Review

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The Antioxidant Effect of Vitamin D and Its Implications on Diabetes Syndrome

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Abstract

The incidence of insulin resistance and its complications is rising across societies worldwide, making its treatment a significant economic challenge. The disease is multifactorial, and its pathophysiology varies accordingly. Genetic factors, aging, and coexisting diseases are major contributors to its development. Among the coexisting conditions are autoimmune diseases and other conditions requiring treatment with therapeutic agents, some of which can induce insulin resistance. Research indicates that the free radical theory plays a significant role in initiating this complex cycle and in shaping the full clinical picture of diabetes syndrome. In this work, we discuss the pathophysiology of insulin resistance, the role of free radicals in its etiology, and drug treatments for diseases that may contribute to insulin resistance. We also explore the antioxidant effects of vitamin D and oral hypoglycemic agents, as well as their notable adverse effects, including cobalamin (vitamin B12) deficiency. A total of 147 scientific studies, including comprehensive meta-analyses, have been selected to address these questions and have been analyzed and discussed objectively to minimize scientific bias and confusion. This narrative work will help doctors and primary health caregivers envision the dimensions of diabetes syndrome from multiple perspectives and update their knowledge about the significance of vitamin D as an effective tool to combat insulin resistance.

Keywords: vitamin D; insulin resistance; free radicals; reactive oxygen species; mitochondrial dysfunction; β-cells; aging; GLUTs; SGLTs

Classification: Endocrinology-Biochemistry

Prelude, definition, and types:

Diabetes mellitus is a chronic metabolic disease that occurs when the pancreas does not produce enough insulin, due to an autoimmune process that attacks the β-cells of the pancreas (type 1 diabetes), or when the body cannot effectively use the insulin produced by the pancreas (type 2 diabetes). Sometimes, both types can coexist in the same individual, causing a condition known as double or hybrid diabetes [1], as is the case with latent autoimmune diabetes in adults (LADA). Although being largely a preventable disease, diabetes is increasing in incidence in all societies across the world without exception, according to the World Health Organization [2]. The disease is creating an economic burden on the budgets of societies, especially those with low annual incomes.

Type 1 diabetes is an autoimmune disease:

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Type 1 diabetes is an autoimmune condition; dozens of references in the medical literature back this assertion. The immune system erroneously attacks the β-cells of the pancreas, leading to a severe or total lack of insulin, the main hormone that regulates glycemic homeostasis in cooperation with glucagon. The key evidence for the disease's autoimmune etiology is:

1) Presence of specific biomarkers, such as GAD (Glutamic Acid Decarboxylase) and insulin autoantibodies, in the blood of these individuals, years before the onset of hyperglycemia symptoms [3,4].
2) Infiltration of pancreatic islets with immune cells, such as T and B lymphocytes, these white blood cells damage the clustered endocrine cells of the islets [5].
3) The other evidence is that the ailment coexists with other autoimmune conditions in the same individuals, such as Hashimoto's thyroiditis and celiac disease [6].

Latent autoimmune diabetes in adults (LADA):

It is a slower-progressing type of type 1 diabetes that occurs in adults. The condition usually shows a clinical picture characteristic of both types 1 and 2 diabetes. An autoimmune process causes it, but the difference is that the symptoms develop gradually, similar to those of type 2 diabetes, which makes diagnosis challenging initially. The key test is detecting a specific autoantibody, known as the GAD antibody, which confirms the autoimmune nature of the disease.

The autoimmune origin of diabetes may also encompass type 2 diabetes, as emerging research suggests this possibility [7].

Type 2 diabetes DM2:

Type 2 diabetes is a metabolic disorder. Known factors that damage β-cells, impair their function, and harm mitochondria include hyperglycemia, lipotoxicity, and oxidative stress. This dysfunction results in impaired insulin function and further mitochondrial damage, which worsens β-cell dysfunction by releasing excess reactive oxygen species (ROS). These events create a feedback loop that accelerates the progression of diabetes. β-cell dysfunction leads to insulin resistance, where tissues fail to respond properly to insulin, causing elevated blood glucose levels, in response β-cells overproduce insulin. When persistent high blood glucose combines with lipotoxic stress, these two factors jointly damage the β-cells, which, over time, lose their ability to produce normal amounts of insulin. The final stage of this cycle is β-cell apoptosis, which further impairs insulin production.

Understanding this classification is essential for grasping the disease's pathophysiology and for designing an appropriate therapy plan for each type.

Pathophysiology:

Insulin is the primary anabolic hormone in the human body [8]. It is a peptide hormone made up of 51 amino acids, with a molar mass of 5808 g/mol. The polypeptide forms two chains (α and β). It remains a stable biomolecule because disulfide covalent bonds cross-link cysteine residues within each chain and between the α and β chains. The human insulin gene (ins) is located on the short arm of chromosome 11 (band 11p15.5). The gene for the insulin receptor (INSR) is found on chromosome 19. The interaction between insulin and its receptor is crucial for glucose metabolism.

Mechanism of insulin release from islets of Langerhans and its effects on GLUTs:

Postprandial increases in glucose levels stimulate the entry of glucose molecules into the clustered β-pancreatic cells of the islets. Inside these cells, glucose is metabolized, raising adenosine triphosphate (ATP) levels. An increase in ATP causes the closure of potassium channels, leading to membrane depolarization. This depolarization opens voltage-gated calcium channels, allowing calcium ions (Ca^{++}) to enter the cells. Ca^{++} acts as a signaling molecule that signals insulin-loaded granules to move toward the cell membrane. Through exocytosis, the granules fuse with the membrane, releasing insulin into the bloodstream. The insulin then targets cells such as skeletal

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myocytes, adipocytes, and hepatocytes to promote glucose uptake from the circulation for energy storage. Insulin is released in a synchronized pattern from the β-cells because these cells are electrically coupled through gap junctions. The releasing process occurs in an oscillating manner with a period of 3-6 minutes [9]. It is worth noting that insulin release is proportional to the amount of glucose detected; in other words, it creates a graded response to maintain smooth and steady glycaemia, but postprandially, the hormone is released in bouts. That is, it oscillates up and down. Its amount is measured either in international units or as a molar concentration. Postprandial insulin levels typically range between 8-11 μIU/mL (57-79 pmol/L) [10]. There is a feedback loop in insulin release; when glucose levels decrease in circulation, the stimulus for insulin release diminishes [11].

GLUTs of pancreatic endocrine tissue:

In humans, the endocrine pancreatic tissue expresses mainly two subtypes of glucose transporters: these are GLUT1 and GLUT3. β-cells, the insulin-secreting cells, express these two transporter subtypes and have a high affinity for glucose molecules. β-cells, by virtue of these transporters, maintain a steady lower glucose threshold that stimulates insulin secretion. Different species express different subtypes of GLUTS, as is the case with rodents, which rely on the GLUT2 subtype, which is also a low-affinity transporter [12–14].

Alpha pancreatic cells also mainly express the same subtypes of high-affinity GLUTs; the reason for this is believed to be that these GLUT subtypes are involved in glucose-dependent regulation of glucagon release to the blood. These two hormones (insulin/glucagon) work hand in hand to keep the glucose homeostasis in balance.

Other transporter subtypes are also expressed, yet in lower levels in different cells of Langerhans clusters, these are: GLUT2, GLUT6, GLUT8, and the SGLT family subtypes [15,16].

GLUT4, the insulin-responsive transporter, is found mainly in adipose and muscle tissues, but it has low levels in pancreatic islets [17].

Mitochondrial Dysfunction in DM:

Mitochondria, the cell's powerhouse, are negatively impacted by oxidative stress caused by hyperglycemia and lipotoxicity. Free radicals, primarily in the form of reactive oxygen species (ROS), damage mitochondrial membranes and their associated proteins. The structures of these molecules are shown in **Figure 1**. This damage severely hampers ATP biosynthesis. ATP is the main energy currency in biological systems, including pancreatic β-cells. It is crucial for insulin secretion in response to glucose, the body's primary energy source. These damaging processes cause mitochondria to produce even more ROS, which further harm β-cells, thus speeding up the development of diabetes. There is a dynamic balance between mitochondrial fusion and fission, and damaged β-cells are unable to maintain this balance [18]. Consequently, impaired insulin function results from β-cell failure and mitochondrial dysfunction. All these distressing effects lead to hyperglycemia, which accelerates the progression of type 2 diabetes [19–21].

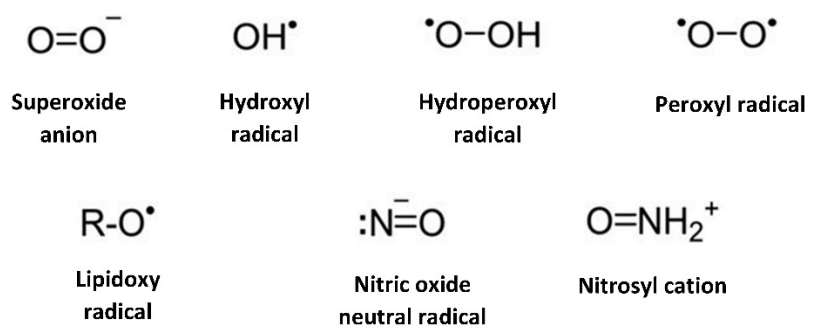

Figure 1. Some important free radicals that can affect biological systems and their chemical structures.

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Aging affects mitochondrial function:

Aging impairs mitochondrial function, leading to a decline caused by accumulated damage over time [22,23]. This results in a decrease in the number and size of mitochondria in human cells, including β-cells of the endocrine pancreas and the liver. Consequently, energy production (ATP biosynthesis) declines, while the release of reactive oxygen species (ROS) [24,25], mitochondrial DNA mutations, and failures in quality control increase [26,27]. Mutations in mitochondrial DNA hinder the production of essential proteins of the electron transport chain (ETC), which are vital for oxidative phosphorylation in the inner mitochondrial membrane. These proteins include complexes I, III, IV, and ATP synthase (complex V), among others [28–30]. Aging also causes an imbalance in mitochondrial dynamics, especially disrupting the fusion and fission processes necessary for mitochondrial and cellular health [31,32].

In conclusion, aging affects mitochondria in the following ways:

1) Continuous and cumulative damage of cellular components and organelles, such as mitochondria and their fragile mtDNA, of β-cells of the pancreas.
2) The quality control machinery becomes less effective in removing the damaged mitochondria or repairing them.
3) Aging is associated with increased inflammation and stress; these two parameters further aggravate mitochondrial dysfunction, which can trigger a more severe inflammatory response.

Diabetes and aging:

Although type 2 diabetes can occur at any age, it is considered an age-related disease because it often develops in middle-aged and older adults [21,22]. However, long-term hyperglycemia caused by diabetes not only contributes to the body's aging process through insulin resistance and oxidative stress, but also causes its acceleration. As people get older, their metabolic pathways decline, making them more susceptible to developing insulin resistance, a key feature of type 2 diabetes. When chronic hyperglycemia and insulin resistance co-occur, they generate oxidative stress, which can lead to shorter telomeres, cellular damage, and other signs of accelerated aging [23–25]. Here, we refer to biological aging rather than chronological age [26]. In other words, individuals with diabetes tend to appear older than their healthy peers of the same age.

All that has been mentioned above impairs the efficacy of oxidative phosphorylation, which is already decreased due to aging, making matters worse.

SGLT2 and SGLT1 receptors and aging:

These are sodium-glucose cotransporters 2 and 1. SGLT2 primarily reabsorbs most of the glucose filtered by the kidneys back into the bloodstream. It is located on the brush borders of the proximal convoluted tubules in the nephrons, especially in the S1 and S2 segments. Each day, it reabsorbs nearly 90-97% of the glucose filtered by the glomerulus. In healthy individuals, the remaining glucose is reabsorbed by SGLT1 in the S3 segment of the proximal tubules [33].

Aging increases the expression of both SGLT2 and SGLT1 in various tissues of the body, especially in the renal and cardiovascular systems [34–36]. Elevated levels of these transporters lead to metabolic dysfunction, inflammation, and cellular senescence throughout the body, including in the β-cells of the endocrine pancreas. The upregulation of SGLT2 and SGLT1 causes hyperglycemia and insulin resistance [37,38]. Additionally, aging contributes to increased oxidative stress and promotes a state of low-grade inflammation, which sometimes appears as inflammaging in medical literature [39,40].

All the factors mentioned up to now, raise the normal renal glucose threshold in older people. This provides a plausible explanation for why older individuals do not show classic symptoms of diabetes, such as polyuria and glycosuria [41]. This is the primary reason for diagnosing diabetes can be difficult and depends mostly on clinical signs of the disease.

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Free radicals and aging:

Free radicals such as superoxide anion (O_2^-), hydroxyl radical (•OH), nitric oxide (•NO), and peroxynitrite ($O_2N_2^-$) are released excessively as aging progresses [42,43]. This occurs because of an imbalance between their production and elimination. ROS generated from physiological processes like cellular respiration increase, while the body's defenses against oxidants decline. As a result, damage to cellular components—such as proteins, DNA, and organelles, including mitochondria—is unavoidable and accelerates the aging process. Neutralizing these harmful metabolites can be achieved by consuming fresh foods high in fiber and antioxidants, such as fruits, vegetables, and dairy products [44]. The mechanism behind the imbalance between the production and neutralization of these damaging molecules in human cells, including pancreatic endocrine cells, is as follows:

1) Damage to mitochondrial DNA by free radicals creates a vicious cycle because it leads to the production of these damaging species [45,46].
2) As we age, the effectiveness of antioxidant enzymes decreases in neutralizing free radicals; moreover, the damage cannot be repaired [47,48].
3) Damage will be more profound as the age advances in such a way that lipids, proteins, and DNA are damaged, which altogether contribute to the decline of all tissue viability seen parallel with aging [49].

Parameters of hematological changes in diabetes:

One of the main pieces of evidence supporting an inflammatory cause of diabetes is the changes in the hematological profile, such as eosinophilia and thrombocytosis [50,51]. Eosinophils are pro-inflammatory white blood cells; when they proliferate and accumulate in human adipose tissue, they disrupt major metabolic pathways throughout the body. As a result, they promote inflammation and insulin resistance [52–54].

Thrombocyte count is another hematological parameter linked to insulin resistance (IR), and it shows a positive association with IR and inflammation. It is a helpful tool to identify IR in adolescents [55,56]. The activation of platelets in obese women is associated with oxidative stress and inflammation, which can be reversed through a scientifically designed weight loss program [57–59]. Hyperglycemia promotes the glycation of platelet proteins and increases platelet activity [60–62]. In other words, a deficiency of insulin, whether relative or absolute, will raise thrombocyte activity. This suggests that diabetes syndrome is closely related to oxidative stress and inflammation. Microangiopathy is one of the characteristic complications of diabetes, which promotes platelet activation via decreased nitric oxide (NO) release from the epithelium of these narrow vessels [63,64].

Oxidative drugs and free radicals release on endocrine pancreatic cells:

An oxidative agent either releases free radicals (ROS) and causes oxidative stress or is inherently oxidative itself. Such agents are used therapeutically to induce oxidation, like hydrogen peroxide (H_2O_2), which acts as a disinfectant to eliminate anaerobic pathogenic microorganisms. Certain drugs with oxidative characteristics can cause insulin resistance, but not all. This is because drug-induced insulin resistance is multifactorial, depending on the drug's pharmacodynamics, concentration, and other parameters. The key issue here, indeed is the high susceptibility of β-pancreatic cells to oxidative damage; however, one thing is certain: not all drugs interact with these cells to the extent that causes cellular dysfunction and insulin resistance. Yet, other agents can protect β-cells from free radicals, such as certain oral hypoglycemic agents, see **Table 1**.

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Table 1. Pharmacodynamic effects of some oral hypoglycemic agents on the human body.

Class	Agent	Mechanism of hypoglycemia	Antioxidant Properties	Decreases B12 levels
Biguanides	Metformin	Increases the body's sensitivity to insulin. Reduces glucose production in the liver. Increases glucose uptake by the body's cells.	✓	✓
	Phenformin	Reduces glucose production by the liver. Increases glucose uptake and utilization in peripheral tissues like skeletal muscle.	✓	✓
Thiazolidinedione	Pioglitazone	Increases the body's sensitivity to insulin. It decreases gluconeogenesis and the release of glucose into the bloodstream.	✓	✓ Only when prescribed in combination with metformin
Sulfonylurea	Glimepiride	Stimulates the pancreas to release more insulin regardless of current blood glucose levels.	✓	✓ Only when prescribed in combination with metformin
SGLT2 inhibitor	Empagliflozin	Removes glucose from the blood through the urine, independent of insulin action.	✓	✓ Only when prescribed in combination with metformin
DPP-4 inhibitor	***Linagliptin**	It helps the body produce more insulin when blood sugar levels are elevated.	✓	✓ Only when prescribed in combination with metformin
Glimins	Imeglimin	Improves glucose-dependent insulin secretion by the pancreas. Decreases gluconeogenesis in the liver. Increases glucose uptake by the muscles.	✓	✓

This table illustrates how these oral hypoglycemic agents manage blood sugar levels, their antioxidant effects, and their potential to cause drug-induced vitamin B12 deficiency. ***Linagliptin** has a pleiotropic effect in preserving vitamin B12 levels and only causes deficiency when used in combination with a biguanide agent. .

The key points that determine this perspective are:

A) β-cells of the pancreatic endocrine tissue are vulnerable to oxidative stress because they have a low capacity to express certain antioxidant enzymes such as glutathione peroxidase, catalase, and peroxiredoxins [65].

B) The physiological context of each patient is crucial, including factors like obesity, hyperglycemia, and various inflammatory conditions. These can influence how a specific drug affects the endocrine pancreas and insulin sensitivity [66–68].

C) Drug-specific mechanisms: the pharmacodynamics of a drug determine how it injures the β-cells, as explained below:

1. Some agents directly damage the pancreatic tissue by releasing free radicals and depleting the antioxidant pool of β-cells, such as valproic acid (an antiepileptic) [69].
2. Other drugs indirectly damage β-cells through various mechanisms, such as affecting insulin signaling pathways in tissues like skeletal muscles, liver, and adipose tissue [70].
3. Another mechanism involves inducing subtle inflammation, as seen with cardioselective beta-blockers such as atenolol, bisoprolol, and metoprolol. These agents increase insulin resistance through mechanisms unrelated to direct free radical damage to the endocrine pancreas [70].

Some drugs, interestingly, have antioxidant properties that enable them to neutralize free radicals, which can damage β-cells, such as gliclazide, a sulfonylurea agent; other oral hypoglycemic drugs also share this ability, as shown in **Table 1**.

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Diabetes medications as antioxidants:

Understanding this pathophysiology of insulin resistance and the corner role of ROS in its etiology has paved the way for designing many agents that can inhibit these transporter subtypes (SGLT2/SGLT1). Examples of such agents include: sotagliflozin, empagliflozin, dapagliflozin, canagliflozin, and others. These agents also, in a way, exhibit antiaging effects, namely, they help improve mitochondrial function, reduce inflammation, and eliminate senescent cells [71,72].

Some oral hypoglycemic drugs used for type 2 diabetes have been found to possess antioxidant properties. The most well-known in this group are glimepiride (a sulfonylurea) and certain thiazolidinediones, such as pioglitazone. These drugs demonstrate anti-inflammatory and antioxidant effects through different mechanisms. Typically, they work by inhibiting inflammatory mediators like cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, and thus indirectly neutralizing free radicals [73–75]. Building on these beneficial qualities, namely hypoglycemic and anti-inflammatory effects, modern medications such as imeglimin (a glimin compound) were developed to incorporate these properties into diabetes management [76].

The benefit of oral hypoglycemic agents lies in their dual action: they lower blood glucose through different mechanisms, which is their main purpose of use; additionally, they neutralize free radicals that can damage pancreatic β-cells. The antioxidant properties of these hypoglycemic agents truly enhance their effectiveness in diabetic patients with coexisting atherosclerosis, as these two conditions are linked to oxidative stress [63,72].

Impact of the recently developed oral hypoglycemic agent imeglimin:

Imeglimin is a newly developed OHA to treat type 2 diabetes. It is an aminotriazine compound, belonging to a class of hypoglycemic agents called glimins. It was developed through a collaboration between the French pharma Poxel and the Japanese Sumitomo.

Imeglimin inhibits hepatic gluconeogenesis while increasing muscle glucose uptake and restoring normal insulin secretion and sensitivity. It achieves these effects by blocking mitochondrial oxidative phosphorylation [77]. The agent is combined with hydrochloride (HCl) to improve stability, absorption, and convenience for oral use; it also enhances mitochondrial function [78]. These properties are also shared with metformin, which is similarly formulated with HCl to achieve the same goals and to make the agent highly water-soluble. Imeglimin has significant efficacy in lowering HbA1c, with or without metformin [79–81]. The disadvantage of this agent is similar to that of metformin; it can also cause vitamin B12 deficiency (especially when combined with metformin) [82], see **Table 1**. They share a significant structural similarity but they are not identical, as metformin is an aliphatic biguanide while imeglimin is a cyclic 1,3,5-triazine glimins, (see **Figure 2**).

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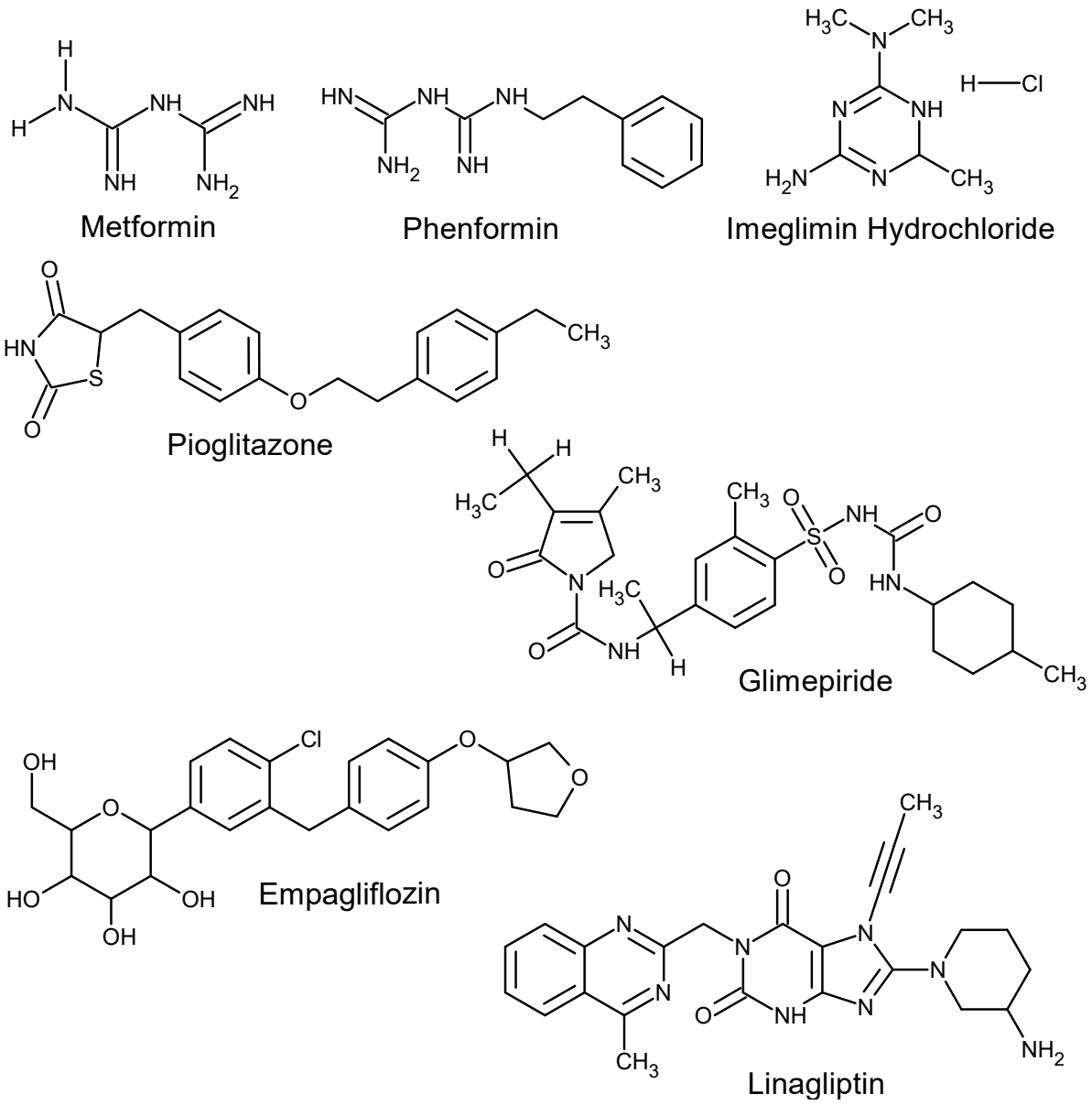

Figure 2. Chemical structures of some of the oral hypoglycemic agents discussed in this work.

Impact of vitamin D in the treatment strategy of diabetes syndrome:

Vitamin D is a fat-soluble micronutrient essential for bone mineralization. The daily requirement for an adult is (200 – 600) International Units, equivalent to 5-15 μg. The deficiency of this micronutrient is a global problem. It affects almost 1 billion people worldwide. The highest prevalence is among older adults, obese individuals, and nursing home and hospitalized home patients [83,84].

It has two main isomers (vitamers), D3 and D2. D3 (cholecalciferol) is synthesized in the human body when ultraviolet rays catalyze the conversion of 7-dehydrocholesterol in the skin. The D2 isomer, ergocalciferol, is obtained through dietary sources such as fish, cod liver oil, and certain types of mushrooms. These isomers share identical metabolic and physiological functions. To perform their hormonal roles, they are hydroxylated twice in the human body by two different hydroxylases in the liver and kidney, successively [85,86]. The active hormonal form of these vitamers is known as calcitriol (1,25-dihydroxycholecalciferol, abbreviated as 1,25-DHCC). Although these two isomers are distinct metabolites and not interchangeable, both are activated through the same mechanisms to form calcitriol. Their chemical structures are shown in **Figure 3**.

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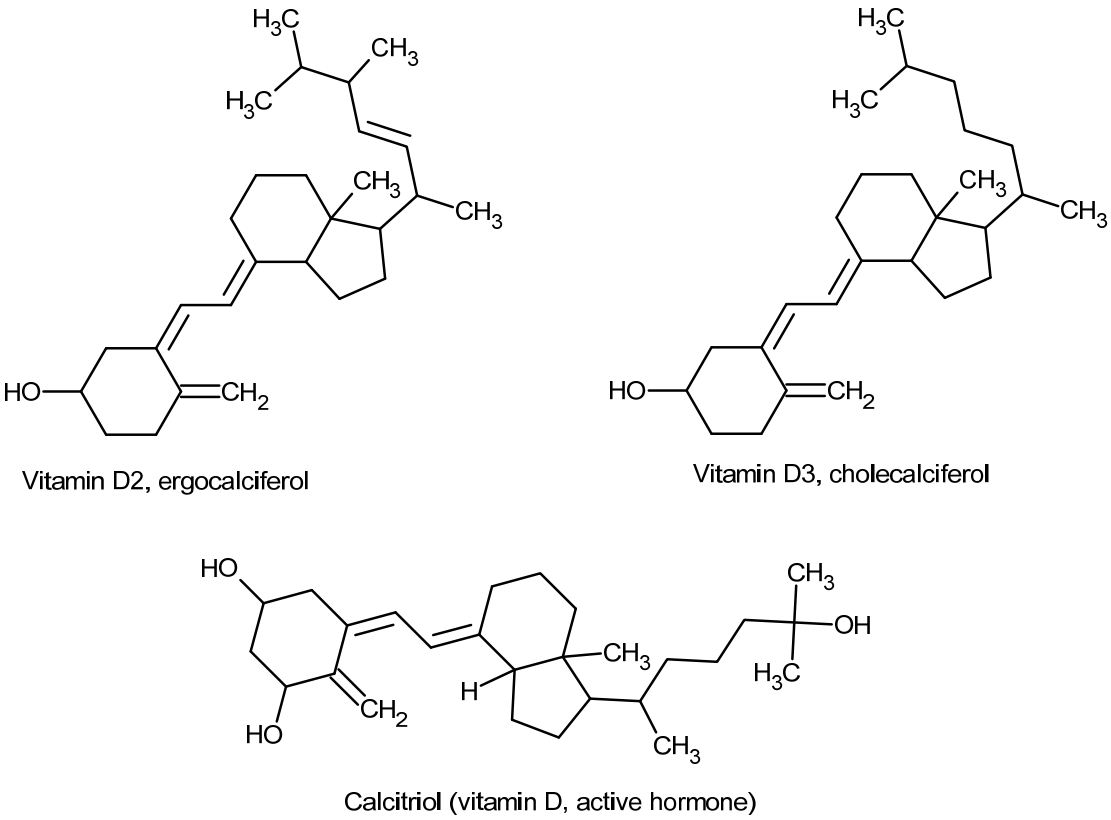

Figure 3. Vitamin D and its isomers.

There is controversy over the antioxidant action of vitamin D and its impact on diabetes. The first evidence of vitamin D's antioxidant activity was reported in 1993 [87]. There exists a strong association between an increased risk of infections and vitamin D deficiency; moreover, a poor prognosis is observed in patients with infections who also have coexisting vitamin D deficiency [88]. Because insulin resistance is an aging disease, attributed to increased production of harmful free radicals as age advances. Neutralizing these devastating metabolites is pivotal to keeping the body's metabolic harmony going. The significance of antioxidants such as vitamin D is revealed as obvious in this context to keep the free radical/antioxidant balance going on continuously [89].

Discussion:

Why vitamin D and no other antioxidants?

One important element of drug therapy for diabetes, especially type 2, is vitamin D supplementation. There are many reasons and arguments about this issue. Is this beneficial therapeutic effect attributed to the antioxidant characteristics of this micronutrient or something else? If this is so, why not other vitamins and micronutrients that have absolute and much more potent antioxidant activities, such as vitamins **A**, **E**, and **C.**

Vitamin **C** (L-ascorbic acid), the universal antioxidant in the human body, is a water-soluble essential micronutrient; it operates in a hydrophilic milieu, such as serum, cytosol, and interstitial fluids. It raises glutathione levels, which in turn increase the effectiveness of the antioxidant action of vitamin D [90–92]. It synergistically acts with vitamin D to support the immune system and thus indirectly improves insulin resistance. It exerts these effects especially (when administered in lower doses) by activating vitamin D [93]. As regards vitamin **A**, the action is context-dependent [94]. That is, they can either function synergistically or compete with each other for the same cellular process [95,96]. The plausible reason for this phenomenon is that both vitamins use the **retinoid X receptor** to exert their functions, creating a sort of competition where an excess of one antagonizes the action

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of the other. A similar mechanism is also true for vitamin **E**; it acts both as an enhancer and an inhibitor of vitamin D, that is, its action is also context dependent [97,98].

One thing is for sure, that there exists strong evidence that links insulin resistance to vitamin D [99,100]. Moreover, there is a strong link between autoimmune pathology (including insulin resistance and its complications) and vitamin D deficiency [101]. The role of vitamin D cannot be referred only to its controversial antioxidant characteristics. Therapeutic use of vitamin D improves insulin secretion and sensitivity, reduces inflammation, and supports metabolic health generally [102–104]. In other words, it promotes insulin production in the β-pancreatic cell, and it also increases the effectiveness of insulin in cells. Moreover, it lowers pro-inflammatory cytokines that negatively affect β-pancreatic cells and thus aggravate insulin resistance [105–107]. Taken together, what is mentioned above leads to better control of glucose homeostasis, may help lower the fasting blood sugar, insulin levels, and different markers of insulin resistance.

Both isomers of vitamin D exert antioxidant activity:

Both vitamin D2 (ergocalciferol) and D3 (cholecalciferol) possess antioxidant properties; in that sense, they have similar potential as free radical scavengers. Since they are fat-soluble metabolites, they exhibit their functions mainly in the biomembranes. They inhibit iron-dependent liposomal lipid peroxidation [108–110]. The difference between these two isomers is not in their direct antioxidant capacity/concentration unit, but rather in their efficacy at increasing the vitamin D levels to maintain the vitamin D pool of the body [111–113]. Vitamin D3 is more effective and potent than D2 [114]. Vitamin D is considered as an antioxidant because it possesses the following properties:

A) It inhibits lipid peroxidation; this is because it is a lipid-soluble biomolecule and operates in a lipophilic environment [87,115].
B) It promotes the expression of enzymes that have antioxidant activity, such as superoxide dismutase, catalase, and glutathione peroxidase [116,117].
C) It decreases ROS release by the mitochondria and thus modulates different cellular inflammatory reactions [118].
D) It regulates the production of glutathione, the major intracellular antioxidant [90,115,119].

The mechanisms by which vitamin D exerts its antioxidant actions:

This function is primarily achieved through the regulation of gene expression that encodes various antioxidant enzymes, as well as through the direct antioxidant effects of vitamin D on membrane phospholipids, a property it shares with vitamin E [87,120,121].

The known mechanisms of how vitamin D operates as an antioxidant at the cellular level are as follows:

1) Through its active form, calcitriol, enhances the production of key antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, catalase, and glutathione (the master antioxidant). Calcitriol achieves this function by binding to the vitamin D receptor (VDR), as also mentioned elsewhere in this work.
2) It activates the Nrf2 pathway by inducing the expression and activation of nuclear factor erythroid 2-related factor 2 (Nrf2), the master transcriptional regulator of antioxidant responses. Nrf2 upregulates a wide spectrum of protective genes that, in concert, suppress the release of various ROS originating from intracellular sources such as NADPH oxidase and the mitochondria [122–124].
3) Vitamin D suppresses the generation of free radicals, directly or indirectly. It downregulates the expression of genes that encode enzymes linked to the production of ROS, such as NADPH oxidase. It also inhibits nitric oxide synthase (NOS), thereby indirectly regulating the production of nitric oxide (NO) and the release of reactive nitrogen species (RNS) [125,126].
4) It protects membrane phospholipids. As a fat-soluble molecule, it can incorporate into biomembranes and acts as a direct antioxidant, protecting the unsaturated fatty acids of membrane phospholipid leaflets from free radicals generated during peroxidation.

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Taken together, vitamin D maintains the hair-fine balance between free radicals and antioxidants in the human body in such a way that it can protect different cells and tissues from oxidative stress, which is the causative etiology of many chronic diseases affecting humans, including type 2 diabetes.

The interplay between vitamin D and insulin sensitivity:

Insulin resistance and vitamin D deficiency are indeed linked to each other, although the parameters of exact nature of this connection is unclear, and therefore it is a popular research topic. Evidence suggests that vitamin D deficiency may cause insulin resistance, while other research indicates the opposite or at least insulin resistance worsens vitamin D deficiency [127–129]. This concept is explained as follows:

A) How does vitamin D deficiency contribute to insulin resistance?

1) Vitamin D is an important parameter in insulin signaling; it regulates calcium flux and different other pathways in β-cells of the pancreas, which are pivotal to insulin synthesis and secretion [130].
2) Vitamin D deficiency is associated with an increased inflammatory state in the endocrine pancreatic tissue, which ultimately contributes to insulin resistance [103,131].
3) This essential micronutrient can upregulate the expression of insulin receptors in target tissues such as skeletal muscles, the liver, and adipose tissues, by which it improves the body's responsiveness to insulin [132].

B) How does insulin resistance contribute to vitamin D deficiency?

The possible parameters are as follows;

1) The corner contributing factor to insulin resistance is obesity. Obesity often coexists with low vitamin D levels; the plausible reason behind this phenomenon is that adipose tissue can sequester and deposit vitamin D [133]. A fact that also explains why intoxication with vitamin D takes a longer time to subside than water-soluble vitamins, in cases of intoxication with this lipophilic micronutrient.
2) Insulin resistance can lead to other metabolic complications, such as oxidative stress and inflammation, which adversely impact vitamin D status in the human body [134].
3) Insulin resistance is linked to dietary habits and lifestyle choices. For instance, a high-calorie diet is often a poor source of vitamin D.

The mechanism by which vitamin D improves insulin resistance:

Vitamin D boosts insulin secretion and sensitivity, reduces inflammation, and supports overall metabolic health. These effects, collectively, can improve blood sugar homeostasis, potentially reducing fasting blood sugar, insulin levels, and other signs of insulin resistance. The way vitamin D helps improve insulin resistance can be summarized as follows:

A) It enhances the body's response to insulin, increases synthesis, and promotes insulin release from pancreatic β-cells. It upregulates the expression of the insulin receptor gene to facilitate glucose uptake by various cells [135].
B) Calcitriol has anti-inflammatory properties; it modulates immune responses to reduce inflammation, especially a subtle chronic inflammation, which is known to cause insulin resistance [136,137].
C) Vitamin D influences energy homeostasis, and it promotes the proliferation of what is known as **beige** adipocytes, which are thermogenically more active than their white counterpart [138–140].
D) Being a fat-soluble, hormone-like metabolite, vitamin D easily permeates biomembranes, including those of cells and organelles such as the nucleus, affecting specific genes like IRS, PPAR-γ, and NF-kB [141,142]. These genes play a crucial role in insulin resistance. It promotes the expression of PPAR-γ while suppressing NF-kB expression.
E) Its effect on the IRS complex often leads to reduced phosphorylation. Considerable scientific evidence indicates that vitamin D supplementation reduces both fasting blood sugar and the glycosylated hemoglobin Hb1c [143,144].

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F) Vitamin D supplementation, especially in obese people with low vitamin D levels, improves their metabolic functions and may help decrease insulin resistance [128,145], although the same might not be true for obese individuals with normal serum vitamin D levels [146,147].

Conclusion and future perspectives:

What has been demonstrated in this work is that the incidence of insulin resistance and its outcome, namely type 2 diabetes, is rising worldwide. The condition has a multifactorial etiology, with the most significant factors including subtle inflammation, autoimmune mechanisms, and aging, often collectively called inflammaging. This does not mean that the disease doesn't occur in young people and adolescents. The production of free radicals in our bodies increases with age, which can be neutralized through a proper diet rich in antioxidants, including vitamin D. Genetic factors also contribute as a potential etiology for insulin resistance, which in fact, there is little we can do to avoid in contemporary medicine. Dietary habits and lifestyle choices play a key role in managing insulin resistance alongside proper medication. The controversial antioxidant role of vitamin D and its impact on insulin resistance therapy suggest that this essential micronutrient truly has multiple functions; that extends well beyond simply being an antioxidant. The résumé of what has been mentioned hitherto in this work is: **firstly**, Individuals with prediabetes (insulin resistance) should take a check-up every 3 months to see if they have adequate levels of vitamin D; **Secondly**, vitamin D supplementation is a crucial therapeutic adjuvant to oral hypoglycemic to treat obesity and type 2 diabetes. **Thirdly**, Lifestyle modification via physical activity, in addition to a healthy diet, can improve both insulin resistance and vitamin D deficiency and the complications of these two conditions.

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Abbreviations

free radicals = (FRs); Reactive oxygen species = ROS; Insulin resistance = IR; oral hypoglycemic agents = OHAs; Insulin receptor substrate = IRS.

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