Association of Vitamin D Level in Type II Diabetic Patients With Inflammatory Biomarkers: A Review

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled - Association of Vitamin D Level in Type II Diabetic Patients With Inflammatory Biomarkers: A Review is submitted by – Akshay Ghosh (Student ID 19346061) of Summer 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of pharmacy on [2nd May, 2024].

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Ethics Statement

This study does not involve any kind of animal and human trial.

Abstract

Type II Diabetes Mellitus (T2DM) is a disorder characterized by insulin resistance and chronic low-grade inflammation. Several studies have reported a high rate of Vitamin D deficiency among individuals with T2DM and increased rate of inflammation. Inflammatory biomarkers such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are commonly elevated in T2DM patients and are indicative of inflammation. Moreover, vitamin D plays a crucial role in modulating immune function and inflammatory responses. Vitamin D receptors are expressed in immune cells and Vitamin D has been shown to suppress the production of pro-inflammatory cytokines while promoting anti-inflammatory cytokine secretion. Additionally, Vitamin D may regulate immune cell function and modulate inflammatory signaling pathways. Clinical studies regarding the effects of Vitamin D supplementation in T2DM patients have shown promising results in reducing inflammatory biomarker levels and improving glycemic control. However, further research is needed to confirm the specific mechanisms by which Vitamin D reduces inflammation in T2DM and to determine possible strategies for using Vitamin D in T2DM patients. This can open a new effective therapy for reducing complications of type II diabetes patients and improve their overall condition. Further research is needed to validate these findings and to explore the therapeutic potential of Vitamin D supplementation in T2DM management.

Keywords: T2DM (Type II diabetes), TNFα (Tumor necrosis factor), Vitamin D, CRP (C-reactive protein), Interleukins, Cytokines, Inflammatory biomarkers.

Dedication

Dedicated to my parents.

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List of Acronyms

T2DM: Type II Diabetes

IL 6: Interleukin 6

IL 7: Interleukin 7

IL 8: Interleukin 8

TGF B: Tumor Growth Factor Beta

TNF-α : Tumor Necrosis Factor Alpha

CRP: C reative protein

Chapter 1

Introduction:

One of the most common long-term medical conditions characterized by elevated levels of blood glucose and abnormal protein and fat metabolism is called diabetes. In this condition pancreas stops making adequate amount of insulin or, in the contrary, the insulin cannot be utilized by the cells. As a result blood glucose levels increase because the glucose metabolism does not happen. Three main forms of diabetes exist: Type 1 diabetes (T1DM) is known for the inability of pancreas to produce insulin. Type 2 diabetes (T2DM) is known for the body's cells' resistance to the action of insulin, which causes the body to produce less insulin over time. Type 3 diabetes or gestational diabetes, that is seen during pregnancy, leads to complications during and after childbirth. It also elevates risk of type 2 diabetes development in mother (Roglić, 2016). T1DM can be treated by insulin replacement therapy but oral hypoglycemic are used for treating T2DM Generally, with the progression of the diabetes, pathological changes for example nephropathy, retinopathy and cardiovascular disease may occur (Padhi et al., 2020).

Biomarkers are defined as parameters that are used in clinical diagnosis to detect and calculate the progression of disease. These parameters might be chemical, physical, or biological. They indicate changes in the expression or status of genes, peptides, proteins, and other factors that are associated with risk or disease progression, initial diagnosis, response of drug, treatment sensitivity, drug target identification, and disease intervention (Mayeux, 2004). Inflammatory biomarkers are quantifiable chemicals that gives necessary information on the presence and state of inflammation in the body. In clinical medicine, these indicators play an essential role in disease diagnosis, severity assessment, therapy efficacy monitoring. Low-grade inflammation is linked to a variety of chronic disorders, including cancer, chronic

obstructive pulmonary disease, type 2 diabetes, obesity, peripheral/coronary artery disease, and autoimmune disorder. As a result, inflammatory biomarkers may be used to detect and track the evolution of inflammation. Stable biomarkers should be available via non-invasive procedures, and their detection should be inexpensive and simple. Common inflammatory markers include CRP, serum amyloid A, fibrinogen as well as cytokines such as TNFα, interleukins 1β, 6, 8, 10, and 12, and their receptors, and IFNγ (Menzel et al., 2021).

Some research suggests that resistance of insulin and diabetes mellitus are interconnected with vitamin D deficiency. Polymorphisms in genes that are passed down through generations have been assumed as the primary mechanism that links vitamin D deficiency with the diabetes development. However, vitamin D regulates the immune system and acts as an anti-inflammatory agent. Vitamin D insufficiency may cause insulin resistance and type 2 diabetes mellitus (Mitri et al., 2011). Lower 25(OH)D levels in blood have been associated with decreased pancreatic beta-cell activity and resistance of insulin. Beta cells and other essential organs involved in glucose homeostasis physiology may produce active metabolite of vitamin D by expressing 1-alpha-hydroxylase (CYP27B1). In addition, supplementing with vitamin D restores impaired insulin secretion in animals who have insufficiency of vitamin D. A higher concentration of inflammatory markers is linked to low blood 25(OH)D levels. This suggests that systemic inflammation plays a role in the type 2 diabetes pathogenesis (Pittas et al., 2020). Moreover, pancreatic β cells and immune system cells both contain receptors for Vitamin D. Furthermore, the significance of vitamin D in the control of calcium absorption is widely recognised. Vitamin D plays a crucial role in β-cell endopeptidases functions that rely on calcium, and it shows its effects through two primary pathways. Vitamin D plays a crucial role in the functioning of cells (pancreatic) by binding 1,25-dihydroxyvitamin D to a specific receptors in the beta cell. In an alternative approach, vitamin D has the potential to enhance insulin sensitivity by directly affecting pancreatic beta

cells. This is achieved when by 1-alpha-hydroxylase activates 25 hydroxyvitamin D (25(OH)D). Vitamin D can positively impact acid metabolism (fatty acid) in skeletal muscle and adipose tissue by stimulating insulin receptor expression and activating PPAR-δ (peroxisome proliferator activated receptor delta) (Van Etten & Mathieu, 2005).

1.1 Aim

This is why the aim of this study is to investigate the inter-relationship between serum vitamin D and inflammatory biomarkers in type II diabetic patients.

1.2 Objectives

1. To observe vitamin D impact on type II diabetic patients and inflammation.
2. To find out the relationship between inflammatory biomarkers and type II diabetes mellitus.
3. To find out the potential mechanism of actions of vitamin D in regulating inflammatory biomarkers in T2DM.

Chapter 2

Methodology

To conduct this literature review, key words are searched in a structured way at different databases such as PubMed, Elsevier, google scholar. A thorough search was also conducted in peer reviewed publications, official papers and articles. Books were also used to get relevant and trustworthy information to support the review. Key words such as T2DM, insulin resistance in T2DM, inflammatory markers, function of vitamin D, level of vitamin D in type II diabetes, inflammatory disorder, inflammatory biomarkers were used to search the articles. Some clinical trial data is also used here to support the review. Articles from 2000- 2023 were used to ensure the use of valid data.

Chapter 3

Findings and Discussion

3.1 What is Vitamin D?

Vitamin D is a hormone that is acquired via food sources and through skin.Wwhen ultraviolet B (UVB) light (290 to 315nm) touches the surface of skin, it transforms 7-dehydrocholesterol to previtamin D. Isomerization at high temperatures transforms this previtamin D into vitamin D. It is possible to measure vitamin D levels by calculating 25-hydroxyvitamin D, which is a byproduct of the liver's metabolism of vitamin D. 25-hydroxyvitamin D-1 alpha-hydroxylase (CYP27B1) enzyme transforms 25 hydroxyvitamin D into the physiologically active form, 1,25-dihydroxy vitamin D (1,25 (OH)). Moreover, parathyroid, calcium, and phosphorus levels can maintain production of 1,25-dihydroxy vitamin (Nair & Maseeh, 2012). Cancer, autoimmune illnesses, hypertension, and other conditions have all been linked with insufficient levels of vitamin D. The liver activates the metabolism process of vitamin D because it is responsible for the first hydroxylation of carbon 25(Fig. 1).

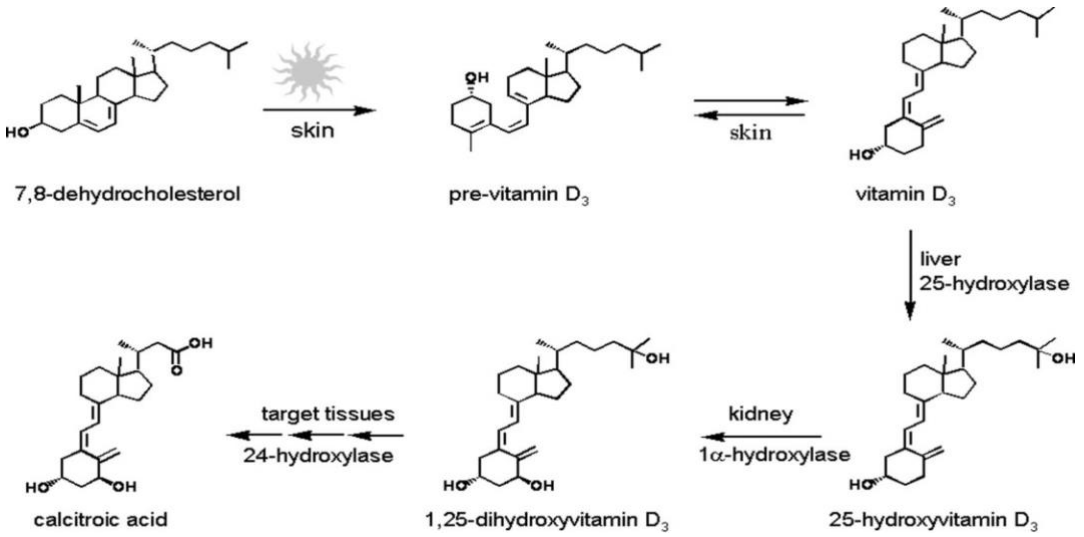

Figure 1: The synthesis, activation of Vitamin D3 (Holick, 1981).

Skin produces vitamin D3 by photolytically cleaving 7-dehydrocholesterol and then thermally isomerizing. Vitamin D3-25-hydroxylase and the 25(OH) D3-1 alpha hydroxylase enzyme breaks down vitamin D into its active metabolite, 25-hydroxyvitamin D3, which is then released into the bloodstream. It is in the kidney where the last activation step, 1 alpha-hydroxylation, occurs. In this process, vitamin D3's hormonal form, 1,25-dihydroxyvitamin D3, is formed. Through a cascade of oxidation reactions that culminate in side chain breakage, 24-hydroxylase renders catabolism inactive. Vitamin D compounds may be 25-hydroxylate by a number of hepatic cytochrome P-450s. Unlike humans, rat males exclusively have CYP2C11 in their bodies (Hayashi, 1988). Hydroxylation on vitamin D3 is not performed by CYP3A4 (Guillemant & Guillemant, 1980). But CYP2R1 seems like a promising candidate anyway. The discovery was made that this cytochrome P-450, which was previously unknown for its activities, may hydroxylate vitamin D2 and D3. It mostly resides into testes and liver. In its role as 25-hydroxylase, CYP2R1 plays a pivotal step in vitamin D metabolism. It is not easy to control vitamin D 25-hydroxylation. Since plasma 25(OH)D level rise in reaction to vitamin D supplementation, it is used as a hallmark of vitamin D level (Holick, 1981).

3.2 What is type II diabetes?

World Health Organization (WHO) suggests that high blood glucose levels are the hallmarks of diabetes mellitus. Issues with the heart, blood vessels, eyes, kidneys, and nervous system are among scenarios that might play out. The majority of instances of diabetes mellitus, especially type 2 diabetes is a result of tissues developing insulin resistance, pancreatic islet cell insufficiency in secreting insulin, and a reduced compensatory secretory effect to insulin (Stümvoll et al., 2005). As the disease advances and insulin production falls short of glucose regulation, blood sugar levels increase. Type 2 diabetic patients tend to weigh more overall

and have a high quantity of body fat, especially in abdominal region. Adipose tissue stops a series of inflammatory reactions that worsen insulin resistance in this area. These actions cause a disruption in adipokine regulation and the production of more free fatty acids (FFAs). Type 2 diabetes is increased due to including an aging population, calorie-heavy diets, lack of physical exercise, and the epidemic of obesity throughout the globe. Because of this, type 2 diabetes patients number has increased fourfold (Zeng et al., 2016).

The organs that contribute to T2DM include liver, adipose tissue , skeletal muscle, brain, small intestine, kidneys, pancreatic (beta- and alpha-cells) (DeFronzo, 2009). There is strong evidence that adipokines, gut microbiota, and immunological dysfunction all have an impact in progression of certain illnesses (Schwartz et al., 2016).. The International Diabetes Federation reports that 4.2 million people lost their lives to diabetes in 2019. The bulk of the 700m diabetic people will be in the age group of 20–79. It is predicted to enhance from 463m in 2018 to 700m by 2045. In 2019, healthcare expenditures reached a record $720 billion USD due to diabetes and its complications. Keep in mind that many diabetics go undiagnosed, therefore the actual number of individuals affected by type 2 diabetes can be higher than reported. A staggering 232 million individuals, or over one-third of all diabetes, experience this underdiagnosis. People in their forties and fifties have the highest prevalence of diabetes. Although the incidence and prevalence of type 2 diabetes varies by area, most of the patients reside in countries with low to medium socioeconomic levels. Because of this, providing effective treatment becomes even more difficult. Having type 2 diabetes increases the chance of mortality from any cause by 15% compared to not having the illness. Among the many complications that may arise from type 2 diabetes, one of them that leads to death is cardiovascular disease (CVD) (Gæde et al., 2003). Diabetes raises the risk of CVD, stroke, and other deaths caused by vascular disease. According to the study, those with diabetes had a hazard ratio of 2.00 (coronary heart

disease), 2.27 (ischemic stroke) and 1.73 for other vascular disease-related mortality. Potential threats for type 2 diabetes include both internal and external factors. It is possible that a person's genetic composition is affected by living in an environment that encourages inactive lives and excess calorie intake. Although common genetic variations for type 2 diabetes have been recognized by studies of genome-wide association, variations only responsible for a small portion of the total phenotypic variance. This implies that rare variants might potentially play a significant role as well (Grarup et al., 2014).

It is plausible that phenotypes vary across ethnic groups, rendering certain populations more susceptible to cardiovascular disease risk factors than others. A few of the possible causes include high blood pressure, insulin resistance, and abnormal lipid profile (Galicia-García et al., 2020).

3.3 Association of Vitamin D and T2DM

Deficiency of vitamin D enhances the risk of certain chronic diseases. Hypovitaminosis D may have several origins. Sunscreen usage, skin tone, season, latitude, and amount of solar exposure are some of these factors. Vitamin D mal-absorption may be caused by a number of factors, including some drugs and supplements, cystic fibrosis, liver disease, inflammatory bowel disease, celiac disease, and other autoimmune disorders. An ideal plasma 25(OH)D3 level for a healthy individual is more than 30 ng/mL. Getting additional sun exposure or using dietary supplements can be necessary for certain people to reach this level. Among the many variables that increase the rate of acquiring type 2 diabetes are hypoinsulinemia and reduced insulin synthesis by the pancreas. Insulin resistance is also linked with low level of vitamin D. Type 2 diabetes is linked with inadequate vitamin D consumption (Alvarez & Ashraf, 2010). There may not be a direct connection between low vitamin levels and insulin

resistance/type 2 diabetes. Raising blood 25(OH)D3 levels has mixed results about whether or not they may slower the progression of type 2 diabetes. Many randomized clinical trials have shown that in this context, plasma levels of active 25(OH)D3 do not correlate at the start of the type II diabetes (Lotta et al., 2016). Notably, several clinical trial have failed to give strong evidence regarding the long-term efficacy of high-dose of vitamin D supplementation or proper vitamin D status maintenance in blood sugar levels maintaining in type 2 diabetic individuals (Elkassaby et al., 2014). Additional validation is necessary via large-scale clinical studies that include various demographics, study methodologies, and sample sizes. A loss of beta-cell mass and an imbalance in insulin secretory responses lead to type 2 diabetes mellitus (T2DM). Characteristic of this condition matches with hyperglycemia and it is potentially life-threatening also (Prentki & Nolan, 2006). Reducing insulin resistance and improving islet dysfunction are essential for preventing and treating type 2 diabetes. A feature of hyperlipidemia, a disease strongly related with chronic hyperglycemia, an increased lipid production and accumulation in the pancreatic islets and liver. An over-abundance of lipids in the liver may lead to endoplasmic reticulum (ER), inflammation, and reduced sensitivity of insulin (Flamment et al., 2012). Furthermore, inflammation inside the islets are caused by an increase in intra-islet lipid buildup, which limits glucose's capacity to trigger insulin release. In the long run, this may cause beta cells to die and the islets to stop functioning (Del Prato, 2009).

Since vitamin D levels are involved in T2DM development and in the maintenance of good pancreatic and liver functions, there is certainly a connection between the potential therapeutic necessity of vitamin D and the VDR. New medications with vitamin D may successfully treat the liver with metabolic abnormalities and islets. That would greatly improve our ability to prevent and cure type 2 diabetes (Leung, 2016).

Moreover, pancreatic β cells and immune system cells both contain receptors for Vitamin D. Furthermore, the significance of vitamin D in the control of calcium absorption is widely recognised. Vitamin D plays a crucial role in the functioning of β-cell endopeptidases that rely on calcium, and it exerts its effects through two primary pathways, such as:

1. Stimulating β-cells so that it can release insulin by increasing intracellular calcium concentration via Ca channels.

2. By facilitating the proinsulin transformation to insulin through the mediation of β-cell calcium-dependent activation (Mathieu et al., 2005).

Vitamin D has a crucial role in the pancreatic cells functions by the binding of 1,25-dihydroxyvitamin D to its specific receptors in the beta cell. Moreover, vitamin D has the potential to enhance insulin sensitivity by directly affecting pancreatic beta cells. This is achieved with the 25 hydroxyvitamin D (25(OH)D) activation in presence of 1-alpha-hydroxylase. Vitamin D can stimulate expression of insulin receptor and activate PPAR-δ (peroxisome proliferator activated receptor delta) and positively impact on fatty acids metabolism in skeletal muscle and adipose tissue (Van Etten & Mathieu, 2005).

3.4 Inflammation and Inflammatory Biomarkers

When immune system detects a threat, such as a virus, damaged cells, poisonous substances, or radiation, the body's natural reaction is inflammation (Medzhitov, 2010). The elimination of these damaging stimuli and the beginning of the healing process are its intended purposes (Ferrero-Miliani et al., 2006). It is essential to recognize that inflammation is an essential component in the process of preserving one's current state of health (Nathan & Ding, 2010). In most instances of acute inflammatory reactions, the interplay between cells and molecules helps to minimize infection or damage. Resolving the acute inflammation and restoring tissue homeostasis are both aided by this process. Conversely, several chronic inflammatory disorders may arise from acute inflammation if it is not treated in a timely manner (Wang et al., 2018). Redness, edoema, heat, discomfort, and functional impairment are hallmarks of tissue-level inflammation. In reaction to pathogens or damage, the body's immunological, circulatory, and inflammatory cell systems react, causing these symptoms (Takeuchi & Akira, 2010). Damage to the microcirculation occurs when inflammatory mediators are released, leukocyte recruitment and accumulation occur, and changes in vascular permeability occur (Chertov et al., 2000).

A number of things may set off inflammation, which in turn can cause tissue damage; they include infections, injuries, and myocardial infarction. Many different things may cause inflammation, and some of those things are contagious while others aren't. After a tissue damage occurs, the body responds by sending out a cascade of chemical signals that help the injured tissues repair. In response to these cues, white blood cells are redirected from the circulation to the site of damage. When these white blood cells get activated, they release inflammatory chemicals called cytokines (Jabbour et al., 2009).

Biomarkers are parameters that can be utilised in both preclinical research and clinical diagnostics to identify and measure the progression of disease. These parameters can encompass chemical, physical, or biological aspects. Biomarkers of inflammation are measurable substances that tell us a lot about the level of inflammation in our bodies. These indicators are crucial in clinical medicine for diagnosing diseases, assessing their severity, and monitoring the effectiveness of therapies. Various chronic disorders, such as cancer, chronic obstructive pulmonary disease, T2DM, obesity, peripheral/coronary artery disease, and autoimmune diseases, are found to be in association with low-grade inflammation. Consequently, inflammatory biomarkers have the potential to be utilised in the detection and monitoring of inflammation progression (Menzel et al., 2021).

Higher levels of certain proteins have been observed in individuals with diabetes, including serum amyloid A, C-reactive protein (CRP), fibrinogen, haptoglobin, plasminogen activator inhibitor, sialic acid, interleukin (IL)-1β, IL-1 receptor antagonist (IL-1Ra), IL-6, and tumour necrosis factor (TNF)-α. Increased levels of CRP, IL-1β, IL-1Ra, and IL-6 in the bloodstream have been found to be indicative of the future onset of type 2 diabetes mellitus (T2DM) (Fröhlich et al., 2000).

Moreover, research has shown that nuclear factor-kappa B (NF-κB) plays a crucial role in the development of diabetes. The activation of the NF-κB pathway is triggered by various types of stress, including genotoxic, oxidative, and inflammatory stress. This pathway plays an important role in controlling cytokines, growth factors, and genes that are involved in apoptosis, cell-cycle progression, and inflammation regulation (Yuan et al., 2001). Research findings suggest a link between activation of NF-κB and resistance of insulin, as well as metabolism of glucose. Increased activation of NF-κB signalling in hepatocytes leads to the

type 2 diabetes mellitus (T2DM) development and triggers an innate immune response and inflammatory reaction that could potentially contribute to the pathogenesis of T2DM. Hence, the activation of NF-κB in adipose tissue, pancreas, and liver, shows a role in the T2DM development (Matsumori, 2022).

3.5 Relation Between Inflammatory Biomarkers and Vitamin D

Furthermore, vitamin D has an impact in controlling the inflammatory response. Multiple investigations have hinted to a possible connection between insufficient vitamin D and elevated inflammatory biomarkers in blood. Biomarkers such as IL-6, TNF-α, and C-reactive protein (CRP) are discussed here. Both healthy people and those with obesity have shown this connection. Be much as it may, not every study has been able to confirm these results. Because of their observational nature, cross-sectional studies cannot prove causation or rule out the chance that unmeasured variables impacted the outcomes.

Vitamin D supplementation effects on blood levels of inflammatory biomarkers have been studied in clinical studies (Table 1) and their results are presented. It seems that including vitamin D into the therapy for several inflammatory medical illnesses, such as kidney disease (chronic), osteoporosis, and chronic heart failure, lowers blood levels of tumor necrosis factor-alpha and raises IL-10 concentrations (Schleithoff et al., 2006b). Researchers have administered calcium and vitamin D supplements to normal and impaired fasting glucose levels for three years. No change in systemic CRP or IL-6 levels was seen as a consequence of this supplementation. Nevertheless, after taking vitamin D supplements for a year, those who were considered overweight but otherwise healthy and participating in a program to lose

weight saw a significant decline in blood TNF-α levels. Contrary to expectations, there was no decline in IL-6 and CRP levels (Chagas et al., 2012).

Table 1: Vitamin D impact on inflammatory biomarkers in the bloodstream of type II diabetic patients.

Ref.	**Participants**	**Dosage**	**Result**
(Von Hurst et al., 2009)	81 women (South Asia)have insulin resistance. The median serum 25OHD level at baseline was 21 nmol/L.	vitamin D_3 (100 µg)/ 6 months.	No effect on CRP
(Schleithoff et al., 2006)	(123 individuals had congestive heart failure. The mean serum 25OHD level was 36 nmol/L.) .	Oral supplementation vitamin D_3/ 50 µg/day	No reduction in TNF-α and CRP butelevates IL 10
(Borazan et al., 2003)	(34 patients who are going through haemodialysis. Mean serum 25OHD at baseline was not	Calcitriol was administered orally (0.5 µg per day) or intravenously (One µg three times per week; n = 16) for six months.	TNF-α, IL 1, and IL 6 levels did not alter between oral and intravenous calcitriol. However,

	reported.)		intravenous calcitriol significantly reduced these levels.
(İnanır et al., 2004)	(70 women (post-menopausal with osteoporosis) (Mean serum 25OHD at baseline was not reported)	For 6 months, participants were given either 0.5 µg/day of calcitriol plus 1,000 mg/day of calcium or a placebo (calcium alone).	TNF-α and interleukin 1 levels decreased significantly, whereas IL 6 levels remained unchanged.
(Pittas et al., 2006)	(There were 222 non-obese volunteers (normal fasting glucose) and 92 non-obese patients (impaired fasting glucose). The mean blood 25OHD level in both groups was 76 nmol/L)	700 IU vitamin D3 for three years.	There are no reduction in CRP and IL 6.
(Zittermann et al., 2009)	(200 healthy, overweight individuals. The mean serum 25OHD level was 30 nmol/L).	Effects of 83 µg/day vitamin D3 during a weight-loss program.	TNF-α levels decreased faster.

(Björkman et al., 2009)	(218 long-term patients and their mean serum 25OHD level at baseline was 23 nmol/L.)	Vitamin D3/ 400 or 1200 IU/day till 6 months.	No reduction in CRP (C-reactive protein.)
(Gadrey et al., 2009b)	(125 patients (haemodialysis) and their mean serum 25OHD level at baseline was 32 nmol/L.)	For 15 months, 100,000 IU/month of vitamin D3.	No reduction in CRP (C-reactive protein.)
(Matias et al., 2010)	(158 patients on haemodialysis. 39 had diabetes, while 54 had hypertension. The mean blood 25OHD level at baseline was 55.75 nmol/L.)	for 25OHD serum levels, 50,000 IU/week < for 25OHD, 15 ng/mL; - 10,000 IU/week - Take 2,700 IU three times per week for patients with 25OHD levels above 30 ng/mL.	Significant reduction in C-reactive protein.
(Bucharles et al., 2012)	Thirty haemodialysis patients. The mean blood 25OHD level at baseline was 45.5 nmol/L.	Weekly vitamin D3 supplementation for 24 weeks: 50,000 IU in the first 12 weeks and 20,000 IU in the last 12 weeks.	Rapid reduction in CRP and interleukin 6(C-reactive protein and IL 6.)

Table 1 shows clinical studies that examined the effect of vitamin D supplementation on blood inflammatory biomarkers. Administration of vitamin D can reduce serum TNF-α levels and raise serum IL-10 concentration in inflammatory disorders (such chronic heart failure, chronic kidney disease, and osteoporosis) (Schleithoff et al., 2006). A 3-year investigation of patients with normal or altered glucose fasting found that administration of 500 mg calcium + 700 IU cholecalciferol per day had no effect on systemic CRP or IL-6 levels (Pittas et al., 2007b). Supplementing healthy overweight participants with vitamin D (3332 IU cholecalciferol/day) for 12 months resulted in a significant drop in serum TNF-α levels, but no reduction in IL-6 or CRP concentration (Zittermann et al., 2009b).

3.6 Association of Vitmin D in Type II Diabetic Patients Inflammatory Biomarkers

Nowadays, scientists are trying to figure out how T2DM is related to the production of inflammatory factors. Dendritic cells, antigen-presenting B-cells, and Kupffer cells are only a few of the liver cells that work together to identify and react to certain patterns in dietary ingredients or bacteria. Specific receptors called toll-like receptors (TLR) activate and detect patterns when ligands with conserved structural compounds bind to TLR and such patterns include free fatty acids (FFAs) and bacterial lipopolysaccharide (LPS) (Shi et al., 2006).

Upon activation of NFκB and AP-1, PRR interactions turn off inflammatory reactions (Takeda & Akira, 2004). On activation of these molecular pathways, inflammatory mediators and pro-inflammatory cytokines are produced more effectively by cells. When activated, these molecular cascades within the cell increase the transcription of genes that produce pro-inflammatory cytokines. As a result, acute-phase inflammatory mediators are produced. It

also activates enzymes such as c-Jun N-terminal kinase (JNK) and inhibitor of NFκB kinase-β (IKK). When applied to hepatic and adipose tissues, these two chemicals inhibit insulin receptor (INSR) activity, namely IRS-1. Consequently, the signaling pathway that results in metabolic consequences is reduced (Aguirre et al., 2000). PRR expression and activity play a crucial role in starting the dysregulation cascade due to the complex web of interconnected metabolic targets. In response to cytokines for example TNF-α and IL-1β, insulin-target cells have the ability to activate JNK and IKK. Through post-transcriptional mechanisms, its activation induces resistance to insulin and Type 2 Diabetes Mellitus; it is a critical metabolic route in inflammation and lipotoxicity. Specifically, obese mice showed a significant increase in insulin sensitivity after having one copy of IKKH deleted (in IKKH+/-mice).The degradation of IRS-1 occurs as a result of the binding of SOCS proteins, which are induced to increase in synthesis by TNF-α (White, 2014).

Furthermore, AP-1 and NFκB expression levels are raised as a result of the transcriptional up-regulation of JNK and IKK induced by cytokines. Afterwards, TNF-α is activated by these substances, leading to an intensification of inflammatory reactions both locally and systemically.60 Hence, inflammation and insulin signaling disruption are largely caused via the JNK-AP-1 and IKK-NFκB pathways. To improve insulin sensitivity and keep glucose levels stable, these pathways can be studied and maybe changed (Hotamışlıgil, 2006).

The cascade of events begins with insulin secretion, which triggers INSR activation, which phosphorylates many IRS tyrosine residues, and ultimately initiates a cascade of physiological responses. The findings of a study that looked at what happens when you increase transport of glucose into muscle and adipose tissue cells are presented here. As a result of fatty acids activating TLR4, which in turn activates the JNK-AP-1 and IKK-NFκB axes, the expression of genes producing cytokines increases. Not only do cytokines start the production of APPs (like CRP, fibrinogen, haptoglobin, etc.), but they also disrupt insulin

action by dysregulating the INSR-IRS-mediated transportation of glucose. This alteration reduces IRS's tyrosine activity by causing it to be phosphorylated on serine rather than tyrosine (Hu et al., 2006).

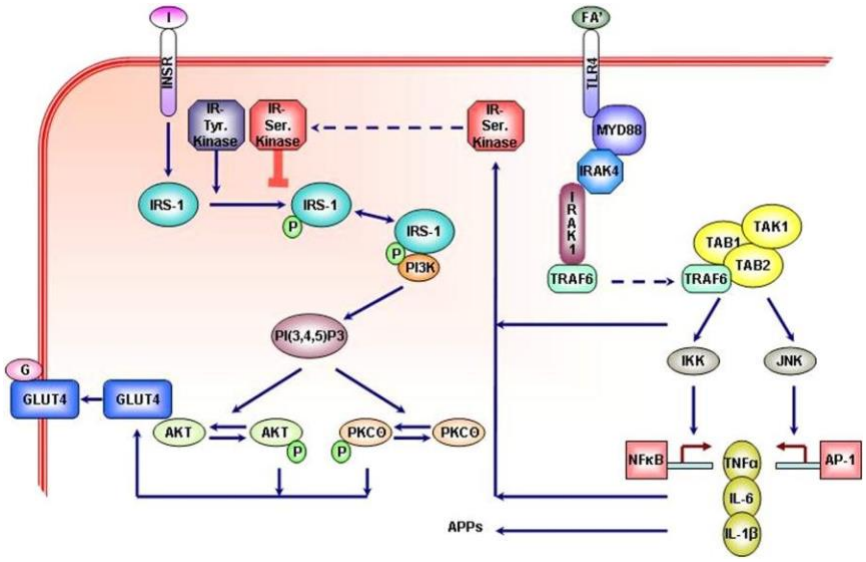

Figure 2: Inter relation between insulin signaling and in the production of inflammatory markers (Badawi, 2010).

CRP: When the body receives signals from inflammatory chemicals and fat cells, it produces CRP (C-reactive protein) in the liver. Evidence from its many features points to an essential role in immunological control. To be more precise, CRP is an oligomeric protein that activates PRRs; a pentraxin family member. In addition to these functions, CRP increases leukocyte reactivity, allows complement fixation, controls platelet activation, and helps clear inflammatory regions of cellular debris. Elevated blood C-reactive protein may be associated with one-third of type 2 diabetes occurrences. It is crucial to take into account the substantial effect of CRP on pancreatic β-cell activity, especially in connection with T2DM (Anan et al., 2006). CRP's has a great impact on enhancing programmed cell death and inhibiting cell

growth. Moreover, protein kinase B (PKB) might increase the synthesis of TNF-α, IL-1β, and matrix metalloproteinase-9 (MMP-9) (Cirillo et al., 2005).

TNF-α: TNF-α is a crucial indicator in the systemically acute responses associated with severe infections caused by gram-negative bacteria (Vassalli, 1992). Natural killer (NK) cells, stimulated mononuclear phagocytes, mast cells, and antigen-stimulated T-cells are the main cellular sources of tumor necrosis factor-α. Adipose tissue consistently expresses the TNF-α gene, mostly due to the fact that macrophages rather than adipocytes themselves invade it. Compared to lean individuals, obese people had 2.5 times higher levels of TNF-α mRNA expression in adipose tissue. Hyperinsulinemia is intimately linked to this increased expression. Reducing blood TNF-α levels by weight loss in obese patients and in vivo TNF-α suppression led to notable improvements in insulin sensitivity. Elevated TNF-α level can lead to the insulin resistance and T2DM development. This could be because it promotes the death of pancreatic β-cells or because it has effects on IRS-1(Hotamışlıgil et al., 1995).

IL-6: Independent of weight, many studies have connected elevated IL-6 levels to an advanced risk of type 2 diabetes (Wannamethee et al., 2008). There are a number of theories put forward to explain the importance of IL-6 in mediating insulin resistance. Class I cytokine receptors, of which the JNK signal transduction pathway is a member, include the IL-6 receptor (IL6R) (Ihle et al., 1995).

The STAT proteins undergo phosphorylation, dimerization, and nuclear translocation once IL-6 activates JNK. Many target genes, including as IRS, AP-1, and NFκB, are regulated by this mechanism in hepatocytes and adipocytes (Kristiansen & Mandrup-Poulsen, 2005).

3.6.1 Vitamin D and Cytokines (IL 6, IL 8, IL 10. IL 17A, TGF Beta)

IL-6 is a pro-inflammatory cytokine known for its importance in promoting tumour growth and progression in prostate cancer and colorectal cancer (Nguyen et al., 2014). As an example, consider how IL-6 enhances gene transcription of MC-1 via the p38-MAPK and JAK-STAT pathways, therefore blocking the apoptotic effects of TRAIL on tumor cells (Lippitz, 2013). IL-6 was found to be a significant factor in promoting angiogenesis and tumour growth (Dalwadi et al., 2005). Researchers found that interleukin-6 (IL-6) reduced p53 protein levels and enhanced MMP-14 expression. The ultimate outcome is an increased probability of cancer cell penetration and metastasis. Vitamin D and the maintenance of IL-6 production have been the subject of many studies. Following prior treatment with 25(OH)D, the IL-6 synthesis of normal cells is effectively decreased. This suppression is achieved by blocking the p38 MAPK pathway, which shows that 25(OH)D has strong anti-inflammatory actions (Cathcart, 2016).

When it comes to initiating angiogenesis, IL-8 is a major player. Many variables play in tumor development, such as those that stimulate neoplastic cell growth, elevate collagenase activity, prevent tumor cell death, and increase MMP-2 and MMP-9 expression (Cheng et al., 2013). IL-8 presence a great role in breast cancer. HER-2 positive cancers control IL-8 via ligands of chemokine receptor 1/2 (CXCR1/2). Changes in interleukin-8 (IL-8) levels have a significant impact on the cancer-promoting or -inhibiting actions of stem cells (Singh et al., 2013). Scientists discovered that calcitriol changed how stable IL-8 messenger RNA was. The 3′-flanking region's ATTTA motif or post-transcriptional regulators make this possible. Therefore, PCa causes a holdup in the transmission and tube formation of endothelial cells in the human umbilical vein (Bao et al., 2008). A recent research on colon cancer cells found that calcitriol may decrease IL-8 production. One possible explanation for this anti-

inflammatory effect is a decrease in IL-8 production brought about by an increase in the metabolism of sCD14, the soluble form of CD14, via the ERK1/2 pathway.

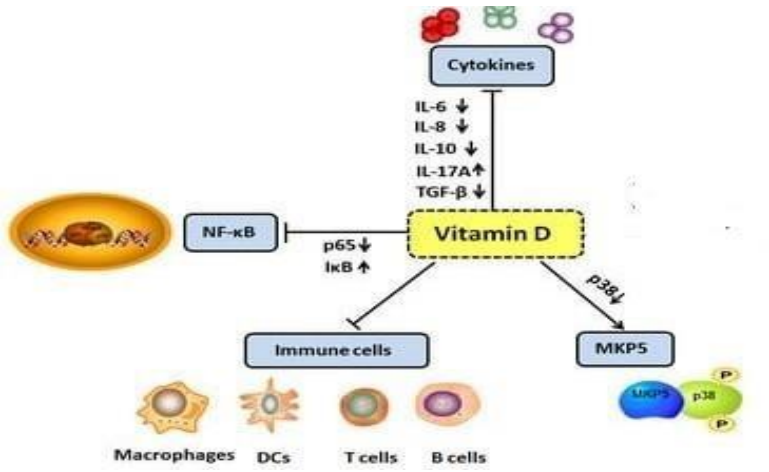

Figure 3: Effects of vitamin D in regulating cytokines, Immune cells, MKP5 and NF-κB (Liu et al., 2018).

An important function of IL-10 is to decrease the synthesis of cytokines that promote inflammation, including IL-2, IFN-γ, TNF-α, IL-6, and IL-8. Another benefit is that it can help reduce inflammation (Pype et al., 1999). In most cases, IL-10 is pivotal in controlling how chronic inflammatory diseases develop. Normal enteric antigens probably cause persistent inflammatory reactions in its absence, which manifest mostly in the gastrointestinal tract (Ilinskaya & Dobrovolskaia, 2014). Research has shown that IL-10 may inhibit the generation of cytokines that promote inflammation and, in turn, tumor development (Dennis et al., 2013). Researchers found that IL-10+ developed for a specific treatment. The inducible co-stimulator ligand (ICOS) expression and the presence of indoleamine 2,3 dioxygenase (IDO) endowed these Tregs with exceptional anti-inflammatory capabilities (Coquerelle et al., 2009). It was found that patients with PCa who expressed ICOS had positive clinical responses to anti-CTLA-4 therapy, hence these results are interesting. Studies have shown

that calcitriol influences the levels of TLR9 in populations of adaptable IL-10-Tregs in humans (Wilkinson & Lange, 2009).

Enzymes including matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), matrix metalloproteinase-1 (MT-MMP1), and urokinase-like plasminogen activator have been associated to an increase in tumor invasiveness in both hepatocarcinoma and pancreatic ductal adenocarcinoma (Sannino, 2016). According to research, TGF-β1 enhances responses by increasing the production of integrin αvβ3. Epithelial cells found in lung fibroblasts go through a process known as epithelial-mesenchymal transition (EMT). By influencing many pro-fibrotic proteins, vitamin D can hinder fibrosis caused by TGF-β and elevates MMP-8 levels in mesenchymal cells and decrease collagen I and III expression (Artaza & Norris, 2008).

3.6.2 Vitamin D and MKP 5

The discovery of the calcitriol-responsive gene MKP5 occurred quite recently. MKP5 binds selectively to a group of kinases known as stress-activated kinases, including p38 MAPK, and blocks their activation. An upregulation of inflammatory cytokines occurs with p38 activation, exacerbating the condition (Heo et al., 2017). Calcitriol inhibits the production of IL-6 and other cytokines that promote inflammation by increasing the expression of MKP5. This indicates that calcitriol may contribute to prevent and/or treat PCa, as it disrupts the mechanism of inflammatory cytokines like TNFα (Nonn et al., 2006).

3.6.3 Vitamin D and NF-κB

When p50 and p65 come together, they form a heterodimer, which is the NF-κB. Within the cytoplasm, it resides as an inactive hetero-oligomer, and it establishes a connection with its inhibitory protein, which is known as the NF-κB (IκB) inhibitor. An essential function of NF-

κB is to regulate gene expression, which in turn controls many responses in eukaryotic cells (Xia et al., 2014). New research has revealed that calcitriol can modulate the NF-κB signal pathway to successfully reduce inflammatory reactions, which is an intriguing property. In both mice and humans, calcitriol inhibits the generation of TNF-α and IL-6, as well as lipopolysaccharide (LPS)-induced p38 phosphorylation, by increasing the VDR binding and activating histone H4 acetylation at specific VDRS in the promoters of MKP1 (Calton et al., 2015). Furthermore, In addition to other techniques, calcitriol may increase IκB levels by decreasing phosphorylation and improving mRNA stability. (Cohen-Lahav, 2006). Colon cancer cells are unable to activate the p65 component of the NF-κB complex when calcitriol is present because it inhibits the bonding of NF-κB to DNA (Tse et al., 2010). Therefore, calcitriol has the potential to be a powerful inhibitor by suppressing the NF-κB signal pathway.

Chapter 4

Conclusion

According to researchers, vitamin D levels are linked to the events that lead to type 2 diabetes and have the ability to counteract those occurrences. Vitamin D may regulate inflammatory responses, according to laboratory data, but there is a dearth of human research on inflammatory markers in T2DM patients or at high risk for progression of the disease. Inflammation, insulin secretion, and sensitivity are all areas that vitamin D helps with, according to scientific studies. While preliminary evidence showss a relationship of vitamin

D, inflammation, and type 2 diabetes. Research on genetic polymorphisms may provide light on the causes of vitamin D deficit and the risk factors for type 2 diabetes (Chagas et al.,2012). Vitamin D is important because it targets MAPK signaling pathways. The fact that MAPK may activate inflammatory mediators should be emphasized. In macrophages, vitamin D affects in vitro human adipocytes' signaling pathways in relation to inflammatory responses. Based on the characteristics of the investigation, the macrophage-conditioned media containing 25% adipocyte medium resulted in a notable reduction in the IkB-α protein expression and an increase in the levels of NF-κB. The medium's IκB-α expression was enhanced and NF-κB phosphorylation was reduced with the introduction of 1,25(OH)2D3. The NF-κB signaling activation was then prevented by macrophages. By reducing levels of p38 MAPK, ERK1/2 that are phosphorylated, two examples of traditional MAPKs, 1,25(OH)2D3 function may also reduce the MAPK signal (Ding et al., 2013). Several studies have shown that the ERK1/2 signaling module may regulate the insulin production in the cells of the pancreas in reaction to glucose stimulation (Sidarala & Kowluru, 2017). When comparing groups of people with pre-diabetes or diabetes, those with vitamin D deficiency had significantly higher serum MAPK levels than those with adequate vitamin D levels. In the pre DM and DM groups with low vitamin D levels and high NF-κB and MAPK levels are likely explained by the effect of vitamin D on pro-inflammatory markers such as IL1-H, IL-6, and TNF-α. These indicators subsequently alter the signaling pathways of NF-κB and MAPK (Fenercioğlu et al., 2023). It is hypothesized that the genotype-phenotype relationship in the innate immune system may be altered by micronutrient supplementation. That question is the intended target of this proposal. It also explores different subpopulations that are more susceptible to certain diseases, as well as the overall population, and the possible uses of these traits. A more thorough examination and optimization of micronutrient supplementation's effectiveness in modulating the innate immune response and subsequent

inflammation is needed (Orgogozo et al., 2015). The development of equipment capable of routinely and reliably assessing the levels of potential biomarkers in tissues or blood may be needed to ascertain the connection between these variables and clinical outcomes. It is important to learn how vitamin D influence the occurrence of T2DM. Effective and valid research should be conducted with maintaining proper procedure. Moreover, maintaining proper diet, exercise, and lifestyle modifications can help in reducing risk and complications of T2DM (Badawi, 2010).

4.1 Limitations of The Study

1. Some articles were not accessible as they were paid articles.
2. Less data was found due to lack of research in this field.
3. Exact mechanisms were hard to find with relevant figures.

4.2 Future Research Plan

The effects of Vitamin D in type II diabetic patients and in controlling inflammation are noteworthy. More active research is required in this field. From the above findings, it is clear that vitamin d has prominent role in regulating both T2DM and inflammation. It is crucial to have biomarkers that are stable and can be obtained using non-invasive methods. Additionally, it is important that determining these biomarkers is affordable and easy. In

future, vitamin d can be a crucial element in the future to reduce the complications of T2DM and make good progress in treating T2DM.

During my literature review, I found a lot of data about clinical trials from various articles. These clinical trials indicate that Vitamin D supplementation is helpful to reduce some inflammatory biomarkers in T2DM patients. But the exact mechanism of actions of how vitamin D actually works on reducing inflammation was not clear. So my future research plan is to establish a verified mechanism of action of vitamin D in regulating inflammation during T2DM. For this, I will try to make collaborations with other researchers who are doing works in similar topic. After that, I want to collect blood sample from type II diabetic patients who is suffering from inflammation. I will measure the vitamin D level of those samples. After that, I will conduct some in vitro tests to see the effects of vitamin D in inflammatory biomarkers of type II diabetic patients. If the results will be positive, I will try to conduct some clinical trials to justify my findings.

References

1. Aguirre, V., Uchida, T., Yenush, L., Davis, R. J., & White, M. F. (2000). The c-Jun NH2-terminal Kinase Promotes Insulin Resistance during Association with Insulin Receptor Substrate-1 and Phosphorylation of Ser307. *Journal of Biological Chemistry*, *275*(12), 9047–9054. https://doi.org/10.1074/jbc.275.12.9047
2. Ahmed, L., Butler, A. E., Dargham, S. R., Latif, A., Robay, A., Chidiac, O., Jayyousi, A., Suwaidi, J. A., Crystal, R. G., Atkin, S. L., & Khalil, C. A. (2020). Association of vitamin D2 and D3 with type 2 diabetes complications. *BMC Endocrine Disorders*, *20*(1). https://doi.org/10.1186/s12902-020-00549-w
3. Alvarez, J. A., & Ashraf, A. P. (2010). Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. *International Journal of Endocrinology*, *2010*, 1–18. https://doi.org/10.1155/2010/351385
4. Anan, F., Takahashi, N., Shinohara, T., Nakagawa, M., Masaki, T., Katsuragi, I., Tanaka, K., Kakuma, T., Yonemochi, H., Eshima, N., Saikawa, T., & Yoshimatsu, H. (2006). Smoking is associated with insulin resistance and cardiovascular autonomic dysfunction in type 2 diabetic patients. *European Journal of Clinical Investigation*, *36*(7), 459–465. https://doi.org/10.1111/j.1365-2362.2006.01650.x
5. Artaza, J. N., & Norris, K. C. (2008). Vitamin D reduces the expression of collagen and key profibrotic factors by inducing an antifibrotic phenotype in mesenchymal multipotent cells. *Journal of Endocrinology*, *200*(2), 207–221. https://doi.org/10.1677/joe-08-0241
6. Badawi. (2010a). Type 2 diabetes mellitus and inflammation: Prospects for biomarkers of risk and nutritional intervention. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 173. https://doi.org/10.2147/dmsott.s9089

7. Bao, B., Ting, H., Hsu, J., & Lee, Y. (2008). Protective role of 1α, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. *International Journal of Cancer*, *122*(12), 2699–2706. https://doi.org/10.1002/ijc.23460

8. Björkman, M., Sorva, A., & Tilvis, R. S. (2009). C-reactive protein and fibrinogen of bedridden older patients in a six-month vitamin D supplementation trial. *The Journal of Nutrition Health & Aging*, *13*(5), 435–439. https://doi.org/10.1007/s12603-009-0080-3

9. Borazan, A., Üstün, H., Çefle, A., Sekitmez, N., & Yılmaz, A. (2003). Comparative efficacy of oral and intravenous calcitriol treatment in haemodialysis patients: Effects on serum biochemistry and cytokine levels. *Journal of International Medical Research*, *31*(6), 489–496. https://doi.org/10.1177/147323000303100604

10. Bucharles, S. G. E., Barberato, S. H., Stinghen, A. E. M., Gruber, B., Piekala, L., Dambiski, A. C., Custódio, M. R., & Pecoits-Filho, R. (2012). Impact of cholecalciferol treatment on biomarkers of inflammation and myocardial structure in hemodialysis patients without hyperparathyroidism. *Journal of Renal Nutrition*, *22*(2), 284–291. https://doi.org/10.1053/j.jrn.2011.07.001

11. Calton, E. K., Keane, K. N., Newsholme, P., & Soares, M. (2015). The impact of vitamin D levels on inflammatory status: A systematic review of immune cell studies. *PLOS ONE*, *10*(11), e0141770. https://doi.org/10.1371/journal.pone.0141770

12. Cathcart, J. (2016). *Interleukin-6 increases matrix metalloproteinase-14 (MMP-14) levels via down-regulation of p53 to drive cancer progression*. https://www.semanticscholar.org/paper/Interleukin-6-increases-matrix-metalloproteinase-14-Cathcart-Banach/8660d67aefa29537c27cf0403216d9b702e6742d

13. Chagas, C., Borges, M. C., Martini, L. A., & Rogero, M. M. (2012a). Focus on vitamin D, inflammation and Type 2 diabetes. *Nutrients*, *4*(1), 52–67. https://doi.org/10.3390/nu4010052

14. Chen, H., Liakou, C., Kamat, A. M., Pettaway, C. A., Ward, J. F., Tang, D. N., Sun, J., Jungbluth, A. A., Troncoso, P., Logothetis, C. J., & Sharma, P. (2009). Anti-CTLA-4 therapy results in higher CD4 + ICOS hi T cell frequency and IFN-γ levels in both nonmalignant and malignant prostate tissues. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(8), 2729–2734. https://doi.org/10.1073/pnas.0813175106

15. Cheng, D., Kong, H., & Li, Y. (2013). Prognostic value of interleukin-8 and MMP-9 in nasopharyngeal carcinoma. *European Archives of Oto-Rhino-Laryngology*, *271*(3), 503–509. https://doi.org/10.1007/s00405-013-2580-3

16. Chertov, O., Yang, D., Howard, O. M. Z., & Oppenheim, J. J. (2000). Leukocyte granule proteins mobilize innate host defenses and adaptive immune responses. *Immunological Reviews*, *177*(1), 68–78. https://doi.org/10.1034/j.1600-065x.2000.17702.x

17. Cirillo, P., Golino, P., Calabrò, P., Calı, G., Ragni, M., De Rosa, S., Cimmino, G., Pacileo, M., De Palma, R., Forte, L. A., Gargiulo, A., Corigliano, F. G., Angri, V., Spagnuolo, R., Nitsch, L., & Chiariello, M. (2005). C-reactive protein induces tissue factor expression and promotes smooth muscle and endothelial cell proliferation. *Cardiovascular Research*, *68*(1), 47–55. https://doi.org/10.1016/j.cardiores.2005.05.010

18. Cohen-Lahav, M. (2006). *Vitamin D decreases NFkappaB activity by increasing IkappaBalpha levels.* https://www.semanticscholar.org/paper/Vitamin-D-decreases-

NFkappaB-activity-by-increasing-Cohen-Lahav-Shany/ae64313977de5c86dd48c7746540ef20b05a7cd0

19. Cohen-Lahav, M., Shany, S., Tobvin, D., Chaimovitz, C., & Douvdevani, A. (2006). Vitamin D decreases NFκB activity by increasing IκBα levels. *Nephrology Dialysis Transplantation*, *21*(4), 889–897. https://doi.org/10.1093/ndt/gfi254

20. Coquerelle, C., Oldenhove, G., Acolty, V., Denoeud, J. N., Vansanten, G., Verdebout, J., Mellor, A. L., Bluestone, J. A., & Moser, M. (2009). Anti-CTLA-4 treatment induces IL-10-producing ICOS+ regulatory T cells displaying IDO-dependent anti-inflammatory properties in a mouse model of colitis. *Gut*, *58*(10), 1363–1373. https://doi.org/10.1136/gut.2008.162842

21. Dalwadi, H., Krysan, K., Heuzé-Vourc'h, N., Dohadwala, M., Elashoff, D., Sharma, S., Cacalano, N. A., Lichtenstein, A., & Dubinett, S. M. (2005). Cyclooxygenase-2-Dependent activation of signal transducer and activator of transcription 3 by interleukin-6 in Non–Small cell lung cancer. *Clinical Cancer Research*, *11*(21), 7674–7682. https://doi.org/10.1158/1078-0432.ccr-05-1205

22. DeFronzo, R. A. (2009). From the triumvirate to the ominous octet: A new paradigm for the treatment of Type 2 diabetes mellitus. *Diabetes*, *58*(4), 773–795. https://doi.org/10.2337/db09-9028

23. Del Prato, S. (2009). Role of glucotoxicity and lipotoxicity in the pathophysiology of Type 2 diabetes mellitus and emerging treatment strategies. *Diabetic Medicine*, *26*(12), 1185–1192. https://doi.org/10.1111/j.1464-5491.2009.02847.x

24. Dennis, K. L., Blatner, N. R., Gounari, F., & Khazaie, K. (2013). Current status of interleukin-10 and regulatory T-cells in cancer. *Current Opinion in Oncology*, *25*(6), 637–645. https://doi.org/10.1097/cco.0000000000000006

25. Ding, C., Wilding, J., & Chen, B. (2013). 1,25-dihydroxyvitamin D3 Protects against Macrophage-Induced Activation of NFκB and MAPK Signalling and Chemokine Release in Human Adipocytes. *1,25-dihydroxyvitamin D3 Protects Against Macrophage-induced Activation of NFκB and MAPK Signalling and Chemokine Release in Human Adipocytes.*, *8*(4), e61707. https://doi.org/10.1371/journal.pone.0061707

26. Elkassaby, S., Harrison, L. C., Mazzitelli, N., Wentworth, J. M., Colman, P. G., Spelman, T., & Fourlanos, S. (2014). A randomised controlled trial of high dose vitamin D in recent-onset type 2 diabetes. *Diabetes Research and Clinical Practice*, *106*(3), 576–582. https://doi.org/10.1016/j.diabres.2014.08.030

27. Fenercioğlu, A. K., Gönen, M. S., Uzun, H., Sipahioğlu, N. T., Can, G., Taş, E., Kara, Z., Özkaya, H. M., & Atukeren, P. (2023). The Association between Serum 25-Hydroxyvitamin D3 Levels and Pro-Inflammatory Markers in New-Onset Type 2 Diabetes Mellitus and Prediabetes. *Biomolecules*, *13*(12), 1778. https://doi.org/10.3390/biom13121778

28. Ferrero-Miliani, L., Nielsen, O. H., Andersen, P. S., & Girardin, S. E. (2006). Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1β generation. *Clinical and Experimental Immunology*, *147*(2), 227–235. https://doi.org/10.1111/j.1365-2249.2006.03261.x

29. Flamment, M., Hajduch, É., Ferré, P., & Foufelle, F. (2012). New insights into ER stress-induced insulin resistance. *Trends in Endocrinology and Metabolism*, *23*(8), 381–390. https://doi.org/10.1016/j.tem.2012.06.003

30. Fritsche, J., Mondal, K., Ehrnsperger, A., Andreesen, R., & Kreutz, M. (2003). Regulation of 25-hydroxyvitamin D3-1α-hydroxylase and production of 1α,25-

dihydroxyvitamin D3 by human dendritic cells. *Blood*, *102*(9), 3314–3316. https://doi.org/10.1182/blood-2002-11-3521

31. Fröhlich, M., Imhof, A., Berg, G., Hutchinson, W. L., Pepys, M. B., Boeing, H., Muche, R., Brenner, H., & Köenig, W. (2000). Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care*, *23*(12), 1835–1839. https://doi.org/10.2337/diacare.23.12.1835

32. Gadrey, J., Souberbielle, J., & Chazot, C. (2009). Monthly cholecalciferol administration in haemodialysis patients: a simple and efficient strategy for vitamin D supplementation. *Nephrology Dialysis Transplantation*, *24*(12), 3799–3805. https://doi.org/10.1093/ndt/gfp370

33. Gæde, P., Vedel, P., Larsen, N., Jensen, G. V., Parving, H. H., & Pedersen, O. (2003). Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. *The New England Journal of Medicine*, *348*(5), 383–393. https://doi.org/10.1056/nejmoa021778

34. Gæde, P., Vedel, P., Larsen, N., Jensen, G. V., Parving, H. H., & Pedersen, O. (2003). Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. *The New England Journal of Medicine*, *348*(5), 383–393. https://doi.org/10.1056/nejmoa021778

35. Galicia-García, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. S. (2020). Pathophysiology of Type 2 diabetes mellitus. *International Journal of Molecular Sciences*, *21*(17), 6275. https://doi.org/10.3390/ijms21176275

36. Grarup, N., Sandholt, C. H., Hansen, T., & Pedersen, O. (2014). Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants

and beyond. *Diabetologia*, *57*(8), 1528–1541. https://doi.org/10.1007/s00125-014-3270-4

37. Guillemant, J., & Guillemant, S. (1980). Early rise in cyclic GMP after 1,25-dihydroxycholecalciferol administration in the chick intestinal mucosa. *Biochemical and Biophysical Research Communications*, *93*(3), 906–911. https://doi.org/10.1016/0006-291x(80)91161-4

38. Hayashi, S. (1988). *Sex-related difference in vitamin D3 25-hydroxylase of rat liver microsomes.* https://www.semanticscholar.org/paper/Sex-related-difference-in-vitamin-D3-25-hydroxylase-Hayashi Usui/3b14a1dd0e1f6b1a314eb709a7943a6754f9e026

39. Hayashi, S. I., Usui, E., & Okuda, K. (1988). Sex-Related difference in vitamin D3 25-Hydroxylase of rat liver microsomes1. *The Journal of Biochemistry*, *103*(5), 863–866. https://doi.org/10.1093/oxfordjournals.jbchem.a122362

40. Heo, J. H., Shin, D. H., Jang, M. H., Lee, M. L., Kang, M. G., & Im, S. H. (2017). Highly flexible, high-performance perovskite solar cells with adhesion promoted AuCl3-doped graphene electrodes. *Journal of Materials Chemistry. A, Materials for Energy and Sustainability*, *5*(40), 21146–21152. https://doi.org/10.1039/c7ta06465a

41. Holick, M. F. (1981). The cutaneous photosynthesis of previtamin D3: a unique photoendocrine system. *Journal of Investigative Dermatology*, *77*(1), 51–58. https://doi.org/10.1111/1523-1747.ep12479237

42. Hotamışlıgil, G. S. (2006). Inflammation and metabolic disorders. *Nature*, *444*(7121), 860–867. https://doi.org/10.1038/nature05485

43. Hotamışlıgil, G. S., Arner, P., F, J., Atkinson, R. L., & Spiegelman, B. M. (1995). Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity

and insulin resistance. *Journal of Clinical Investigation*, *95*(5), 2409–2415. https://doi.org/10.1172/jci117936

44. Ihle, J. N., Witthuhn, B. A., Quelle, F. W., Yamamoto, K., & Silvennoinen, O. (1995). Signaling through the hematopoietic cytokine receptors. *Annual Review of Immunology*, *13*(1), 369–398. https://doi.org/10.1146/annurev.iy.13.040195.002101

45. Ilinskaya, A., & Dobrovolskaia, M. A. (2014). Immunosuppressive and anti-inflammatory properties of engineered nanomaterials. *British Journal of Pharmacology*, *171*(17), 3988–4000. https://doi.org/10.1111/bph.12722

46. İnanır, A., Özoran, K., Tutkak, H., & Mermerci, B. B. (2004). The Effects of Calcitriol Therapy on Serum Interleukin-1, Interleukin-6 and Tumour Necrosis Factor-α Concentrations in Post-menopausal Patients with Osteoporosis. *Journal of International Medical Research*, *32*(6), 570–582. https://doi.org/10.1177/147323000403200602

47. Jabbour, H. N., Sales, K. J., Catalano, R., & Norman, J. E. (2009). Inflammatory pathways in female reproductive health and disease. *Reproduction*, *138*(6), 903–919. https://doi.org/10.1530/rep-09-0247

48. *JNK: bridging the insulin signaling and inflammatory pathway*. (2005, October 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/16259218/

49. Knekt, P., Laaksonen, M. A., Mattila, C., Härkänen, T., Marniemi, J., Heliövaara, M., Rissanen, H., Montonen, J., & Reunanen, A. (2008). Serum vitamin D and subsequent occurrence of type 2 diabetes. *Epidemiology*, *19*(5), 666–671. https://doi.org/10.1097/ede.0b013e318176b8ad

50. Kristiansen, O. P., & Mandrup-Poulsen, T. (2005). Interleukin-6 and diabetes. *Diabetes*, *54*(suppl_2), S114–S124. https://doi.org/10.2337/diabetes.54.suppl_2.s114

51. Leung, P. S. (2016). The potential protective action of vitamin D in hepatic insulin resistance and pancreatic islet dysfunction in type 2 diabetes mellitus. *Nutrients*, *8*(3), 147. https://doi.org/10.3390/nu8030147

52. Lippitz, B. (2013). Cytokine patterns in patients with cancer: a systematic review. *The Lancet Oncology*, *14*(6), e218–e228. https://doi.org/10.1016/s1470-2045(12)70582-x

53. Liu, E., Meigs, J. B., Pittas, A. G., Economos, C. D., McKeown, N. M., Booth, S. L., & Jacques, P. F. (2010). Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study. *The American Journal of Clinical Nutrition*, *91*(6), 1627–1633. https://doi.org/10.3945/ajcn.2009.28441

54. Liu, P. T., Stenger, S., Li, H., Wenzel, L., Tan, B. H., Krutzik, S. R., Ochoa, M. T., Schauber, J., Wu, K., Meinken, C., Kamen, D. L., Wagner, M., Bals, R., Steinmeyer, A., Zügel, U., Gallo, R. L., Eisenberg, D., Hewison, M., Hollis, B. W., . . . Modlin, R. L. (2006). Toll-Like receptor triggering of a vitamin D-Mediated human antimicrobial response. *Science*, *311*(5768), 1770–1773. https://doi.org/10.1126/science.1123933

55. Liu, W., Zhang, L., Xu, H., Li, Y., Hu, C., Yang, J., & Sun, M. (2018). The Anti-Inflammatory effects of Vitamin D in tumorigenesis. *International Journal of Molecular Sciences*, *19*(9), 2736. https://doi.org/10.3390/ijms19092736

56. Lotta, L. A., Scott, R. A., Sharp, S. J., Burgess, S., Luan, J., Tillin, T., Schmidt, A. F., Imamura, F., Stewart, I. D., Perry, J. R. B., Marney, L. C., Koulman, A., Karoly, E. D., Forouhi, N. G., Sjögren, R. J. O., Näslund, E., Zierath, J. R., Krook, A., Savage, D. B., . . . Langenberg, C. (2016). Genetic predisposition to an impaired metabolism of the Branched-Chain amino acids and risk of Type 2 diabetes: a Mendelian randomisation analysis. *PLOS Medicine*, *13*(11), e1002179. https://doi.org/10.1371/journal.pmed.1002179

57. Mathieu, C., Gysemans, C., Giulietti, A., & Bouillon, R. (2005). Vitamin D and diabetes. *Diabetologia*, *48*(7), 1247–1257. https://doi.org/10.1007/s00125-005-1802-7

58. Matias, P., Jorge, C., Ferreira, C., Borges, M., Aires, I., Amaral, T., Gil, C., Cortez, J., & Ferreira, A. (2010). Cholecalciferol supplementation in hemodialysis patients. *Clinical Journal of the American Society of Nephrology*, *5*(5), 905–911. https://doi.org/10.2215/cjn.06510909

59. Matsumori, A. (2022). Novel biomarkers of inflammation for the management of diabetes: Immunoglobulin-Free light chains. *Biomedicines*, *10*(3), 666. https://doi.org/10.3390/biomedicines10030666

60. Mayeux, R. (2004). Biomarkers: Potential uses and limitations. *NeuroRx*, *1*(2), 182–188. https://doi.org/10.1602/neurorx.1.2.182

61. Medzhitov, R. (2010). Inflammation 2010: New Adventures of an Old Flame. *Cell*, *140*(6), 771–776. https://doi.org/10.1016/j.cell.2010.03.006

62. Menzel, A., Samouda, H., Dohet, F., Loap, S., Ellulu, M. S., & Bohn, T. (2021). Common and Novel markers for Measuring inflammation and oxidative stress ex vivo in Research and Clinical Practice—Which to use regarding disease outcomes? *Antioxidants*, *10*(3), 414. https://doi.org/10.3390/antiox10030414

63. Mitri, J., Muraru, M., & Pittas, A. G. (2011). Vitamin D and type 2 diabetes: a systematic review. *European Journal of Clinical Nutrition*, *65*(9), 1005–1015. https://doi.org/10.1038/ejcn.2011.118

64. Mitri, J., Muraru, M., & Pittas, A. G. (2011). Vitamin D and type 2 diabetes: a systematic review. *European Journal of Clinical Nutrition*, *65*(9), 1005–1015. https://doi.org/10.1038/ejcn.2011.118

65. Nair, R., & Maseeh, A. (2012). Vitamin D: The ―sunshine‖ vitamin. *PubMed*. https://doi.org/10.4103/0976-500x.9550

66. Nathan, C., & Ding, A. (2010). Nonresolving inflammation. *Cell*, *140*(6), 871–882. https://doi.org/10.1016/j.cell.2010.02.029

67. Nguyen, D. P., Li, J., & Tewari, A. (2014). Inflammation and prostate cancer: the role of interleukin 6 (IL-6). *BJU International*, *113*(6), 986–992. https://doi.org/10.1111/bju.12452

68. Nonn, L., Peng, L., Feldman, D., & Peehl, D. M. (2006). Inhibition of p38 by Vitamin D Reduces Interleukin-6 Production in Normal Prostate Cells via Mitogen-Activated Protein Kinase Phosphatase 5: Implications for Prostate Cancer Prevention by Vitamin D. *Cancer Research*, *66*(8), 4516–4524. https://doi.org/10.1158/0008-5472.can-05-3796

69. Orgogozo, V., Morizot, B., & Martin, A. (2015). The differential view of genotypeâ€—phenotype relationships. *Frontiers in Genetics*, *6*. https://doi.org/10.3389/fgene.2015.00179

70. Padhi, S., Nayak, A. K., & Behera, A. (2020). Type II diabetes mellitus: a review on recent drug based therapeutics. *Biomedicine & Pharmacotherapy*, *131*, 110708. https://doi.org/10.1016/j.biopha.2020.110708

71. Pittas, A. G., Dawson-Hughes, B., Li, T., Van Dam, R. M., Willett, W. C., Manson, J. E., & Hu, F. B. (2006). Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care*, *29*(3), 650–656. https://doi.org/10.2337/diacare.29.03.06.dc05-1961

72. Pittas, A. G., Harris, S. S., Stark, P. C., & Dawson-Hughes, B. (2007). The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care*, *30*(4), 980–986. https://doi.org/10.2337/dc06-1994

73. Pittas, A. G., Harris, S. S., Stark, P. C., & Dawson-Hughes, B. (2007). The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care*, *30*(4), 980–986. https://doi.org/10.2337/dc06-1994

74. Pittas, A. G., Jorde, R., Kawahara, T., & Dawson-Hughes, B. (2020). Vitamin D Supplementation for Prevention of Type 2 Diabetes Mellitus: To D or Not to D? *J Clin Endocrinol Metab*, *105*(12), 3721-3733. https://doi.org/10.1210/clinem/dgaa594

75. Pittas, A. G., Sun, Q., Manson, J. E., Dawson-Hughes, B., & Hu, F. B. (2010). Plasma 25-Hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. *Diabetes Care*, *33*(9), 2021–2023. https://doi.org/10.2337/dc10-0790

76. Prentki, M., & Nolan, C. (2006). Islet cell failure in type 2 diabetes. *Journal of Clinical Investigation*, *116*(7), 1802–1812. https://doi.org/10.1172/jci2910

77. Pype, J. L., Dupont, L., Menten, P., Van Coillie, E., Opdenakker, G., Van Damme, J., Chung, K. F., Demedts, M., & Verleden, G. M. (1999). Expression of monocyte chemotactic protein (MCP)-1, MCP-2, and MCP-3 by human airway Smooth-Muscle cells. *American Journal of Respiratory Cell and Molecular Biology*, *21*(4), 528–536. https://doi.org/10.1165/ajrcmb.21.4.3660

78. Roglić, G. (2016). WHO Global report on diabetes: A summary. *International Journal of Noncommunicable Diseases*, *1*(1), 3. https://doi.org/10.4103/2468-8827.184853

79. Sannino, G. (2016). *Role of BCL9L in transforming growth factor-β (TGF-β)-induced epithelial-to-mesenchymal-transition (EMT) and metastasis of pancreatic cancer*. https://www.semanticscholar.org/paper/Role-of-BCL9L-in-transforming-growth-factor-%CE%B2-(EMT)-Sannino-Armbruster/918d6793bb8afe1896c64984735c478dbe0de296

80. Sannino, G. (2016). *Role of BCL9L in transforming growth factor-β (TGF-β)-induced epithelial-to-mesenchymal-transition (EMT) and metastasis of pancreatic cancer*. https://www.semanticscholar.org/paper/Role-of-BCL9L-in-transforming-growth-factor-%CE%B2-(EMT)-Sannino-Armbruster/918d6793bb8afe1896c64984735c478dbe0de296

81. Schleithoff, S. S., Zittermann, A., Tenderich, G., Berthold, H. K., Stehle, P., & Koerfer, R. (2006b). Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *The American Journal of Clinical Nutrition*, *83*(4), 754–759. https://doi.org/10.1093/ajcn/83.4.754

82. Schleithoff, S. S., Zittermann, A., Tenderich, G., Berthold, H. K., Stehle, P., & Koerfer, R. (2006). Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *The American Journal of Clinical Nutrition*, *83*(4), 754–759. https://doi.org/10.1093/ajcn/83.4.754

83. Schwartz, S., Epstein, S., Corkey, B. E., Grant, S. F., Gavin, J. R., & Aguilar, R. (2016). The time is right for a new classification system for diabetes: Rationale and implications of the B-Cell–Centric Classification Schema. *Diabetes Care*, *39*(2), 179–186. https://doi.org/10.2337/dc15-1585

84. Shi, H., Kokoeva, M. V., Inouye, K., Tzameli, I., Yin, H., & Flier, J. S. (2006). TLR4 links innate immunity and fatty acid–induced insulin resistance. *Journal of Clinical Investigation*, *116*(11), 3015–3025. https://doi.org/10.1172/jci28898

85. Sidarala, V., & Kowluru, A. (2017). The Regulatory Roles of Mitogen-Activated Protein Kinase (MAPK) Pathways in Health and Diabetes: Lessons Learned from the Pancreatic β-Cell. *The Regulatory Roles of Mitogen-Activated Protein Kinase*

(MAPK) Pathways in Health and Diabetes: Lessons Learned From the Pancreatic B-cell., *10*(2), 76–84. https://doi.org/10.2174/1872214810666161020154905

86. Singh, J., Simões, B. M., Howell, S. J., Farnie, G., & Clarke, R. B. (2013). Recent advances reveal IL-8 signaling as a potential key to targeting breast cancer stem cells. *Breast Cancer Research*, *15*(4). https://doi.org/10.1186/bcr3436

87. Stümvoll, M., Goldstein, B. J., & Van Haeften, T. W. (2005). Type 2 diabetes: principles of pathogenesis and therapy. *The Lancet*, *365*(9467), 1333–1346. https://doi.org/10.1016/s0140-6736(05)61032-x

88. Takeda, K., & Akira, S. (2004). TLR signaling pathways. *Seminars in Immunology*, *16*(1), 3–9. https://doi.org/10.1016/j.smim.2003.10.003

89. Takeuchi, O., & Akira, S. (2010). Pattern recognition receptors and inflammation. *Cell*, *140*(6), 805–820. https://doi.org/10.1016/j.cell.2010.01.022

90. Tse, A. K., Zhu, G., Wan, C., Shen, X., Yu, Z., & Fong, W. (2010). 1α,25-Dihydroxyvitamin D3 inhibits transcriptional potential of nuclear factor kappa B in breast cancer cells. *Molecular Immunology*, *47*(9), 1728–1738. https://doi.org/10.1016/j.molimm.2010.03.004

91. Urakawa, I., Yamazaki, Y., Shimada, T., Iijima, K., Higuchi, H., Okawa, K., Fujita, T., Fukumoto, S., & Yamashita, T. (2006). Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*, *444*(7120), 770–774. https://doi.org/10.1038/nature05315

92. Van Etten, E., & Mathieu, C. (2005). Immunoregulation by 1,25-dihydroxyvitamin D3: Basic concepts. *The Journal of Steroid Biochemistry and Molecular Biology*, *97*(1–2), 93–101. https://doi.org/10.1016/j.jsbmb.2005.06.002

93. Van Etten, E., & Mathieu, C. (2005). Immunoregulation by 1,25-dihydroxyvitamin D3: Basic concepts. *The Journal of Steroid Biochemistry and Molecular Biology*, *97*(1–2), 93–101. https://doi.org/10.1016/j.jsbmb.2005.06.002

94. Vassalli, P. (1992). The Pathophysiology of tumor necrosis Factors. *Annual Review of Immunology*, *10*(1), 411–452. https://doi.org/10.1146/annurev.iy.10.040192.002211

95. Von Hurst, P., Stonehouse, W., & Coad, J. (2009). Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial. *British Journal of Nutrition*, *103*(4), 549–555. https://doi.org/10.1017/s0007114509992017

96. Wang, L., Zhang, L., Hou, Q., Zhu, X., Chen, Z., & Liu, Z. (2018). Triptolide attenuates proteinuria and podocyte apoptosis via inhibition of NF-κB/GADD45B. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-29203-1

97. Wannamethee, S. G., Sattar, N., Rumley, A., Whincup, P. H., Lennon, L., & Lowe, G. D. O. (2008). Tissue Plasminogen Activator, von Willebrand Factor, and Risk of Type 2 Diabetes in Older Men. *Diabetes Care*, *31*(5), 995–1000. https://doi.org/10.2337/dc07-156

98. White, M. F. (2014). IRS2 integrates insulin/IGF1 signalling with metabolism, neurodegeneration and longevity. *Diabetes, Obesity and Metabolism*, *16*(S1), 4–15. https://doi.org/10.1111/dom.12347

99. Wilkinson, R. J., & Lange, C. (2009). Vitamin D and tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, *179*(9), 740–742. https://doi.org/10.1164/rccm.200902-0186ed

100. Xia, Y., Shen, S., & Verma, I. M. (2014). NF-KB, an active player in human cancers. *Cancer Immunology Research*, *2*(9), 823–830. https://doi.org/10.1158/2326-6066.cir-14-0112

101. Yuan, M., Konstantopoulos, N., Lee, J., Hansen, L., Li, Z., Karin, M., & Shoelson, S. E. (2001). Reversal of Obesity- and Diet-Induced Insulin Resistance with Salicylates or Targeted Disruption of Ikkβ. *Science*, *293*(5535), 1673–1677. https://doi.org/10.1126/science.1061620

102. Zeng, B., Lu, Y., Hajifathalian, K., Bentham, J., Di Cesare, M., Danaei, G., Bixby, H., Cowan, M., Ali, M., Taddei, C., Lo, W., Reis-Santos, B., Stevens, G., Riley, L., Miranda, J. J., Bjerregaard, P., Rivera, J. L. G., Fouad, H., Ma, G., . . . Cisneros, J. Z. (2016). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. *The Lancet*, *387*(10027), 1513–1530. https://doi.org/10.1016/s0140-6736(16)00618-8

103. Zittermann, A., Frisch, S., Berthold, H. K., Götting, C., Kühn, J., Kleesiek, K., Stehle, P., Koertke, H., & Köerfer, R. (2009). Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *The American Journal of Clinical Nutrition*, *89*(5), 1321–1327. https://doi.org/10.3945/ajcn.2008.27004

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