. Shiba, S.; Ikeda, K.; Horie-Inoue, K.; Azuma, K.; Hasegawa, T.; Amizuka, N.; Tanaka, T.; Takeiwa, T.; Shibata, Y.; Koji, T.; et al. Vitamin K-Dependent  $\gamma$ -Glutamyl Carboxylase in Sertoli Cells Is Essential for Male Fertility in Mice. *Mol. Cell. Biol.* **2021**, *41*, e00404-20. [[CrossRef](#)]

265. Deng, H.; Chen, Y.; Xing, J.; Zhang, N.; Xu, L. Systematic Low-Grade Chronic Inflammation and Intrinsic Mechanisms in Polycystic Ovary Syndrome. *Front. Immunol.* **2024**, *15*, 1470283. [[CrossRef](#)]
266. Orisaka, M.; Mizutani, T.; Miyazaki, Y.; Shirafuji, A.; Tamamura, C.; Fujita, M.; Tsuyoshi, H.; Yoshida, Y. Chronic Low-Grade Inflammation and Ovarian Dysfunction in Women with Polycystic Ovarian Syndrome, Endometriosis, and Aging. *Front. Endocrinol.* **2023**, *14*, 1324429. [[CrossRef](#)]
267. Ragusa, F.; Fallahi, P.; Elia, G.; Gonnella, D.; Paparo, S.R.; Giusti, C.; Churilov, L.P.; Ferrari, S.M.; Antonelli, A. Hashimoto's Thyroiditis: Epidemiology, Pathogenesis, Clinic and Therapy. *Best Pract. Res. Clin. Endocrinol. Metab.* **2019**, *33*, 101367. [[CrossRef](#)] [[PubMed](#)]
268. McGrogan, A.; Seaman, H.E.; Wright, J.W.; De Vries, C.S. The Incidence of Autoimmune Thyroid Disease: A Systematic Review of the Literature. *Clin. Endocrinol.* **2008**, *69*, 687–696. [[CrossRef](#)]
269. Landrier, J.-F.; Marcotorchino, J.; Tourniaire, F. Lipophilic Micronutrients and Adipose Tissue Biology. *Nutrients* **2012**, *4*, 1622–1649. [[CrossRef](#)] [[PubMed](#)]
270. Tilg, H.; Ianiro, G.; Gasbarrini, A.; Adolph, T.E. Adipokines: Masterminds of Metabolic Inflammation. *Nat. Rev. Immunol.* **2025**, *25*, 250–265. [[CrossRef](#)]
271. Shea, M.K.; Booth, S.L. Update on the Role of Vitamin K in Skeletal Health: Nutrition Reviews. *Nutr. Rev.* **2008**, *66*, 549–557. [[CrossRef](#)]
272. AlBlooshi, S. Vitamin K and Women's Health: A Review. *Front. Glob. Womens Health* **2025**, *6*, 1590414. [[CrossRef](#)]
273. Villa, T.H.C.; Ruiz-Vivanco, G.; Porchia, L.M.; Torres-Rasgado, E.; López-Bayghen, E.; Gonzalez-Mejia, M.E. Dietary Vitamins A and K Are Inversely Associated with Visceral Adiposity in US Adults: NHANES 2011–2018. *Nutr. Res.* **2025**, *146*, 26–39. [[CrossRef](#)] [[PubMed](#)]
274. Harshman, S.G.; Finnan, E.G.; Barger, K.J.; Bailey, R.L.; Haytowitz, D.B.; Gilhooly, C.H.; Booth, S.L. Vegetables and Mixed Dishes Are Top Contributors to Phylloquinone Intake in US Adults: Data from the 2011–2012 NHANES. *J. Nutr.* **2017**, *147*, 1308–1313. [[CrossRef](#)]
275. Shea, M.K.; Booth, S.L. Vitamin K. *Adv. Nutr.* **2022**, *13*, 350–351. [[CrossRef](#)]
276. Shea, M.K.; Dawson-Hughes, B.; Gundberg, C.M.; Booth, S.L. Reducing Undercarboxylated Osteocalcin With Vitamin K Supplementation Does Not Promote Lean Tissue Loss or Fat Gain Over 3 Years in Older Women and Men: A Randomized Controlled Trial. *J. Bone Miner. Res.* **2017**, *32*, 243–249. [[CrossRef](#)]
277. Koitaya, N.; Ezaki, J.; Nishimuta, M.; Yamauchi, J.; Hashizume, E.; Morishita, K.; Miyachi, M.; Sasaki, S.; Ishimi, Y. Effect of Low Dose Vitamin K2 (MK-4) Supplementation on Bio-Indices in Postmenopausal Japanese Women. *J. Nutr. Sci. Vitaminol.* **2009**, *55*, 15–21. [[CrossRef](#)] [[PubMed](#)]
278. Rønn, S.H.; Harsløf, T.; Pedersen, S.B.; Langdahl, B.L. Vitamin K2 (Menaquinone-7) Increases Plasma Adiponectin but Does Not Affect Insulin Sensitivity in Postmenopausal Women: A Randomized Controlled Trial. *Eur. J. Clin. Nutr.* **2021**, *75*, 1661–1667. [[CrossRef](#)]
279. Dalmeijer, G.; van der Schouw, Y.; Magdeleyns, E.; Ahmed, N.; Vermeer, C.; Beulens, J. The Effect of Menaquinone-7 Supplementation on Circulating Species of Matrix Gla Protein. *Atherosclerosis* **2012**, *225*, 397–402. [[CrossRef](#)]
280. Zhao, Q.-Y.; Li, Q.; Hasan Rashedi, M.; Sohoul, M.; Rohani, P.; Velu, P. The Effect of Vitamin K Supplementation on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis. *J. Nutr. Sci.* **2024**, *13*, e3. [[CrossRef](#)]
281. Kristensen, M.; Kudsk, J.; Bügel, S. Six Weeks Phylloquinone Supplementation Produces Undesirable Effects on Blood Lipids with No Changes in Inflammatory and Fibrinolytic Markers in Postmenopausal Women. *Eur. J. Nutr.* **2008**, *47*, 375–379. [[CrossRef](#)]
282. Yoshida, M.; Jacques, P.F.; Meigs, J.B.; Saltzman, E.; Shea, M.K.; Gundberg, C.; Dawson-Hughes, B.; Dallal, G.; Booth, S.L. Effect of Vitamin K Supplementation on Insulin Resistance in Older Men and Women. *Diabetes Care* **2008**, *31*, 2092–2096. [[CrossRef](#)]
283. Grossmann, M. Hypogonadism and Male Obesity: Focus on Unresolved Questions. *Clin. Endocrinol.* **2018**, *89*, 11–21. [[CrossRef](#)] [[PubMed](#)]
284. Thirumalai, A.; Anawalt, B.D. Epidemiology of Male Hypogonadism. *Endocrinol. Metab. Clin. N. Am.* **2022**, *51*, 1–27. [[CrossRef](#)]
285. Seftel, A.D. Male Hypogonadism. Part I: Epidemiology of Hypogonadism. *Int. J. Impot. Res.* **2006**, *18*, 115–120. [[CrossRef](#)] [[PubMed](#)]
286. Forouhi, N.G.; Wareham, N.J. Epidemiology of Diabetes. *Medicine* **2019**, *47*, 22–27. [[CrossRef](#)]
287. Clynes, M.A.; Harvey, N.C.; Curtis, E.M.; Fuggle, N.R.; Dennison, E.M.; Cooper, C. The Epidemiology of Osteoporosis. *Br. Med. Bull.* **2020**, *133*, 105–117. [[CrossRef](#)] [[PubMed](#)]
288. Lee, S.J.; Lee, I.-K.; Jeon, J.-H. Vascular Calcification—New Insights into Its Mechanism. *Int. J. Mol. Sci.* **2020**, *21*, 2685. [[CrossRef](#)] [[PubMed](#)]

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.