Review

Immunomodulation through Nutrition Should Be a Key Trend in Type 2 Diabetes Treatment

Katarzyna Napiórkowska-Baran * , Paweł Treichel , Marta Czarnowska , Magdalena Drozd , Kinga Koperska , Agata Węglarz , Oskar Schmidt , Samira Darwish , Zbigniew Bartuzi

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Immunomodulation through Nutrition Should Be a Key Trend in Type 2 Diabetes Treatment

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Abstract: In order for the body to function properly, it needs not only food, but also nutrients and non-nutritive bioactive compounds that have an immunomodulating effect. This applies not only to healthy people, but especially to people with accompanying chronic diseases, including type 2 diabetes. Unfortunately, the current food industry and the use of highly processed food promote nutritional deficiencies. Many studies confirm their occurrence in patients with type 2 diabetes. The article presents the influence of selected nutrients on the functioning of the immune system, which ensures homeostasis of the body, with particular emphasis on type 2 diabetes. The role of macroelements, microelements, vitamins and selected substances, such as omega-3 acids, coenzyme Q10 and alpha-lipoic acid. The minimum scope of tests that should be performed in patients to directly or indirectly determine the degree of malnutrition in this group of patients is presented.

Keywords: type 2 diabetes; immunomodulation; immune system; nutrients; macroelements; microelements; vitamins; omega-3 acids; coenzyme Q10; alpha-lipoic acid

1. Introduction

Diabetes is a disease that affects more and more people around the world. It is one of the leading causes of disability and mortality regardless of origin, gender or age. It is estimated that in 2021 536.6 million people aged 20-79 suffered from diabetes around the world, of which approximately 96% were cases of type 2 diabetes, especially among the elderly population. The growing problem of diabetes was associated with the co-occurrence of high BMI in over 50% of cases. Unfortunately, the latest analyzes indicate that the problem of diabetes will increaseand by 2045 over 783.2 billion people aged 20-79 will suffer from diabetes. It should be noted that approximately 1/3 of deaths due to diabetes and its complications occurred in people under 60 years of age [1, 2].

Diabetes is not only a health problem but also an economic one. The estimated cost of diabetes-related burden among people aged 20-79 increased by as much as 366% between 2007 and 2021, reaching $966 billion and will reach one trillion dollars by 2030 [2].

Diabetes complications are one of the greatest challenges in its treatment. One of the divisions divides diabetes complications into macrovascular and microvascular. Macrovascular complications include cardiovascular diseases, including coronary artery disease, peripheral vascular disease and cerebrovascular disease. Microvascular complications of diabetes include diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. Approximately 50% of patients with type 2 diabetes have macrovascular complications, and microvascular complications occur in 27% of patients. The mentioned complications significantly increase mortality and worsen the quality of life of patients with diabetes [3, 4].

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Treating diabetes requires a holistic approach, including physical activity, appropriate diet, as well as pharmacological treatment, constant education and motivation of patients, and in selected cases the care of a psychologist and/or psychiatrist.

According to the still valid concept of Marc Lalonde, modifiable factors have the greatest impact on human health, approximately 70%, and lifestyle - as much as 50% [5]. A proper diet is undeniably crucial in managing diabetes. Unfortunately, the current food industry does not support proper nutrition, which is related to the high degree of food processing, the use of food additives and, above all, the conditions in which plants are grown. Many studies confirm a systematic decrease in the concentrations of microelements, macroelements and vitamins in products of plant origin, which should be the basis of a properly balanced diet [6,7,8]. As a result, we are currently dealing with malnourished patients with normal or excessive body weight because their bodies lack non-nutritive bioactive compounds.

The immune system is the most important system in the human body, which determines its efficient functioning in every aspect. This also applies to the impact on the development and course of chronic diseases, including diabetes. However, for the immune system to function properly, it needs not only protein (necessary, among others, for the synthesis of key enzymes), but above all, non-nutritive bioactive compounds [9,10].

Immunomodulation through nutrition, otherwise understood as immunonutrition, is a science that relates aspects of nutrition, the functioning of the immune system and the impact of inflammation and pathological processes in the body. Its beneficial effect has been demonstrated in many diseases such as: gastrointestinal cancer or Crohn's disease. [11, 12]. The use of immunomodulation through appropriate nutrition should also be a priority in such an important disease as diabetes.

2. Pathogenesis of diabetes with particular emphasis on the role of the immune system

Obesity is one of the main risk factors for insulin resistance and, consequently, type 2 diabetes. Insulin resistance is caused, among others, by tumor necrosis factor alpha (TNF-α tumor necrosis factor α), the increased production of which is observed in people with excessive adipose tissue. Berbudi et al. observed that, in addition to increased levels of TNF-α, obese patients also have increased levels of C-reactive protein and plasminogen activator inhibitor in the blood. Reactive oxygen species, free fatty acids and the above-mentioned inflammatory cytokines activate Iκβα kinase (IKKβ) and c-Jun N-terminal kinase I (JNK1), resulting in the inhibition of the insulin receptor substrate (IRS-1, Insulin receptor substrate 1). In addition to inhibiting IRS-1, the above kinases influence the activation of the transcription of inflammatory genes, which only increases insulin resistance. IRS-1 is also inhibited by STAT tyrosine phosphorylation, which the body achieves using JAK kinase. The consequence of these two mechanisms is the impairment of GLUT-4 translocation to cell membranes, which leads to hyperglycemia [13].

Interleukins are inflammatory cytokines responsible, among other things, for defense against pathogens. Mooradian et al. observed that isolated monocytes in people with diabetes, regardless of the type, secreted less interleukin 1β (Il-1β) after stimulation with liposaccharides (LPS) [14]. Additionally, based on other studies, the authors showed that hyperglycemia causes a decrease in Interleukin 2, 6, and 10 [15, 16]. Particularly important in this combination is Il-6, which is responsible for the adaptive induction of antibody production and the development of effector T lymphocytes [13].

Kumar et al. research showed that hyperglycemic mice have impaired infiltration of CD45+ leukocytes and CD8+ T lymphocytes. Additionally, a correlation of the above phenomenon with a weaker expression of adhesion molecules - E-selectin and intracellular adhesion molecule (ICAM) is observed [17].

The issue of Toll-like receptor (TLR) expression in response to hyperglycemia remains unresolved. In the studies performed, a complete decrease in expression was observed, and in others it was normal in patients with well-controlled hyperglycemia [18, 19].

In obese patients, who constitute the largest group of diabetic patients, the level of resistin, a protein that stimulates the endothelium to store lipids, is higher. Increased resistin levels have a negative impact on the production of reactive oxygen species by neutrophils (ROS) [20]. In conditions of hyperglycemia, we observe not only a reduction in ROS production by neutrophils, but also

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impaired degranulation, reduced phagocytosis, weakened formation of neutrophil extracellular networks (NETs), but also weakened opsonization of pathogens by antibodies [13].

Evidence of the impairment of many immunological mechanisms by hyperglycemia is also its effect on the complement system - reduced opsonization of the C4 fragment and dysfunction of natural killer cells are observed [13].

3. Novel therapeutic options in the treatment of diabetes

The field of diabetes care is constantly developing and new therapeutic options are emerging. Novel therapeutic option can increased a quality of health and well-being of people with diabetes. Changes regarding new research, technology and treatments leads to an update in recommendation.

In 2023 new Standards of Care in Diabetes were released and according to them something new guidelines were settled. The changes concerned revisions to incorporate person-first and inclusive language. Moreover, an additional language and some new definitions were added along to benefits of using them in telemedicine subsection. Recommendation regarding an address of use of statins and regular monitoring of glucose levels for individuals at high risk of developing type 2 diabetes who were prescribed statin therapy were added. The recommendation was added to discussion of the use of pioglitazone to reduce the risk of stroke or myocardial infarction in people with a history of stroke, and evidence of insulin resistance and prediabetes. A dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (Tirzepatide) has been added as a glucose-lowering option that may cause weight loss. It was enhanced that either small or larger weight losses should be considered as treatment goals on a case-by-case basis [21].

Moreover, the blood pressure treatment goals were changed and it is recommended to achieve <130/80mmHg in individuals with diabetes. In the case of people with diabetes and achieving a blood pressure ≥130/80mmHg pharmacological treatment should be considered. In individuals with diabetes aged 40-75 years and at higher risk included atherosclerotic cardiovascular disease risk factors, the LDL cholesterol level should be reduced to ≥50% of baseline and to achieve an LDL cholesterol goal of <70 mg/dL. Additionally, ezetimibe should be used in such cases or a PCSK9 inhibitor to achieve maximally tolerated statin therapy. In individuals with type 2 diabetes and diagnosed heart failure with either preserved or reduced ejection fraction, treatment with a sodium–glucose cotransporter 2 inhibitor is recommended. [22].

Major changes were introduced in immunization subsection to consider new indications and guidelines, especially regarding COVID-19 and pneumococci pneumonia vaccinations, including age recommendations and bivalent booster against Covid-19[21].

Some attention had been given to nutrition especially in diabetes in pregnancy. The nutrition counseling was endorsed to ameliorate quality of diet particularly balance of macronutrients inclusive of nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that embodied in nuts, seeds and fish in the eating pattern [21].

3.1. Tirzepatide

Tirzepatide is a dual agonist of receptors of Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) and according to its activity both play a role in controlling a glucose blood levels [23].

GIP and GLP-1 are the incretin hormones, which are produced and realized in the intestine as a response to intake of nutrients. Both stimulate beta cells of pancreas to secrete insulin. GIP and GLP-1 are responsible for about 65% of postprandial insulin secretion[23,24]. The action of GIP and GLP-1 is related to the incretin effect. The phenomenon consists in increasing the production and release of GIP and GLP-1 due to the increase in the concentration of glucose absorbed from gut. Intravenous administration of glucose does not affect the secretion of GIP and GLP-1. Released GIP and GLP-1 stimulate pancreatic beta cells to secrete insulin and as a consequence lower the blood concentration of glucose. The difference between insulin secretion in response to glucose absorbed from oral administration and intravenous administration of glucose is called The Incretin Effect. The intensity of this phenomenon depends on the glucose amount that was ingested. The insulinotropic activity of GIP and GLP-1 are depended on plasma glucose concentrations, thus high level of GIP and GLP-1 do

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not results in hypoglycemia. Dysfunction of the incretins effect is associated with impairments in oral glucose tolerance called impaired glucose tolerance or diabetes [25,26].

Furthermore, both GIP and GLP-1 may affect other metabolic functions. GIP has an influence on gastric secretion activity, which it inhibits. Additionally, GIP stimulates beta cells of pancreas to secrete insulin. It has insulin-like activity on adipose tissue, where it inhibits lipolysis and promotes lipogenesis [27,28]. The activity GLP-1 leads to stimulate insulin secretion and inhibits glucagon release. What is more, GLP-1 reduces food intake and leads to a delay in gastric emptying, and resulted in induces a sense of satiety and lowers body weight [26,29].

Tirzepatide is a new molecule that exhibits agonist activity towards GIP and GLP-1 receptors. It is the first "twincretin" synthetic peptide, which is composed of 39 amino acids with the structure based on native sequence of the GIP [30,31]. Tirzepatide by stimulating GIP and GLP-1 receptors, it is able to control the level of glycemia in the blood and reduce body weight through the same mechanisms caused by native GIP and GLP-1. It has been proved that Tirzepatide reduces level of HbA1c and body weight in individuals with type 2 diabetes more effectively than others selective GLP-1 receptor agonists [26,32-34]. Tirzepatide has five times lower affinity for the GLP-1 receptor than native GLP-1, however it binds to the GIP receptor with the same strength as native GIP [35,36].

Currently, Tirzepatide is indicated for treatment of type 2 diabetes mellitus (T2DM). According to the SURPASS trials, which assessed the safety and efficacy of Tirzepatide in people with T2DM, it turned out that Tirzepatide improved multiple cardiometabolic risk factors such as: reduction in liver fat, new-onset macroalbuminuria, blood pressure, and lipids [34,37].

3.2. Thiazolidinediones

Pioglitazone belongs to the thiazolidinediones and it is a peroxisome proliferator-activated receptor gamma (PPARγ) agonist. Pioglitazone decreased the risk of myocardial infarctions and ischemic strokes. Currently, the use of this drug is indicated for people with T2DM with a history of stroke, and evidence of insulin resistance and prediabetes [38,39].

Peroxisome proliferator-activated receptors (PPARs) are a group of transcription factors that have a significant impact on glucose and lipid metabolism. Three isoforms have been discovered in mammals: PPARα (NR1C1), PPARβ/δ (NR1C2) and PPARγ (NR1C3). PPARs are mainly responsible for control genes involved in lipid metabolism, including transport, storage, lipogenesis, and fatty acid oxidation. PPARs are expressed in various types of cells in the body, such as pancreatic beta cells and cells of the immune system, and therefore PPARs play a role in regulating insulin secretion and T cell differentiation [40,41]. PPARγ is expressed in adipose, intestine, liver, and kidney, where it participates in regulation of fat cell differentiation and lipid storage. Moreover, PPARγ has an anti-inflammatory activity and has an influence on differentiation of monocytes into macrophages and inhibits their conversion to the M2 phenotype [42, 43]. It has been proven that polymorphisms in the PPAR β/δ and PPAR γ promoter regions may resulted in a genetic predisposition to type 1 diabetes and can influence the severity of islet autoimmunity. Moreover, PPAR γ is correlated to the evolution of insulin resistance and type 2 diabetes. Therefore, PPARs have become an interesting target in the treatment of diabetes [44,45]. Thiazolidinediones through activation of PPARγ receptors are able to decrease insulin resistance directly. Stimuling the PPARγ results in simplify differentiation of mesenchymal stem cells into adipocytes, intensify lipogenesis in peripheral adipocytes, decrease concentration of hepatic and peripheral triglycerides, decrease activity of visceral adipocytes, and increase adiponectin, which has anti-apoptotic activity cardiomyocytes and in beta cells of pancreas [46-48]. Moreover, adiponectin has anti-inflammatory activity and increase insulin-sensitizing [49,50].

Pioglitazone, through stimulation of PPARγ, promotes insulin sensitivity in skeletal and cardiac muscle, activates the insulin signal transduction system, which results in improved glucose transport, enhances glycogen synthesis and glucose oxidation. In addition, it increases glucose consumption by intensifying the function of mitochondria. Thus reduces plasma free fatty acids levels and promotes reversal of lipotoxicity [51-55]. Pioglitazone reduces the risk of recurrence of major adverse cardiovascular events, myocardial infarction and stroke, new-diagnosis dementia [55, 56].

In vivo studies in rats and mice have proved that long-term treatment with rosiglitazone or troglitazone, both PPARγ agonists, maintains beta-cell proliferation and prevents age-related loss of

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pancreatic mass in these animals. Additionally, troglitazone may prevent pancreatic abnormalities which are related to age and increases in fasting insulin levels [40].

The number of diabetes cases is constantly increasing and constitutes a significant problem in the population. Therefore, research is ongoing to find new potential therapeutic targets for the treatment of diabetes such as GPCR 119, Vaspin, Metrnl and Fetuin-A [57-62].

3.3. GPCR119 receptor

GPR119 is a class-I G protein-coupled receptor found in skeletal and cardiac muscle, liver and pancreatic β-cells [58,63,64]. Activation of the GPR119 receptor leads to the activation of a cascade of Gα-stimulating proteins that induce adenylate cyclase activity. As a result, intracellular cyclic adenosine monophosphate (cAMP) increases, which may result in the release of GLP-1. Activation of GPR119 in pancreatic β-cell leads to glucose-stimulated insulin secretion similar to GLP-1 and GIP. Therefore, GPR119 plays a role in regulating glucose homeostasis and appetite. [58,65,66]. Due to its dual activity and low risk of hypoglycemia, agonists of GPR119 receptor are considered as potential target for the treatment of T2DM. So far, phase-2 clinical trials testing DS-8500 as GPR119 agonist are ongoing [67].

The antidiabetic effect of DA-1241 as another agonist of GPR119 receptor was tested in vitro and in vivo in mice. According to the results it turned out that, administration of DA-1241 does not affect body weight gain and amount of food intake, however fasting blood glucose level decreased along with increase in concentration of GLP-1. DA-1241 significantly improved only the oral glucose tolerance test, with no changes in the intraperitoneal glucose tolerance test as well as in the insulin tolerance test. DA-1241 caused a reduction of triglyceride content in the liver, which led to improvement in fatty liver. The outcomes of the research suggested that DA-1241 has a significant effect on glucose-dependent insulin release by stimulation of GLP-1 secretion, and contributes to reduced hepatic gluconeogenesis [68].

3.4. Vaspin

Vaspin also known as Serpin A12 is a adipokine that is a part of the serum and originally comes from the fat cells. It has an insulin sensitizing effect and contributes to reduced food intake. In studies conducted on rats, it was observed that administration of the vaspin into those animals resulted in the improvement in insulin sensitivity along with increased glucose tolerance [57,69,70].

Vaspin performs a significant effect on insulin modification and plays a role in modulating adipocyte differentiation and glucose homeostasis [71,72]. Moreover, Vaspin is an inhibitor of the kallikrein 7 (KLK7), which is responsible for degradation of insulin, which consequently reduces its concentration. By influencing KLK7, Vaspin contributes to the enhancement of insulin signaling and extends the half-life of insulin. That leads to increased the insulin concentration and affect on the blood glucose levels [70]. Vaspin has the effect of reducing inflammatory adipokines, therefore it may influence inflammatory processes. This action may contribute to some extent to improving insulin resistance [73].

3.5. Metrnl

Metrnl is an adipokine which originally comes from the adipose tissues particularly form the subcutaneous white fat, but also in intestinal, and epithelium of respiratory tract [74,75].

Metrnl contributes to the increase in lipid metabolism and has an impact on inflammation caused by a high-fat diet, which it alleviates. By acting on PPARγ receptors, it intensifies the remodelling of adipose tissue, which also improves insulin resistance and promotes the expression of GLUT4 receptors in skeletal muscle. Therefore, metrnl influences insulin sensitivity and reduces inflammation [60,76,77]. In addition, decreased serum merntl levels were reported in people with T2DM and with newly diagnosed T2DM [78-81]. It has been proven that metrnl deficiency may cause a decrease in blood level of HDL and increases concentrations of triglyceride. As a results, it has the additional function of controlling alter blood lipids [60,82].

3.6. Fetuin-A

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Fetuin -A is a glycopeptide mainly synthesized in the liver. As far, many function has been discovered [83,84]. Fetuin-A participated in development in diabetes and kidney disease [85].

Fetuin-A is able to bind the extracellular portion of the transmembrane β-subunit of the insulin receptor (InsR). Fetuin-A, through its interaction with insulin, has a significant effect on glucose homeostasis. Only two proteins can interact with the extracellular part of InsR: insulin and fetuin-A. Insulin turns on the receptor's intrinsic tyrosine kinase activity which is responsible for glucose transport. Meanwhile, Fetuin-A has the opposite effect and turns off tyrosine kinase. As a results, insulin signaling is impaired and caused in development in insulin resistance [86,87]. Fetuin-A also participates in modulating FFA-mediated pancreatic β-cell inflammation, which also increases insulin resistance [88,89].

According to obtain researches, it was concluded that higher circulating fetuin-A levels are correlated with incidence of T2DM and it is more relevant in women [90,91]. A high-fat diet intensifies the increase in Fetuin-A expression [92]. Furthermore, there is a strong correlation between Fetuin-A and obesity-related complications, and certain factors such as weight loss, taking pioglitazone or metformin can contribute to lower Fetuin-A levels [90,93].

4. The role of immunomodulation through nutrition as a key therapeutic strategy in patients with diabetes

The proper functioning of the immune system depends not only on genetic factors and accompanying diseases, but also on whether the building material for the synthesis of its components is provided. For example, metals, which play a key role in virtually all basic biological processes, are essential components of almost half of all enzymes [94]. Microelements, macroelements and vitamins are necessary for the proper functioning of the entire immune system. Their deficiency disrupts the functioning of physical barriers, impairs the innate immune response (both cellular and biochemical), inflammatory response and adaptive response (antigen presentation, humoral and cell-mediated immunity) [95]. A proper diet should provide the body with all the necessary nutrients and non-nutritive bioactive compounds. Unfortunately, changes introduced in the food industry have resulted in a significant loss of ingredients necessary for the proper functioning of the immune system. This is due to, among others, from the use of artificial fertilizers containing much less valuable ingredients than natural fertilizers. A decline in essential minerals in fruit and vegetables has been reported in the UK and other countries. New analysis of long-term trends in mineral content in fruit and vegetables from three editions of the British Food Composition Tables (1940, 1991 and 2019) was carried out. Concentrations of all elements except phosphorus decreased between 1940 and 2019 - the largest overall reductions in this 80-year period concerned Na (52%), Fe (50%), Cu (49%) and Mg (10%) [96]. Research conducted by GeigyPharmaceutical Company comparing the concentration of vitamins and minerals in selected plant foods in the years 1985-2002 showed a significant decrease in the concentration of calcium, magnesium, folic acid, vitamin B6 and vitamin C. The greatest reduction occurred in bananas and concerned vitamin B6 (95% loss)[97]. The loss of selected components results not only from the reduced concentration of specific elements in the soil. This loss is intensified by food storage and processing. For example, thiamine occurs mainly in the bran and germ of wheat grains, and up to 50% of it is lost during milling [98,99]. Fresh leafy vegetables stored at room temperature lose up to 70% of folic acid within 3 days. Maharaj P.P. et al. conducted research examining the effects of cooking and frying on folic acid retention in commonly consumed Fijian dishes vegetables (drumstick leaves, taro leaves, bale leaves, amaranth leaves, fern, okra and green beans). Folic acid loss varied among vegetables from 10–64% when cooking and 1–36% when frying. A greater loss of folic acid was observed during cooking. The content of folic acid in water obtained after cooking various vegetables ranged from approx 11.9 ± 0.5 to 61.6 ± 2.5 μg/100 ml. Boiling is a better choice for cooking vegetables tested for folic acid intake, provided cooking water is drunk with the vegetables [100]. Human levels of vitamin and trace minerals are no longer adequately supported by low-micronutrient cultured meats and plant-based products produced within existing agricultural food systems [101]. Unfortunately, the need for additional supplementation is underestimated by doctors who are not aware of the changes that have occurred in food. On the part of patients, supplementation, if it is carried out, is often done in an uncontrolled manner on their own.

4.1. Macroelements

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In the case of humans, macroelements are those elements whose dietary requirement exceeds 100 mg per day. They constitute not less than 0.01% of the dry weight of each organism. They are necessary for the proper functioning of the human body, and their deficiencies are often associated with unpleasant health consequences.

4.1.1. Magnesium

As the second most common intracellular cation and the fourth most abundant mineral occurs magnesium (Mg^{2+}). This element comes in bonded form and serves many functions in important physiological process. This element in human body is found in intracellular space, mostly in bones but also muscle cells, soft tissues and organs. In less than 1-2% Mg^{2+} is also found in blood and it is present in three times greater concentration in erythrocytes than in plasma [102]. This mineral that can be consumed together with fruits, vegetables, seeds grain cereals, meat and fish, berries, is an important cofactor in over 600 activities [103]. Daily allowance of magnesium for female is 320 mg and 420 mg for males [104]. Mg^{2+} is a part of numerous organic substances like proteins, nucleic acids and nucleotides. Magnesium economy is regulated by intestinal absorption, renal reabsorption/excretion by hormonal control and from the source of magnesium in the intracellular space (bones etc.) [102]. Increased magnesium excretion takes place in unregulated diabetes and metabolic acidosis. This nutrient role is to regulate cell cycle progression, stabilize membrane structure and its potential, participate in DNA and RNA synthesis, to aid nervous system functioning or aid the secretion of enzymes and hormones [105,106]. Its variety role includes also oxidative phosphorylation and muscle contraction and glucose, protein and lipid metabolism. Also Mg^{2+} is essential for ATP production in mitochondrium. [102,106].

Magnesium has a major impact in the regulation of wide range of immunological process. It affects on the acute phase response and macrophages function. Mg influences the development and proliferation of lymphocytes. It has been found that adequate amount of magnesium is required for the immune T cells so that they can fulfill their function in combating pathogens properly Mg^{2+} insufficiency make the cell more sensitive to oxidative stress in diabetes which accelerates the development of diabetes - related complications. [103].

This cation has also control of blood glucose and blood pressure. Studies on animals have been carried out that dietary Mg consumption (50mg/ml in drinking water) for 6 weeks lowered glucose level, ameliorated mitochondrial function and reduced oxidative stress and decline oxidative stress as this both are two main factors of insulin resistance [107,108].

There are some studies that show the connection between chronic Mg deficiency and the occurrence of symptoms such as overweight and obesity, insulin resistance (IR) and T2DM. In that case the protective role of Mg^{2+} is about to attenuating inflammatory process, improve glucose and insulin metabolism and normalize the lipid profile [105].

There is a strong cooperation between magnesium and insulin signaling pathway activation. The cation affects the tyrosine kinase (TK) of insulin receptor activity and also regulates peripheral insulin sensitivity and at the same time insulin regulates the magnesium homeostasis. When the concentration of magnesium is decreased, TK activity is damaged, the insulin activity in cell is blocked and insulin tolerance grows. Insulin signaling pathway allows for the regulation of glucose transport or glycogen synthesis and mistakes in this way can lead to decreased insulin transport and glucose uptake which may cause hyperglycemia. There is a study that shows that deficiency of Mg^{2+} can cause the development and progression of diabetes. It is said that magnesium deficiency can predict faster deterioration of kidney function, promotes atherosclerosis and increases the changes for diabetic microvascular complications [109].

There are some studies that shows that dietary Mg intake and higher risk of T2DM are interconnected [110]. Some of them shows that magnesium supplementation improves insulin sensitivity markers, has the favorable impact in glucose concentration in diabetics [105].

4.1.2. Calcium

Calcium (Ca^{2+}) is the most abundant mineral in human body. It can be absorbed mainly from the diet with dairy products, dark green leafy vegetables and calcium- fortified food. The main store of calcium - 99% in the body are bones where it has a structural function, residual 1% is in the

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intracellular and extracellular fluid. Calcium metabolism regulation is based on adequate intestinal calcium absorption, proper storage of calcium in bones and excretion of excess calcium by the kidneys and its all under control the 1,25-dihydroxyvitamin D, parathyroid hormone and ionized calcium [111].

It serves an important function in wide range of biological process such as muscle contraction, blood coagulation, hormone secretion, neurotransmission [112,113]. Adequate Ca2+ consuming may have an impact for releasing harmful substances that may enhance risk of diabetes [114]. In the immune system cellular processes such as a proliferation, division, activation and gene transcription may occur because of the calcium signals. Immune response decreases intracellular Ca2+ and than activates its flow to increase the intracellular Ca2+ concentration and it happens because of CRAC channels activation [115]. Diabetes (DM) is a disease that disturb normal functions of organs in human body and also affects a disorders in calcium metabolism which makes it difficult to organs that regulates calcium, function property. Incorrigible calcium economy may disturb regulation process in blood cells or cardiac and skeletal muscles. Calcium signaling is indispensable for the work of pancreatic β-cells and its insulin secretion in the response of increased glucose level through calcium channels. [116].

The study involving a 10-year follow-up showed that higher dietary calcium consumption was related with reduced risk of diabetes. Another study in 2011 showed that yoghurt consumption with high level of Ca2+ improved fasting glucose and fasting insulin [117]. There are also studies that shows the patients with uncontrolled hyperglycemic have higher risk of hypocalcemia [107].

4.1.3. Potassium

Influence on insulin secretion has also the mineral that is the most abundant cation in 98% in intracellular fluid in muscle cells and this remaining 2% is in extracellular fluid. K+ is mostly found in higher concentration in fruits, vegetables and milk. It is recommended to consume more than 3,5 g per day [118]. [Potassium (K+) participates in maintaining cell function, especially in muscle and nerve system cells. Adding salt to food reduces the potassium and increases the sodium content. The Food and Nutrition Board of the Institute of Medicine has established the recommended daily intake of K+ for 4700 mg and for WHO it is 3150 mg [119]. Normal serum potassium levels are in between 3,6 mmol/L - 5.0 mmol/L and below this standard it is a condition called hypokalemia and it is said that patients with comorbidities especially diabetics are exposed to an unfavorable course of treatment [120]. K+ concentration in cell depends on the transport of potassium ions through the Na-K APTase pump and its leakage through the K+ channels [121].

Potassium plays an important role in immune cells in human body. K+ gradient is needed for cell maintain a membrane potential for Ca2+ gradient. It is needed for immune cell activation as it happens due to Ca2+ influx to inflammatory gene transcription. Due to potassium channel occurs activation of mononuclear cells and also for nitric oxide production in macrophages [122].

In physiological situation insulin is released when the concentration of extracellular K+ is high. This process occurs through braking the ATP sensitive potassium channels of pancreatic B cells. In uncontrolled diabetics, changes in potassium concentrations outside the normal limits affects the regulation of glucose renal excretion. Low insulin concentration increase renal elimination of glucose, which increases sodium influx and this increases K+ elimination. Low serum potassium may be a disturbing factor for insulin secretion and cause glucose intolerance or diabetes [120].

Research by Chatterjee R. et al. demonstrated the effects of low potassium intake and low serum potassium levels on decreased insulin sensitivity and increased insulin secretion [123]. In case of the K+ and also Ca2+ action for insulin secretion process, its decreased intake have impact for reduced risk of diabetics. Increased potassium intake can may bring good health benefits like improved glucose control, glucose intolerance, insulin resistance, elevated blood pressure and hypertension. [124].

4.1.4. Sodium

Main cation of extracellular fluid that is essential for adequate cell functioning is sodium (Na+). To maintain fluid balance and mineral metabolism at the appropriate level, sodium consumption at the appropriate level is necessary [125]. This element takes part in regulating nerve and muscle

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function. Along with increased consumption of processed foods, salt intake increased. Except many negative effects of increased salt intake, consuming NaCl may protect against dehydration. WHO recommends daily sodium intake in 2000 mg per day [126].

Sodium has its immunostimulatory role in the immune system. Na+ can stimulate immune cells to triggering a stronger immune response [127].

Research by Ming L. et al. shows that higher daily sodium consumption is connected with increased risk of diabetes and the risk gets higher by 1,20 times for every 1g Na+ consumed [126].

Research conducted by Suckling RJ et al. showed that reduced sodium intake did not affect the insulin sensitivity or the fasting glucose or insulin concentration [128]. Another study shows that limiting sodium intake improve insulin resistance because of the increased secretion of adiponectin and diminution of proinflammatory processes. High concentration of sodium in diet increases cortisol secretion and insulin resistance and despite this Na+ still can improve nerve system in diabetics [108].

4.1.5. Phosphorus

Phosphorus (P) is another essential macronutrient that is in 1% of total human body [129]. Recommended daily intake of phosphorus is from 550 to 700 mg [130]. Institute of Medicine set the maximum phosphorus daily diet intake for 4000 mg. It is the element that we consume by eating fast food and restaurant meals rich in phosphate but also mild and diary products, fish and meat and grain products. .Phosphorus economy in human body is hormonally regulated by fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH) by their effect on the production and concentration of vitamin D which regulates bone metabolism and intestinal absorption of calcium and phosphorus, where its absorbed in 55-80% [129]. P is one of the main building blocks of cell membranes and nucleic acids. Its role is mostly about bone mineralization, energy generation and regulating acid-base hot maintain normal pH. High concentration of FGF-23, the hormone that regulates phosphorus economy is connected with insulin resistance. High daily phosphorus intake may be a factor of secondary hyperparathyroidism, bone loss and can have destructive influence in cardiovascular system. Recently, the consumption of processed foods has increased, as has the incidence of diabetics and there is a research that shows the connection between the higher phosphorus consumption and the higher risk of diabetics [130].

4.1.6. Sulfur

As the essential element sulfur is absorbed from digestive tract in the form of amino acids. Two main amino acids (SAAs) are methionine and cysteine and it is essential to synthesis of compounds involved in metabolic process but also a component of antioxidants involved in the body's defense mechanisms [131]. The source of sulfur are mostly vegetables such as broccoli, cauliflower, garlic and onion. The protective effect of sulfur is based on its influence on cardio-vascular system, glucose and anti-inflammatory effect. Protein intake and diabetes but it depends on its type and quantity [132]. One of the protein source is animals - red meat or processed meat and the other one is from plants - nuts, soy food. One of the studies shows the important correlation between consuming animal proteins and the higher risk of diabetics and demonstrate that people who had more plant protein in their diet and reduced their red meat consumption to 30% had lower risk to get diabetes [133]. Decreased consumption of SAA may improve insulin signaling pathway, which may have a beneficial effect on insulin sensitivity and glucose metabolism [132]. SAA through its participation in synthesis of antioxidants, especially glutathione, have the oxidative role. There is a study that shows that consumption of cysteine increases the glutathione level and it may have a good influence for glucose level in blood [134]. Limitind SAA intake may have a beneficial effect on preventing insulin resistance, may reduct the glucose level a glycated hemoglobin [135].

4.2. Microelements

Microelements are trace elements necessary for the proper functioning of the body. Although the demand for them is small (compared to the demand for macroelements), they are necessary for proper development and maintenance of life functions.

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4.2.1. Zinc

Zinc is a crucial microelement in metabolism. It is said to control over 100 enzymes which are responsible for substantial processes such as protein folding, gene expression, cell signaling and cellular processes including cell division and apoptosis. In terms of the immune system, zinc is known to strongly affect factors of an immunological response such as chemokines, proinflammatory cytokines, complement factors and bacterial wall compounds. This leads to early activation of polymorphonuclear leukocytes which together with macrophages are listed among first responders when infection occurs. Both zinc deficiency and zinc excess are undesirable because they are proven to inhibit nicotinamide adenine dinucleotide phosphatate oxidases, which activity is responsible for killing pathogens. This process takes place after phagocytosis, which is also influenced by accessibility of zinc. This microelement can positively influence the amount of cytokines and act as an antioxidant [136,137].

Due to various ways in which zinc affects many signal pathways, it is not fully understood, how does lack of zinc homeostasis contributes to the development of T2DM. It has been proven, that zinc transporter 8 (ZnT8) plays an important part in zinc uptake by insulin secretory granules in beta cells [138,139]. In study conducted in vivo on mice, it was demonstrated that ZnT8 is essential for beta-cell zinc influx, glucose-stimulated insulin secretion and insulin processing as well as formation of insulin granules [139,140]. Another transporter, that is considered important in pathomechanism of the disease is ZIP7. It is a transporter that is involved in process of endoplasmic reticulum (ER) stress. ER is critical for the correct processing and folding of proteins and ER stress arises when the folding capacity of the ER is outpaced with the influx of nascent, unfolded polypeptide chains. Cells undergoing this type of stress will activate a UPR (unfolded protein response) pathway, which will decrease transcription of genes that code for secretory proteins, causing decreasing folding demand on the ER. ZIP7 is a transporter located in early secretory pathway including ER controlling the movement of zinc form this subcellular organelle into cytosol. The importance of ZIP7 is emerging as a key transporter implicated in maintaining ER homeostasis. In that way zinc protects the ER from imbalance and therefore it helps avoiding decreasing transcription of genes that are responsible for secretory proteins [141].

4.2.2. Selenium

Selenium is a microelement, which plays an important role in our immune system. It is indispensable for the function of selenoproteins, which act as redox regulators of several key enzymes, transcription factors, receptors and therefore they affect functioning of leukocytes and NK cells. Selenoproteins function as well as cellular antioxidants [142]. Selenium influences innate immunity as well as adaptive immunity. In terms of innate immunity it regulates the viability of NK cells, macrophages, DCs, granulocytes, mast cells and microglia. Selenium is also proven to promote proliferation of T cells, promote CD4+ T cells differentiation into Th1 cells and suppression of the activity of cellular 5-lipoxygenase, which all are mechanisms enhancing adaptive immunity [143].

Many factors are said to influence the function of pancreatic islets and contribute to their metabolic dysfunction. Some of these factors are chronic low-grade inflammation, redox imbalance, mitochondrial dysfunction and endoplasmic reticulum stress. During the development of T2DM M1-like macrophages become the most abundant immune cells in crucial tissues such as visceral white adipose tissue, liver tissue and pancreatic islets. Inflammation of these tissues is a key component of developing a beta cell dysfunction and M1-like macrophages happen to be a primary source of pro-inflammatory cytokines. This process leads to accumulation of ectopic lipid in beta cells. Moreover H2O2 (ROS), which is required for proper insulin biosynthesis, secretion and signalling, when imbalanced, can lead to oxidative stress resulting in disruption in signalling pathway and even death of the cell. Now taking into consideration, that selenoproteins such as glutathione peroxidases are responsible for removing h2O2, selenoproteins S are involved in ER function and a group of selenoproteins called thioredoxin reductases control redox function, it is safe to say, that the imbalance of selenium may contribute to developing T2DM, but still the exact mechanism remains unclear [144]. More studies have shown a positive correlation between high levels of Se and presence of T2DM [145]. This correlation can be caused by the fact, that high Se exposure might affect the expression of key regulators of glycolysis and gluconeogenesis. This action is potentially meditated

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by selenoprotein GPx-1 and it was demonstrated that overexpression of this selenoprotein causes insulin resistance [146,147].

4.2.3. Iron

Iron is an essential dietary mineral used to support vital human functions, such as erythropoiesis and cellular energy metabolism [148]. It also has a significant influence on our immune system. Iron affects both innate and adaptive immune system. It's role is to regulate macrophage polarization, but it also plays an important part in the functioning of neutrophils. Iron is involved in the formation of neutrophil extracellular traps. It is also important in development, proliferation, activation and function of NK cells in viral infection [149]. Recent studies proved that adaptive T-cell immunity require serum iron by TfR1 (CD71). In terms of B cells function, it has been proven, that dysfunction of these cells can happen due to mutation of transferrin receptor 1 (TfR1) encoded by TFRC, and can lead to immunodeficiency [150,151].

High iron is a risk factor for T2DM and affect most of its cardinal features such as decreased insulin secretion, insulin resistance and increased hepatic gluconeogenesis [152]. One possible mechanism underlying this relationship might be that elevated serum ferritin can interact with other kinds of pathogenic factors, impair the function of islet beta cells, affect the secretion of insulin and increase the risks of T2DM [153]. Another explanation might be that because insulin is involved in regulating the transcription of serum ferritin and increasing the use of iron in peripheral tissues, when there is too much iron, insulin secretion is affected and the overload of iron causes oxidative stress [154]. This phenomenon is caused by an increase in iron-catalysed hydroxyl radicals, which leads to systemic insulin resistance and hyperglycaemia [155]. Iron is a powerful pro-oxidant and it may cause cellular damage in mechanism of producing reactive oxygen species, and taking into consideration, that beta cells in pancreas are particularly susceptible to oxidative injury, it can be another way in which excess iron leads to T2DM [156]. Serum ferritin is also considered as an acute-phase marker, therefore every inflammation causes imbalance in insulin secretion [154].

Although the exact molecular mechanism of iron-regulated pathology in diabetes remains unclear, many studies over the years have proven, that there is definitely a dependence between an excess body iron and presence of T2DM [156].

4.2.4. Iodine

Iodine in humans is primarily studied for its effects on the thyroid gland. There are some evidence that indicate that iodine could also influence functioning of other organs. Iodine is suggested to work in benefit of immune system by neutralizing ROS and making cell membranes less reactive to ROS. I2 acts as a scavenger of a reactive oxygen species like hydroxyl radicals or superoxide anions (O2) generating neutral components hypoiodous acid or hydroiodic acid. Iodine in combination with arachidonic acid, and generating the iodolipid 6-iodolactione (6-IL), inhibits the activity of proinflammatory enzymes like nitric oxide synthase and cyclooxygenase type 2 [157].

Iodine in excessive amount diminishes cell viability and compromise the function of insulin secretion in islet beta cells [158]. Thyroid function is important for regulating metabolism and abnormal thyroid function can have substantial effects on blood glucose control in diabetes [136]. A study conducted by O S Al-Attas et al. showed that concentration of urine iodine was significantly lower in T2DM than in healthy control subjects. The decreased levels of iodine concentration in T2DM patients may have deleterious effects on metabolic functions[159]. Another study that shows a correlation between levels of iodine and T2DM was a study conducted by Cuneyd Anil et al. which resulted in conclusion that TSH level of the diabetic patients was higher than in control group and so was mean thyroid volume [160].

4.2.5. Copper

Copper is a trace element found mainly in the liver, bones and muscles. It carries a particular importance in functioning of the immune system. As a redox active metal, copper is the ideal cofactor for enzymes involved in electron transfer and oxygen chemistry [161]. Around 30 metalloproteins are dependent on the accessibility of copper and their tasks range from respiration (cytochrome c oxidase; COX) to free radical detoxification (superoxide dismutases; SOD) [161,162]. There is also

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ceruloplasmin, which is a multicopper oxidase. It's main role is to oxidize Fe2+ to Fe3+, but it is also an acute phase protein induced in response to inflammation, trauma or infection. [161,163] A possible explanation to why does the amount of multicopper oxidase elevates during infection might be that ceruloplasmin helps deliver copper to sites of infection for attacking pathogens with copper toxicity. Moreover, it has been shown, that enrichment of plasma Cu levels could enhance both innate and adaptive immunity in humans in context of its antiviral activity that can serve preventively and therapeutically against COVID-19 [148,164]. Cu is involved in the function of T-helper cells, B cells, neutrophils, NK cells and macrophages[164].

The results of different studies are inconsistent concerning the association between copper consumption and the likelihood of developing diabetes. The result of a cohort study, performed by Eshak et al. on 16160 Japanese patient, showed that those, who had higher intake of copper and iron had a greater risk of developing T2DM [165].

Another cohort study conducted by Cui et al. assessed the diet of 14711 adults, has resulted in associating dietary copper with higher risk of developing T2DM. The study was based on people who did not have diabetes, hypertension and any cardiovascular diseases who took part in China Health and Nutrition Survey [166]. One possible way of copper influencing the presence of T2DM is that copper is essential for element of the enzyme copper/zinc superoxide dismutase (Cu/Zn SOD) which helps in the clearance of free radicals, which accumulate in cells as a result of metabolic stress. Another mechanism might be that copper is involved in the reactions of glutamic acid decarboxylase (GAD), which is a major beta cell antioxidant that is altered by reactive oxygen species (ROS). Anti-GAD antibodies contribute to the pathogenesis of T2DM [167,168]. Copper in high doses is suggested to have a pro-oxidant activity, so it is also possible for copper to cause the production of ROS through the Fenton reaction, which can hinder many processes, including ones associated with insulin resistance development and impaired glucose metabolism [169].

4.2.6. Cobalt

Cobalt is mainly known due to its necessary role as metal constituent of vitamin B12 [170]. Subsequent sections of this manuscript will elucidate and expound upon the topic of vitamin's B12 role in the immune system. Agata Szade et al. showed that cobalt protoporphyrin IX (CoPP) increases plasma concentrations of granulocyte colony-stimulating factor (G-CSF), IL-6 and MCP-1 in mice, triggering the mobilisation of granulocytes and hematopoietic stem and progenitor cells (HSPC). Compared with recombinant G-CSF, CoPP doesn't increase the number of circulating T cells [171].

To date, a limited body of research has explored the role of cobalt in human immune system. Studies mostly focus on toxicity of inorganic cobalt and how it evokes a chain of changes in cells. In some cases it can lead to immunological reaction known as type IV hypersensitivity reaction [172].

The studies performed on human subjects to assess the levels of cobalt in diabetic patients are inadequate. Saker et al. showed that cobalt choride decreased gluconeogenesis in diabetic rats through its glucose-lowering effect [136,173]. Cobalt treatment showed amelioration in nephropathy as well as heart function in a rat model of T2DM by alleviating oxidative stress [136,174].

4.2.7. Chrome

Chrome is an essential micronutrient for humans. The reduction of Cr(VI) to Cr(III) leads to the generation of reactive intermediates, which, in conjunction with oxidative stress, induces tissue damage. This initiates a cascade of cellular events, including the modulation of the apoptosis regulatory gene p53, contributing to the cytotoxic, genotoxic, and carcinogenic effects associated with Cr(VI)-containing compounds. Conversely, chromium serves as an essential nutrient crucial for insulin action in body tissues, facilitating the utilization of sugars, proteins, and fats. Chromium plays a pivotal role in modulating the immune response through either immunostimulatory or immunosuppressive processes, as evidenced by its effects on T and B lymphocytes, macrophages, cytokine production, and immune responses that may elicit hypersensitivity reactions [175].

Chrome has been found to electively improve glucose tolerance by reducing insulin resistance [136]. A study based in China showed that supplemented Cr improved the blood glucose, insulin, cholesterol and HbA1C levels of patients with T2DM in a dose dependent manner [136,176] Chromium improves the glucose/insulin levels in subjects with hypoglycaemia, hyperglycaemia and

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diabetes with no detectable effects on control group. Cr also improves insulin binding, receptor number and functioning of beta cells [136,177].

Rajendran et al. concluded the relationship between serum Cr levels and T2DM. Decrease in Cr levels occurred in response to oxidative stress in T2DM patients. In their study, patients with uncontrolled glucose levels with T2DM demonstrated lower levels of serum Cr levels compared to control group. The HbA1c and serum Cr levels were inversely correlated in a statistically significant way [178]. The exact mechanism is not thoroughly studied yet. We could definitely benefit from more studies exploring this connection.

4.2.8. Manganese

Manganese is a trace element present in variety of physiological processes such as antioxidant defences, reproduction and neuronal function [179]. Manganese incorporates into a number of metalloenzymes like Mn superoxide dismutase (SOD Mn2+), glutamine synthetase (GS), pyruvate carboxylase and arginase [180]. Mn2+ is required for the host defence against DNA virus by increasing sensitivity of the DNA sensor cGAS and its downstream adaptor protein STING. Mn2+ is released from mitochondria and Golgi apparatus upon virus infection and accumulated in the cytosol where it bound to cGAS, enhancing the sensitivity of cGAS to dsDNA and its enzymatic activity. On this pathway manganese supports antitumor immunity. Mn2+ is also important in innate immune sensing of tumours as Mn-insufficient mice had significantly enhanced tumour growth and metastasis, with greatly reduced tumour-infiltrating CD8+ T cells in a cGAS-STING-dependent ways[181].

There are some studies concerning manganese and its influence on diabetes, but they are ambiguous. Adewuni et al. showed that there is a significantly lower serum concentration of Mn in diabetic patients compared to the control group [182]. Anetor et al. demonstrated that mean serum Mn concentration in patients with T2DM was higher than in the control group [183]. The mechanism in which manganese influences the development of T2DM is not known yet. One possible explanation might be that because intracellular Mn2+ accumulates predominantly in mitochondria, where it may interfere with the electron transport chain and the oxidative phosphorylation process, it may cause a significant formation of ROS. The direct involvement of manganese in electron transport chain may lead to suppressed ATP production, and increased leaked electron flux and formation of highly reactive and damaging hydroxyl radicals [184]. While the initial exploration of the topic is insightful, further research would enhance its usability and provide a more comprehensive understanding.

4.2.9. Molybdenum

Molybdenum is a trace element important for various enzymatic processes. It needs to be complexed by a special cofactor to gain catalytic activity [185]. There are four molybdenum enzymes known in humans, each catalysing either catabolic or detoxifying reactions [186]. All of these enzymes share the same molybdenum cofactor (Moco). For example sulfite oxidase (SOX) catalyses the terminal step in oxidative cysteine catabolism, the oxidation of sulfite to sulfate. SOX links sulfite oxidation to the reduction of cytochrome c[187]. The existing literature does not extensively cover the topic of molybdenum's role in the immune system. There was a study on calves, which was conducted to determine the effects of dietary Cu and Mo on immune function and other features. The conclusion was that claves fed the supplemental Mo had lower antibody production than did calves fed supplemental Cu, which suggests that Mo supplementation without the supplemental Cu induces a more severe functional Cu deficiency [188].

4.2.10. Silicon

The available scientific literature on the influence of silicon on the immune system is notably scarce, with a paucity of comprehensive data addressing this specific relationship. The study of Liangjiao et al. showed that silica nanoparticles (SiNPs) can potentially have a toxic influence on immune system. The main mechanisms were proinflammatory responses, oxidative stress and autophagy. SiNPs cause oxidative stress by increasing membrane lipid peroxidation and the levels of ROS and by decreasing intracellular glutathione levels (GSH) [189].

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4.3. Vitamins

Vitamins are low-molecular-weight organic compounds whose presence in the body in small amounts is necessary for the proper conduct of many metabolic processes. For many organisms, including animals and humans, these compounds are exogenous and must be supplied with food. Vitamins do not have nutritional or energy functions, but only regulatory functions, acting as biocatalysts of metabolic processes in cells. However, without these substances it would be impossible for the body to function properly. In many studies have proven the role of vitamins in modulating the inflammatory response and behavior balance between immune cells or inhibiting the production of cytokines [190]. Due to the immunomodulatory role of vitamins, numerous studies are conducted to investigate their impact supplementation for diabetes by monitoring glucose levels, pancreatic β-cell function and glycated hemoglobin level HbA1c. Many studies have found vitamin deficiencies in course of diabetes, for example vitamin A, vitamin D or vitamin E [191-193].

4.3.1. Vitamin D

Vitamin D is a steroid hormone made from cholesterol. The largest source of vitamin D in our body comes from its synthesis in the skin under the influence of ultraviolet light, for this reason, many factors influence the synthesis of vitamin D, e.g. skin pigmentation, latitude, lifestyle and season. There are several forms of vitamin D-D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D is transported in its inactive form through the DBP-binding protein to the liver, where it is converted into 25-hydroxyvitamin D (25(OH)D). Active form of vitamin D - 1,25-dihydroxyvitamin D – 1,25(OH)2D (calcitriol) - penetrates into target cells and binds to the nuclear receptor vitamin D (VDR). Vitamin D bound to nuclear receptors acts directly on DNA of cells causing the production of special proteins. One of the best-known functions of vitamin D is its participation in the metabolism of calcium and phosphateand bone homeostasis. Additionally, vitamin D affects many others physiological processes in the body through VDR receptors. One of them is the effect of the vitamin D on cells of immune system, where the presence of the VDR receptor was provenin almost all cells of immune system and VDR receptor polymorphism has been associated with an increased frequencyof autoimmune diseases [194].

Vitamin D exerts its effects on both the innate and adaptive immune systems through the VDR. One of the types of cells that contain the VDR receptor are antigen-presenting cells (APCs), T lymphocytes, and macrophages [195-196]. Calcitriol stimulates the differentiation and activation of macrophages. It promotes their antimicrobial activity by increasing chemotaxis and phagocytosis by stimulating the local production of defensins (e.g. cathelicidin and β2-defensin). Calcitriol reduces the ability of macrophages to present antigen and stimulate T cells by reducing the surface expression of MHC class II molecules [193]. Additionally, calcitriol promotes the induction of immune tolerance through its anti-inflammatory effects. It inhibits the differentiation, maturation and function of dendritic cells (DC), making them incapable of acting as mature APCs, which allows the development of immunological tolerance [197,198].

The effect of vitamin D on the immune system has contributed to research on the impact of vitamin D supplementation on the course of diseases related to the immune system, for example type 1 diabetes. It has been studied that it exerts an anti-inflammatory effect directly by affecting the cells of the immune system, thereby weakening the destruction of pancreatic β cells, which produce insulin. The destruction of pancreatic β-cells by autoantibodies underlies the pathophysiology of type 1 diabetes. Vitamin D has the potential to restore immune tolerance, which counteracts the autoimmune response and slows or stops the progression of the disease by preserving residual β-cell mass and function and improving glycemic control [194,199,200]. Vitamin D acts through the VDR receptor on the pancreas and regulates insulin secretion in the pancreatic islets. It also affects insulin sensitivity in many peripheral metabolic organs. In type 1 diabetes, pancreatic β cells are destroyed by autoantibodies. β-cell-specificautoantigens (such as insulin, proinsulin, and IGRP) are presented by antigen-presenting cells (APCs), triggering cytotoxic T-cell responses that cause β-cell damage. It has also been proven that autoantigens are presented to APCs by macrophages[201]. For this reason, the effect of vitamin D based on reducing the presentation of antigens to APCs by macrophages and inhibiting the differentiation of dendritic cells into APCs could reduce the inflammation occurring in type 1 diabetes. Additionally, patients with type 1 diabetes have lower levels of vitamin D. Studies

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have shown that a larger number of diabetic patients have autoantibodies against DBP, which could explain the reduced vitamin D concentration in people with diabetes.

In the case of vitamin D supplementation, the need for insulin was reduced and the risk of diabetes was reduced. After starting supplementation, there was an initial increase in C-peptide concentration. The level did not persist and returned to the level of the control group that did not take supplementation. Some studies also found lower HbA1c levels after starting vitamin D supplementation, which could correlate with better baseline β-cell function because the HbA1c lowering effect was lost over time. For this reason, it was not possible to determine whether the improvement in test results was due to vitamin D supplementation itself or to individual differences in the course of the disease. [193,202] The conducted research leads to the conclusion that supplementation is beneficial mainly at the early stage of diagnosis, because it reduces the need for insulin and the risk of complications related to the disease. [193,199,202] Studies have also been conducted that clearly demonstrate the benefits of vitamin D supplementation in people with type 1 diabetes. Patients have lowered serum glucose and HbA1c levels [203].

The impact of vitamin D supplementation in patients with type 2 diabetes remains invaluable. Supplementation of this vitamin significantly improves the concentration of serum triglycerides, LDL cholesterol and total cholesterol, insulin, HbA1C and HOMA-IR. It also significantly reduces the concentration of highly sensitive C-reactive protein (hs-CRP). Low vitamin D levels are strongly associated with insulin resistance, impaired insulin secretion and increase the risk of T2DM cases, especially in people at high risk of T2DM. vitamin D deficiency is closely associated with many numbers of micro- and macrovascular complications of T2DM, including peripheral neuropathy, erectile dysfunction, retinopathy, diabetic kidney disease, and overall mortality. Interventional studies in people with T2DM and CKD have shown significant improvements in kidney function, especially when vitamin D analogues were combined with RAAS inhibitors [204].

4.3.2. Vitamin E

Vitamin E is the term for a group of tocopherols and tocotrienols, of which alpha-tocopherol has the highest biological activity. It cannot be synthesized in the human body, so we can only obtain it from dietary nutrients such as olive oil, almonds, sunflower oil, hazelnuts, sprouts and grain germs. Vitamin E is an essential nutrient for reproduction[205]. Its functions are mainly based on antioxidant activity, i.e. it has the ability to scavenge free radicals, inhibit lipid peroxidation, and chelate transition metal ions. Recent discoveries have shown that vitamin E has various potentially beneficial effects on human health, such as antiallergic, antiatherosclerotic, anticancer, antidiabetic, antilipidemic, antihypertensive, anti-inflammatory, prevents the development of obesity, and neuroprotective [206].

Vitamin E mainly serves as an antioxidant, reducing the accumulation of lipid peroxides and free radicals. Its effect on the immune system is based on the inhibition of the activity of cyclooxygenase 2 COX2. By affecting COX2, it reduces the production of prostaglandin E2 PGE2, which is involved in the body's inflammatory response. Vitamin E activates T cells and modulates the balance between Th1 and Th2 lymphocytes. Vitamin E reduces the inflammatory response by reducing the production of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 by peripheral blood mononuclear cells [190]. Higher concentrations of the vitamin inhibit the formation of 5-hydroxy-eicosatetraenoic acid 5-HETE and 5-hydroperoxy-eicosatetraenoic acid 5-HPETE in human neutrophils, suggesting an inhibitory effect of vitamin E on 5-LOX 5-lipoxygenase. By blocking 5-LOX, they prevent the transformation of arachidonic acid into leukotrienes, which inhibits the inflammatory response pathway in the body. In addition to the inflammation data, long chain vitamin E has been shown to have cytotoxic potential in several cancer cell lines. Their pro-apoptotic activity has also been observed in human macrophages [206].

A study by Jin Z et al. showed that Vitamin E could effectively reduce urinary microalbumin, urinary albumin excretion rate, and serum nitric oxide levels in patients with type 2 diabetic nephropathy [207]. A study by Mehvari F et al. revealed that vitamin E concentrations were lower in patients with diabetes and coronary artery disease (CAD) compared to diabetic patients without CAD. The results of this study confirm that oxidative stress may be an important factor increasing the susceptibility of some diabetic patients to CAD. Increased oxidative stress may be a potential therapeutic target for the prevention and treatment of CAD in diabetic patients [208].

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4.3.3. Vitamin C

Vitamin C, or ascorbic acid, is a water-soluble vitamin. It is a compound that cannot be synthesized in the body, so the main source of vitamin C for humans is the diet. Due to its solubility in water, it can easily lead to hypovitaminosis, so it is mandatory for humans to supplement it systematically with the diet. Vitamin C is found in citrus fruits - orange, kiwi, lemon, guava, grapefruit and in vegetables - broccoli, cauliflower, Brussels sprouts and peppers.

The main function of vitamin C is the ability to donate electrons, it is a strong antioxidant and additionally acts as a cofactor for biosynthetic and gene-regulating enzymes. It also affects the functioning of the immune system by acting on cell functions of both the innate and adaptive immune systems. Vitamin C supports the epithelial barrier function against pathogens. Supports the removal of oxidants through the skin, protecting eggs from environmental oxidative stress. Vitamin C accumulates in phagocytic cells such as neutrophils. In cells, it increases chemotaxis, phagocytosis and the production of reactive oxygen species. Reduces necrosis and potential tissue damage by promoting apoptosis and removal of neutrophils by macrophages from infected sites. Additionally, vitamin C has been shown to increase the differentiation, proliferation of B and T cells [209]. Recent in vitro experiments investigated the inhibitory effect of vitamin C on the expression of pro-inflammatory mediators, including IL-6 and TNF-α, in blood cells. Additionally, the antioxidant function influences the innate and adaptive immune response [190].

Vitamin C may reduce insulin resistance and cardiovascular complications in patients with T2DM [210]. It plays an inhibitory role in the production of protein oxidation biomarkers such as advanced oxidation protein products (AOPP) and advanced glycation end products (AGE) [211]. Due to the similar structure of vitamin C to glucose, it can be replaced by glucose in response to chemical reactions and prevent non-enzymatic glycosylation of proteins [212].

4.3.4. B vitamins

4.3.4.1. Vitamin B1

Thiamine is a water-soluble vitamin, also known as vitamin B1. Vitamin B1 is not synthesized in the human body, so it must be obtained through the diet. It is found in many foods, including yeast, beef, beans, lentils, and nuts. The most biologically active form of thiamine is thiamine pyrophosphate TPP, which acts as a cofactor for two enzymes in the oxidative pathways after glycolysis of the pyruvate dehydrogenase complex and the α-ketoglutarate dehydrogenase complex. TPP is also involved in regulating metabolism in the brain and in the structure and function of nerves [213]. Vitamin B1 also has an antioxidant function, which protects sulfhydryl groups on the surface of neutrophils against oxidative damage. Therefore, thiamine inhibits the oxidative stress-induced stimulation of nuclear factor kappa-light-chain-enhancer of activated B cells NF-κB. NF-κB is associated with the development of inflammation, autoimmune diseases and viral infections, and even improper development of the immune system. Vitamin B1 also influences the formation of pro-inflammatory cytokines in macrophages [190].

Decreased levels of vitamin B1 in people with T2DM have been associated. A fat-soluble thiamine derivative called benfotiamine is effective in increasing blood levels of thiamine compared to water-soluble thiamine derivatives. Benfotiamine reduces glucose toxicity caused by hyperglycemia in T2DM by activating glucose metabolism and insulin synthesis. It also plays a role in blocking pathways responsible for hyperglycemia-induced damage, such as the hexosamine pathway, formation of advanced glycation end products, and activation of protein kinase C. It also acts by activating transketolase (TK), the rate-limiting enzyme of the non-oxidative branch of the pentose phosphate pathway [214].

4.3.4.2. Vitamin B6

Vitamin B6 is a collection of six different forms - pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM) and related 5′-phosphate derivatives. Vitamin B6 is not synthesized in the human body, but obtained through a diet containing potatoes, bananas, nuts and fish, especially fatty fish such as salmon and tuna. The biologically active form of vitamin B6 is pyridoxal 5′-phosphate PLP. It plays an important role in cellular metabolism, participating as a coenzyme in up to 150 different enzymatic

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reactions, such as the synthesis, transformation and degradation of amines as well as the biosynthesis and degradation of neurotransmitters. It is not classified as an antioxidant compound, but it also affects reactive oxygen species (ROS) and prevents the formation of advanced glycation end products (AGEs), which are involved in the processes of aging and diabetes [215].

The effect of vitamin B6 on the immune system is based on inhibiting the activation of the NOD inflammasome, LRR and pyrin domain-containing protein 3 (NLRP3), which results in a reduction in the secretion of IL-1 production. The function of IL-1 is fundamental to innate immunity and the development of acute and chronic inflammation. Inhibiting the production of IL-1 leads to a reduction in the inflammatory response in the body. Additionally, it has been proven that the administration of PLP significantly reduces the production of mitochondrial reactive oxygen species ROS [190].

Epidemiological and experimental studies have shown an obvious inverse relationship between vitamin B6 levels and diabetes, as well as a clear protective effect of vitamin B6 on diabetes complications [216]. The effect of vitamin B6 on diabetes is related to various processes for which the vitamin is responsible. In vitro experiments on pancreatic perfusion led to the observation that in the case of pyridoxine deficiency, the secretion of insulin and glucagon is impaired. [215]. Low vitamin B6 concentration is associated with the occurrence of cardiovascular diseases in people with T2DM, and this relationship may be mediated by plasma fibrinogen and CRP concentrations [217].

Additionally, it has been studied that the reduction in the production of mitochondrial reactive oxygen species ROS caused by vitamin B6 supplementation causes a decrease in glucose in patients with diabetes. in fasting blood, HbA1c and additionally improves glycemic control [216].

4.3.4.3. Vitamin B12

Vitamin B12 is a microelement that humans cannot produce and must be supplied from animal proteins. It can be found in products such as kidneys and livers (veal, beef, poultry), fish, mussels and other seafood, eggs and dairy products. Vitamin B12 is essential for cell function due to its key role in DNA stability. Vitamin B12 deficiency has been proven to lead to indirect DNA damage, and vitamin B12 supplementation can reverse this effect [218]. It also plays a huge role in the functioning of the central nervous system at all ages. With the participation of folic acid, it participates in the conversion of homocysteine to methionine via methionine synthase, which is necessary for nucleotide synthesis and genomic and non-genomic methylation [219]. Moreover, vitamin B12 has antioxidant properties, which prevents damage caused by reactive oxygen species. DNA protection against reactive oxygen species is based on the removal of free radicals and the reduction of oxidative stress [218]. The effect of vitamin B12 on the immune system concerns maintaining the balance between CD8+ and CD4+ T cells [190].

Reducing vitamin B12 levels in patients with T2DM is one of the side effects of metformin use [220]. Clinical manifestations of metformin-induced vitamin B12 deficiency include hematological manifestations of megaloblastic anemia and neurological complications, i.e. peripheral neuropathy, spinal cord degeneration and cognitive impairment [221].

4.3.4.3. Folic acid

Vitamin B9, known as folic acid, is a vitamin obtained mainly from the diet. Folate is present in animal tissues, leafy vegetables, legumes and nuts. Folic acid participates in many important processes in the body, mainly in cell replication through enzymatic activity in the synthesis of purine bases for DNA. It is also a transamination cofactor in the conversion of amino acids, especially homocysteine to methionine[222].

In addition to its main functions, folic acid affects the immune system. Several studies have demonstrated its effect on Treg cells [190,223]. Folic acid has a positive effect on the proliferation of T lymphocytes, increases phagocytosis and the production of immunoglobulins[190]. Folic acid deficiency also reduces DC cell maturation and impairs CD4+ T cell differentiation. In turn, the administration of high doses of folic acid reduced the inflammatory response by reducing the secretion of pro-inflammatory cytokines IL-4, IL-5, IL-9, IL-13, IL-17, IL-3. Folic acid also has a large impact on processes related to vitamin B12. Research has proven that maintaining the balance

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between these vitamins is important in relation to the immune response. It has been shown to have a particular effect on NK cells and cytotoxic CD8+ lymphocytes [223].

Folic acid and vitamin B12 in the course of diabetes mainly affect the level of homocysteine. Its high level in people with type 2 diabetes promotes the development of atherosclerosis. Vitamin supplementation reduces homocysteine levels. Due to the significant role of folic acid in cell replication, it has also been investigated that DNA damage resulting from oxidative stress in diabetes can be reversed by folic acid supplementation. Thanks to this, folic acid reduces the level of endothelial dysfunction in diabetic patients[224,225]. Additionally, folic acid supplementation improved laboratory results in diabetic patients. improves glycemic control by reducing fasting blood glycosylated hemoglobin, serum insulin and insulin resistance, as well as homocysteinemia in patients with type 2 diabetes [222,226].

It has been proven that folic acid affects the concentration of CRP, which is one of the inflammatory markers. It is likely that the effect of folic acid on Treg lymphocytes, which are responsible for suppressing excessive immune response, thus contributing to maintaining the homeostasis of the immune system, contributes to the reduction of CRP levels in patients with type 2 diabetes who were supplemented with folic acid[227].

4.4. Selected sustances with immunomodulatory effects

4.4.1. Coenzyme Q10 (CoQ10)

Persistent hyperglycemia causes oxidative stress due to an increased production of ROS, which has been proposed as the root cause underlying the development of insulin resistance, β-cell dysfunction, impaired glucose tolerance and T2DM [228]. It has also been implicated in the progression of long-term diabetes complications, including microvascular and macrovascular dysfunction. An overabundance of calories through food intake, combined with an inactive way of life in people with T2DM leads to glucose and fatty acid overload, resulting in the production of ROS. This initiates a chain reaction leading to reduced nitric oxide availability, increased markers of inflammation and chemical modification of lipoproteins [229,230].

Coenzyme Q10 (CoQ10), a lipid-soluble micronutrient that is endogenously synthesized in the body [231], appears to be a promising candidate for treating T2DM and its cardiovascular complications. It precisely targets oxidative stress, owing to its potent antioxidant activity and fundamental physiological role in mitochondrial bioenergetics [232]. CoQ10 has two primary functions: promoting ATP synthesis and serving as a potent antioxidant, making it one of the most active scavengers for ROS and providing protection to mitochondria membrane proteins, lipids and DNA from oxidative damage. The reduced form of CoQ10 - ubiquinol serves as a potent antioxidant since it holds electrons loosely, and can easily give up one or two electrons to neutralise ROS [231].

Given that CoQ10 is predominantly distributed within tissues with heightened energy requirements, its abundance is notable in specific dietary sources, particularly in animal hearts and livers, fatty fish such as salmon, sardines, and herring, as well as in plant-based sources like soybeans, spinach, and nuts - although in a lower concentration compared with meat and fish [233]. Unfortunately, the efficiency of absorption of orally administered CoQ10 is poor because of its insolubility in water, limited solubility in lipids, and relatively large molecular weight - the endogenous synthesis is believed to be its main source [234].

However, when it comes to T2DM there is more evidence that the supplementation of CoQ10 can support the treatment of type 2 diabetes and its complications. Many studies contradicting the theory of its beneficial effects were conducted in the 1990s, when ubiquinol, the reduced form of CoQ10, was not yet accessible as a supplement on the market. Instead, only ubiquinone, the oxidised form of CoQ10, was investigated [231]. What is known today is that depleted CoQ10 levels in the blood (serum and platelets) have been reported in type II diabetic patients [235] and the supplementation with 100 mg of ubiquinone twice daily (200 mg/day) or 100 mg of ubiquinol per day can significantly decrease HbA1C, as well as systolic and diastolic blood pressure for ubiquinone [236–238]. It aligns with another study's results, indicating a significant negative correlation between CoQ10 and HbA1C concentrations [235]. However, data regarding its effect on fasting glucose, fasting insulin and HOMA-IR are found to have low certainty of the evidence (GRADE Evidence Profile) because of inconsistency, indirectness and publication bias [239]. This means that the positive

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impact of CoQ10 supplementation on the above factors cannot be confirmed with certainty, but these results should be taken into consideration, especially in the context of further research.

Alterations in mitochondrial function associated with increased production of ROS have been attributed as significant factors for cardiovascular complications of T2DM, from endothelial dysfunction to heart failure. Several studies suggest that CoQ10 supplementation can counteract abnormal endothelial function by activating endothelial nitric oxide synthase (eNOS) and mitochondrial oxidative phosphorylation [240,241].

Promising outcomes of CoQ10 effectiveness have been presented in a recent Q-SYMBIO study. The potential benefits of ubiquinone supplementation (3 x 100 mg/day for two years) among patients with chronic heart failure (NYHA class III or IV) were assessed. Supplementation with CoQ10 reduced the risk of MACE (major adverse cardiovascular event) by 43%, the risk of cardiac-related death by 43% and all-cause mortality by 42%. The results demonstrated that treatment with CoQ10 in addition to standard therapy for patients with moderate to severe HF is safe, well tolerated, and associated with improvement in NYHA functional class [242].

Regarding diabetic polyneuropathy, a double-blind, placebo-controlled clinical trial was conducted. Patients were given 400 mg of ubiquinone a day for twelve weeks, resulting in significant improvement of clinical outcomes and nerve conduction parameters of diabetic polyneuropathy without adverse effects [243].

4.4.2. Alpha-lipoic acid

Alpha-lipoic acid (ALA), also known as thiotic acid, was first isolated by L. J. Reed et al. from insoluble liver residues. The name of the compound was created based on the high solubility of the ALA in fat and its acidity. Reed et al., based on the proved catalytic properties of lipoic acid in the aerobic decarboxylation of pyruvate, incipientlyclassified this compound to the family of B vitamins [244].

ALA is produced by both plants and animals, including humans. This compound, due to its single chiral center, exists in two forms: as the R isomer and the S isomer. Both isomers occur in equal amounts in alpha-lipoic acid. It is worth mentioning that only the R isomer occurs naturally and the S isomer uprises in the chemical reactions[245-247]**.** Alpa-lipoic acid is produced by humans from fatty acids and cysteine, but its endogenous production is not sufficient to ensure the proper functioning of cells, which means that this compound is supplied to the body mainly through the diet [247, 248]. Both animal and plant tissues contain alpha-lipoic acid in the form of the R isomer andit occurs in a form bound to lysine residues, as lipoyllysine. The sources in which R-ALA occurs in the highest concentration in animal tissues are kidneys, heart and liver, while in plant sources R-ALA is found in the highest concentration in spinach, broccoli and tomatoes [246, 248]. Alpha-lipoic acid available as a dietary supplement is a mixture of both racemic forms. Both ALA and its reduced form, dihydrolipoic acid (DHLA), have antioxidant properties and these forms arecalled together as “universal antioxidant”[246]. It has been shown that this universal antioxidant can play a key role in the regeneration of other antioxidants, including: vitamin C, glutathione and vitamin E, and dihydrolipoic acid, when neutralizing free radicals, does not degenerate and is converted back into the oxidized form - alpha-lipoic acid[246, 249, 250].

Alpha-lipoic acid affects many crucial cellular pathways in the body. One of its actions is to influence the immune system by inhibiting the activation of nuclear factor kapp B [NF-κB]. NF-κB is a protein complex that acts as a transcription factor, participating in the regulation of the immune response. NF-kB is found in most animal cells and is activated by various factors, such as cytokines, free radicals, viruses, bacteria and stress [251, 252]. It has been shown that dysregulation in NF-κB pathway can be associated with disorders such as:cancer, autoimmune diseases, inflammatory and metabolic diseases [253-255].

Alpha-lipoic acid also plays important role as a regulator of gene transcription, modulated by peroxisome proliferator-activated receptors (PPARs). PPARs are significantly involved in cell differentiation and maturation processes as well as in metabolic processes involving carbohydrates, proteins and lipids. The use of fibrates and glitazones in metabolic diseases, which also affect PPARs, confirms the fact that alpha-lipoic acid, through the effect on PPARs, described above, may also play a significant role in modifying the course of metabolic diseases such as diabetes.

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Alpha-lipoic acid affects many pathways involved in the pathogenesis of diabetes. In diabetes, hyperglycemia causes increased production of ROS, which then causes cell damage[251]. ROS negatively affect insulin signaling and contribute to the development of insulin resistance [256]. It has been shown that increased levels of ROS result in the formation of oxidized forms of LDL [ox-LDL], which are not properly recognized by LDL receptors, resulting in an increased concentration of ox-LDL in the blood. These forms are then phagocytosed by macrophages, which turn into foam cells and are deposited in the form of atherosclerotic plaques. It has been proven that ROS, by influencing endothelial cells, disturbs vasorelaxation, causes apoptosis of endothelial cells, increases the proliferation and migration of smooth muscles of blood vessels, and also promotes abnormal angiogenesis. These processes may be related with the micro- and macrovascular complications occurring in diabetes [251, 257, 258]. The antioxidant potential of ALA can prevent the adverse effects of ROS on cells and tissues.

It has been shown that ALA also affects the expression of 5'AMP-activated kinase (AMPK), which plays a significant role in the pathogenesis of diabetes. AMPK activation leads to reduced gluconeogenesis in the liver, increased glucose uptake and fatty acid oxidation by skeletal muscles, which contributes to reducing blood glucose concentration and improving insulin sensitivity of cells [251,259]. AMPK also increases the amount of glucose-uptake transporters 4 on cell membranes in an insulin-independent mechanism, which also contributes to the hypoglycemic effect [250, 251, 259].

Studies on rats have proven that alpha-lipoic acid had an inhibitory effect on hypothalamic AMPK, causing a decrease in food intake and an increase in energy expenditure, contributing to a decrease in the body weight of the tested animals. This discovery opens the way in research on ALA as a potential drug against obesity, which itself is associated with an increased risk of type 2 diabetes [260, 261].

It has been proven that alpha-lipoic acid taken orally has a bioavailability of approximately 29%, which is associated with a significant first-pass effect. It is worth mentioning that a meal reduces its bioavailability, so it is recommended that alpha-lipoic acidshoulf be taken at least 30 minutes before the planned meal [262].

In many clinical trials involving humans, such as: ALADIN, ORPIL, SYDNEY various doses of ALA were used, ranging from 200 to 1800 mg per day, but no specific dose has been established and further research is necessary in this area. However, there were no contraindications to the use of alpha-lipoic acid and side effects were limited only to hypersensitivity reactions [251].

4.4.3. Omega-3 fatty acids

The main representatives of omega-3 acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [263]. Good sources of omega-3 fatty acids are fish such as salmon, tuna, mackerel, anchovies and sardines [264]. The recommended daily intake ranges from 250-500 mg per day and depends on gender and age [265]. Omega-3 polyunsaturated fatty acids (n3-PUFA), mediators of inflammation and adaptive immune responses, have anti-inflammatory and antioxidant properties [108,266]. Omega-3 fatty acids regulate immune responses by producing inflammatory cytokines. EPA influences increased glucose uptake in skeletal muscle cells and regulation of insulin secretion pathways by pancreatic cells. There are studies that show that EPA supplementation reduces fasting plasma glucose, insulin, HbA1c and HOMA-IR levels in patients with type 2 diabetes. It may also affect insulin regulation via PRAR-γ [267]. DHA can reduce blood glucose levels, but its effect on insulin regulation is related to its anti-inflammatory effect. Omega-3 acids, by secreting adipocytokines and affecting adipose tissue, can improve mitochondrial function and, as a result, improve insulin resistance. Some studies show that omega-3 fatty acids have a positive effect on insulin sensitivity in both diabetics and non-diabetics. One of them shows that increased consumption of omega-3 fatty acids was associated with a decrease in serum C-reactive protein levels. Supplementing with omega-3 fatty acids can improve insulin sensitivity, reduce inflammation, and may reduce the risk of developing diabetes [268].

5. Conclusions

For the body to function properly, it needs not only food, but also nutrients and non-nutritive bioactive compounds. This applies not only to healthy people, but especially to people with

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accompanying chronic diseases, including type 2 diabetes. Unfortunately, the current food industry and the use of highly processed food promote nutritional deficiencies. Many of the studies discussed earlier confirm the existence of these deficiencies. The best method to determine the need for compounds necessary for the proper functioning of the body is to initially determine their concentrations, which unfortunately is not possible in practice to the full extent. However, we can use commonly available tests that will allow us to directly and indirectly assess the patient's nutritional status. It is necessary to collect an interview, especially taking into account eating habits, and determine the Body Mass Index (BMI). The tests that should be performed in every patient with diabetes include: complete blood count with smear (lymphopenia may be an indicator of malnutrition), concentration of total protein, albumin, phlic acid, B12, ferritin, vitamin D3, calcium, uric acid and lipid profile[220,221,269].

If the patient suffers from inflammation and we expect that the concentration of ferritin (as an acute phase protein) may be elevated, transferrin saturation (TSAT) should be determined, which requires the concentration of iron and latent iron-binding capacity. Research by Pilar Vaquero M et al. showed that low TSAT levels are very common in diabetes, mainly in women. If TSAT is <15% in men and <12% in women, we are diagnosed with iron deficiency and supplementation is necessary [270].

Research conducted by the author of this article on a group of patients with primary immunodeficiency showed reduced hemoglobin concentration in 32%, total protein in 19%, albumin in 17%, vitamin D3 in 52% (despite recommended supplementation), vitamin B12 in 6.5%. %, folic acid in 34% and ferritin in 26% of patients. It should be noted that this is a group of patients who regularly attend medical appointments and undergo regular examinations [271]. Diabetes is a secondary immune deficiency and patients suffering from this disease should also be carefully examined for nutritional deficiencies. Research conducted in patients with recurrent infections in the Immunology Clinic (including type 2 diabetes) and the implementation of periodic vitamin and mineral supplementation (for 2 months, then every 2-3 months for a month), additional chronic supplementation of vitamin D3, calcium, omega-3 fatty acids significantly improved the functioning of patients, both clinically and laboratory (data not yet published).

Monitoring eating habits and assessing diabetic patients for nutritional deficiencies should be key in the care of this group of patients. Appropriate nutrition affects the proper functioning of the immune system, ensuring homeostasis of the entire body, slows down the development of complications, reduces the risk of other chronic diseases, and thus improves the length and quality of patients' lives.

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References

1. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. **2023**, *402*, 203–234.
2. Magliano DJ, Boyko EJ; IDF Diabetes Atlas 10th edition scientific committee . IDF DIABETES ATLAS [Internet]. 10th edition. Brussels: International Diabetes Federation; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK581934/
3. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. **2018**, *14*, 88–98.

 doi:10.20944/preprints202402.0674.v1

4. Cole, J.B., Florez, J.C. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol* **2020**, *16*, 377–390.
5. Wysocki MJ, Miller M. Lalonde's paradigm, World Health Organization and new public health. *PrzeglEpidemiol.* **2003**, *57*, 505–12.
6. Mayer AB, Trenchard L, Rayns F. Historical changes in the mineral content of fruit and vegetables in the UK from 1940 to 2019: a concern for human nutrition and agriculture. *Int J Food Sci Nutr.* **2022**, *73*, 315–326.
7. Thomas D. A study on the mineral depletion of the foods available to us as a nation over the period 1940 to 1991. *Nutr Health.* **2003**, *17*, 85–115.
8. Hasanaliyeva G, Sufar EK, Wang J, Rempelos L, Volakakis N, Iversen PO, Leifert C. Effects of Agricultural Intensification on Mediterranean Diets: A Narrative Review. *Foods.* **2023**, *12*, 3779.
9. Wang C, Zhang R, Wei X, Lv M, Jiang Z. Metalloimmunology: The metal ion-controlled immunity. *AdvImmunol.* **2020**, *145*, 187–241.
10. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients.* **2020**, *12*, 236.
11. Grimble RF. *Immunonutrition. Curr Opin Gastroenterol.* **2005**, *21*, 216–22.
12. Sánchez-Guillén L, Arroyo A. Immunonutrition in patients with colon cancer. *Immunotherapy.* **2020**, *12*, 5–8.
13. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. *Curr Diabetes Rev.* **2020**, *16*, 442–449.
14. Mooradian AD, Reed RL, Meredith KE, Scuderi P. Serum levels of tumor necrosis factor and IL-1 alpha and IL-1 beta in diabetic patients. *Diabetes Care.* **1991**, *14*, 63–5.
15. Reinhold D., Ansorge S., Schleicher E.D. Elevated glucose levels stimulate trans forming growth factor-β 1 (TGF-β 1), suppress interleukin IL-2, IL-6 and IL-10 production and DNA synthesis in peripheral blond mononuclear cells. *Horm. Metab. Res.* **1996**, *28*, 267–270.
16. Tanaka T., Narazaki M., Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb. Perspect. Biol.* 2014;6, 016295.
17. 5. Kumar M., Roe K., Nerurkar P.V., Orillo B., Thompson K.S., Verma S., Nerurkar V.R. Reduced immune cell infiltration and increased pro-inflammatory mediators in the brain of Type 2 diabetic mouse model infected with West Nile virus. *J. Neuroinflammation.* **2014**, *11*, 80.
18. Jafar N., Edriss H., Nugent K. The effect of short-term hyperglycemia on the inna te immune system. *Am. J. Med. Sci.* **2016**, *351*, 201–211.
19. Gupta S., Maratha A., Siednienko J., Natarajan A., Gajanayake T., Hoashi S., Miggin S. Analysis of inflammatory cytokine and TLR expression levels in Type 2 Diabetes with complications. *Sci. Rep.* **2017**, *7*, 7633.
20. Chao W.C., Yen C.L., Wu Y.H., Chen S.Y., Hsieh C.Y., Chang T.C., Ou H.Y., Shieh C.C. Increased resistin May suppress reactive oxygen species production and inflammasome activation in type 2 diabetic patients with pulmonary tuberculosis infection. *MicrobesInfect.* **2015**, *17*, 195–204.
21. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Cusi K, Das SR, Gibbons CH, Giurini JM, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Kosiborod M, Leon J, Lyons SK, Murdock L, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Sun JK, Woodward CC, Young-Hyman D, Gabbay RA, on behalf of the American Diabetes Association. Summary of Revisions: Standards of Care in Diabetes-2023. Diabetes Care. 2023, 46 (Suppl S1), S5-S9.
22. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Das SR, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Kosiborod M, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA, on behalf of the American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. Diabetes Care. 2023 ;46(Suppl 1):S158-S190.
23. Forzano I, Varzideh F, Avvisato R, Jankauskas SS, Mone P, Santulli G. Tirzepatide: A Systematic Update. *Int J Mol Sci.* **2022**, *23*, 14631.
24. Nowak M, Nowak W, Grzeszczak W. Tirzepatide - a dual GIP/GLP-1 receptor agonist - a new antidiabetic drug with potential metabolic activity in the treatment of type 2 diabetes. *Endokrynol Pol.* **2022**, *73*, 745–755.
25. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. *Diabetes ObesMetab.* 2021;23Suppl 3:5-29
26. Nauck MA, Müller TD. Incretin hormones and type 2 diabetes. *Diabetologia.* **2023**, *66*, 1780–1795.
27. Kim SJ, Nian C, McIntosh CH. GIP increases human adipocyte LPL expression through CREB and TORC2-mediated trans-activation of the LPL gene. *J Lipid Res.* **2010**, *51*, 3145–57.
28. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology.* **2007**, *132*, 2131–57.
29. Zhang Q, Delessa CT, Augustin R, Bakhti M, Colldén G, Drucker DJ, Feuchtinger A, Caceres CG, Grandl G, Harger A, Herzig S, Hofmann S, Holleman CL, Jastroch M, Keipert S, Kleinert M, Knerr PJ, Kulaj K, Legutko B, Lickert H, Liu X, Luippold G, Lutter D, Malogajski E, Medina MT, Mowery SA, Blutke A, Perez-Tilve D, Salinno C, Sehrer L, DiMarchi RD, Tschöp MH, Stemmer K, Finan B, Wolfrum C, Müller TD. The

glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. *Cell Metab.* **2021**, *33*, 833-844.e5.
30. Zhao F, Zhou Q, Cong Z, Hang K, Zou X, Zhang C, Chen Y, Dai A, Liang A, Ming Q, Wang M, Chen LN, Xu P, Chang R, Feng W, Xia T, Zhang Y, Wu B, Yang D, Zhao L, Xu HE, Wang MW. Structural insights into multiplexed pharmacological actions of tirzepatide and peptide 20 at the GIP, GLP-1 or glucagon receptors. *Nat Commun.* **2022**, *13*, 1057.
31. Sun B, Willard FS, Feng D, Alsina-Fernandez J, Chen Q, Vieth M, Ho JD, Showalter AD, Stutsman C, Ding L, Suter TM, Dunbar JD, Carpenter JW, Mohammed FA, Aihara E, Brown RA, Bueno AB, Emmerson PJ, Moyers JS, Kobilka TS, Coghlan MP, Kobilka BK, Sloop KW. Structural determinants of dual incretin receptor agonism by tirzepatide. *Proc NatlAcad Sci U S A.* **2022**, *119*, e2116506119
32. Frías JP. Tirzepatide: a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) dual agonist in development for the treatment of type 2 diabetes. *Expert Rev EndocrinolMetab.* **2020**, *15*, 379–394.
33. Heise T, DeVries JH, Urva S, Li J, Pratt EJ, Thomas MK, Mather KJ, Karanikas CA, Dunn J, Haupt A, Milicevic Z, Coskun T. Tirzepatide Reduces Appetite, Energy Intake, and Fat Mass in People With Type 2 Diabetes. *Diabetes Care.* **2023**, *46*, 998–1004.
34. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, Aizenberg D, Wynne AG, Riesmeyer JS, Heine RJ, Wiese RJ; SURPASS-4 Investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet.* **2021**, *398*, 1811–1824.
35. Willard FS, Douros JD, Gabe MB, Showalter AD, Wainscott DB, Suter TM, Capozzi ME, van derVelden WJ, Stutsman C, Cardona GR, Urva S, Emmerson PJ, Holst JJ, D'Alessio DA, Coghlan MP, Rosenkilde MM, Campbell JE, Sloop KW. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight.* **2020**, *5*, e140532.
36. Fisman EZ, Tenenbaum A. The dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide: a novel cardiometabolic therapeutic prospect. *CardiovascDiabetol.* **2021**, *20*, 225.
37. Sinha R, Papamargaritis D, Sargeant JA, Davies MJ. Efficacy and Safety of Tirzepatide in Type 2 Diabetes and Obesity Management. *J ObesMetabSyndr.* **2023**, *32*, 25–45.
38. Lebovitz HE. Thiazolidinediones: the Forgotten Diabetes Medications. *CurrDiab Rep.* **2019**, *19*, 151.
39. Alhowail A, Alsikhan R, Alsaud M, Aldubayan M, Rabbani SI. Protective Effects of Pioglitazone on Cognitive Impairment and the Underlying Mechanisms: A Review of Literature. *Drug Des DevelTher.* **2022**, *16*, 2919–2931.
40. Holm LJ, Mønsted MØ, Haupt-Jorgensen M, Buschard K. PPARs and the Development of Type 1 Diabetes. *PPAR Res.* **2020**, *2020*, 6198628.
41. Menendez-Gutierrez MP, Roszer T, Ricote M. Biology and therapeutic applications of peroxisome proliferator- activated receptors. *Curr Top Med Chem.* **2012**, *12*, 548–84.
42. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, Morel CR, Subramanian V, Mukundan L, Red Eagle A, Vats D, Brombacher F, Ferrante AW, Chawla A. Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. *Nature.* **2007**, *447*, 1116–20.
43. Le Menn G, Neels JG. Regulation of Immune Cell Function by PPARs and the Connection with Metabolic and Neurodegenerative Diseases. *Int J Mol Sci.* **2018**, *19*, 1575.
44. Holm LJ, Krogvold L, Hasselby JP, Kaur S, Claessens LA, Russell MA, Mathews CE, Hanssen KF, Morgan NG, Koeleman BPC, Roep BO, Gerling IC, Pociot F, Dahl-Jørgensen K, Buschard K. Abnormal islet sphingolipid metabolism in type 1 diabetes. *Diabetologia.* **2018**, *61*, 1650–1661. doi: 10.1007/s00125-018-4614-2.
45. Janani C, Ranjitha Kumari BD. PPAR gamma gene--a review. *Diabetes MetabSyndr.* **2015**, *9*, 46–50.
46. Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of PPARgamma. *Annu Rev Biochem.* **2008**, *77*, 289–312.
47. Lebovitz HE, Banerji MA. Insulin resistance and its treatment by thiazolidinediones. *Recent Prog Horm Res.* **2001**, *56*, 265–94.
48. Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, Davis KE, Bikman BT, Halberg N, Rutkowski JM, Wade MR, Tenorio VM, Kuo MS, Brozinick JT, Zhang BB, Birnbaum MJ, Summers SA, Scherer PE. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. *Nat Med.* **2011**, *17*, 55–63.
49. Straub LG, Scherer PE. Metabolic Messengers: Adiponectin. *Nat Metab.* **2019**, *1*, 334–339.
50. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R; American Heart Association; American Diabetes Association. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. Circulation. **2003**, *108*, 2941–8.

51. van der Meer RW, Rijzewijk LJ, de Jong HW, Lamb HJ, Lubberink M, Romijn JA, Bax JJ, de Roos A, Kamp O, Paulus WJ, Heine RJ, Lammertsma AA, Smit JW, Diamant M. Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus. *Circulation.* **2009**, *119*, 2069–77.
52. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes.* **2009**, *58*, 773–95.
53. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *J ClinEndocrinolMetab.* **2004**, *89*, 463–78.
54. Coletta DK, Sriwijitkamol A, Wajcberg E, Tantiwong P, Li M, Prentki M, Madiraju M, Jenkinson CP, Cersosimo E, Musi N, Defronzo RA. Pioglitazone stimulates AMP-activated protein kinase signalling and increases the expression of genes involved in adiponectin signalling, mitochondrial function and fat oxidation in human skeletal muscle in vivo: a randomised trial. *Diabetologia.* **2009**, *52*, 723–32.
55. de Jong M, van derWorp HB, van der Graaf Y, Visseren FLJ, Westerink J. Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials. *CardiovascDiabetol.* **2017**, *16*, 134.
56. Yen CL, Wu CY, Tsai CY, Lee CC, Li YJ, Peng WS, Liu JR, Liu YC, Jenq CC, Yang HY, See LC. Pioglitazone reduces cardiovascular events and dementia but increases bone fracture in elderly patients with type 2 diabetes mellitus: a national cohort study. *Aging (Albany NY).* **2023**, *15*, 2721–2733.
57. Dhankhar S, Chauhan S, Mehta DK, Nitika, Saini K, Saini M, Das R, Gupta S, Gautam V. Novel targets for potential therapeutic use in Diabetes mellitus. *DiabetolMetabSyndr.* **2023**, *15*, 17.
58. Pola S, Shah SR, Pingali H, Zaware P, Thube B, Makadia P, Patel H, Bandyopadhyay D, Rath A, Giri S, Patel JH, Ranvir RK, Sundar SR, Patel H, Kumar J, Jain MR. Discovery of a potent G-protein-coupled receptor 119 agonist for the treatment of type 2 diabetes. *Bioorg Med Chem.* **2021**, *35*, 116071.
59. Weiner J, Zieger K, Pippel J, Heiker JT. Molecular Mechanisms of Vaspin Action - From Adipose Tissue to Skin and Bone, from Blood Vessels to the Brain. *Adv Exp Med Biol.* **2019**, *1111*, 159–188.
60. Miao ZW, Hu WJ, Li ZY, Miao CY. Involvement of the secreted protein Metrnl in human diseases. *ActaPharmacol Sin.* **2020**, *41*, 1525–1530.
61. Roshanzamir F, Miraghajani M, Rouhani MH, Mansourian M, Ghiasvand R, Safavi SM. The association between circulating fetuin-A levels and type 2 diabetes mellitus risk: systematic review and meta-analysis of observational studies. *J Endocrinol Invest.* **2018**, *41*, 33–47.
62. Mok JX, Ooi JH, Ng KY, Koh RY, Chye SM. A new prospective on the role of melatonin in diabetes and its complications. *Horm Mol BiolClinInvestig.* 2019 Nov 6;40(1):/j/hmbci.2019.40.issue-1/hmbci-2019-0036/hmbci-2019-0036.xml.
63. Shah U, Kowalski TJ. GPR119 agonists for the potential treatment of type 2 diabetes and related metabolic disorders. *VitamHorm.* **2010**, *84*, 415–48.
64. Jang YK, Lee KM, Jung KY, Kang SK, Pagire SH, Lee JM, Pagire HS, Kim KR, Bae MA, Lee H, Rhee SD, Ahn JH. Design, synthesis, and biological evaluation of aryl N-methoxyamide derivatives as GPR119 agonists. *Bioorg Med Chem Lett.* **2017**, *27*, 3909–3914.
65. Albrechtsen NJW, Kuhre RE, Deacon CF, Holst JJ. Targeting the intestinal L-cell for obesity and type 2 diabetes treatment. *Expert Rev EndocrinolMetab.* **2014**, *9*, 61–72.
66. Yang JW, Kim HS, Choi YW, Kim YM, Kang KW. Therapeutic application of GPR119 ligands in metabolic disorders. *Diabetes ObesMetab.* **2018**, *20*, 257–269.
67. Shah N, Abdalla MA, Deshmukh H, Sathyapalan T. Therapeutics for type-2 diabetes mellitus: a glance at the recent inclusions and novel agents under development for use in clinical practice. *TherAdvEndocrinolMetab.* **2021**, *12*, 20420188211042145.
68. Kim Y, Lee SW, Wang H, Kim RH, Park HK, Lee H, Kang ES. *DA*-1241, a Novel GPR119 Agonist, Improves Hyperglycaemia by Inhibiting Hepatic Gluconeogenesis and Enhancing Insulin Secretion in Diabetic Mice. *Diabetes Metab J.* **2022**, *46*, 337–348.
69. Kurowska P, Mlyczyńska E, Dawid M, Jurek M, Klimczyk D, Dupont J, Rak A. Review: Vaspin (SERPINA12) Expression and Function in Endocrine Cells. *Cells.* **2021**, *10*, 1710.
70. Dimova R, Tankova T. The role of vaspin in the development of metabolic and glucose tolerance disorders and atherosclerosis. *Biomed Res Int.* **2015**, *2015*, 823481.
71. Carrión M, Frommer KW, Pérez-García S, Müller-Ladner U, Gomariz RP, Neumann E. The Adipokine Network in Rheumatic Joint Diseases. *Int J Mol Sci.* **2019**, *20*, 4091.
72. Feng R, Li Y, Wang C, Luo C, Liu L, Chuo F, Li Q, Sun C. Higher vaspin levels in subjects with obesity and type 2 diabetes mellitus: a meta-analysis. Diabetes Res ClinPract. **2014**, *106*, 88–94.
73. Escoté X, Gómez-Zorita S, López-Yoldi M, Milton-Laskibar I, Fernández-Quintela A, Martínez JA, Moreno-Aliaga MJ, Portillo MP. Role of Omentin, Vaspin, Cardiotrophin-1, TWEAK and NOV/CCN3 in Obesity and Diabetes Development. *Int J Mol Sci.* **2017**, *18*, 1770.

74. Li ZY, Zheng SL, Wang P, Xu TY, Guan YF, Zhang YJ, Miao CY. Subfatin is a novel adipokine and unlike Meteorin in adipose and brain expression. *CNS NeurosciTher.* **2014**, *20*, 344–54.
75. Li ZY, Fan MB, Zhang SL, Qu Y, Zheng SL, Song J, Miao CY. Intestinal Metrnl released into the gut lumen acts as a local regulator for gut antimicrobial peptides. *ActaPharmacol Sin.* **2016**, *37*, 1458–1466.
76. Li ZY, Song J, Zheng SL, Fan MB, Guan YF, Qu Y, Xu J, Wang P, Miao CY. Adipocyte Metrnl Antagonizes Insulin Resistance Through PPARγ Signaling. *Diabetes.* **2015**, *64*, 4011–22.
77. Ushach I, Burkhardt AM, Martinez C, Hevezi PA, Gerber PA, Buhren BA, Schrumpf H, Valle-Rios R, Vazquez MI, Homey B, Zlotnik A. METEORIN-LIKE is a cytokine associated with barrier tissues and alternatively activated macrophages. *ClinImmunol.* **2015**, *156*, 119–27.
78. Dadmanesh M, Aghajani H, Fadaei R, Ghorban K. Lower serum levels of Meteorin-like/Subfatin in patients with coronary artery disease and type 2 diabetes mellitus are negatively associated with insulin resistance and inflammatory cytokines. *PLoS One.* **2018**, *13*, e0204180.
79. El-Ashmawy HM, Selim FO, Hosny TAM, Almassry HN. Association of low serum Meteorin like (Metrnl) concentrations with worsening of glucose tolerance, impaired endothelial function and atherosclerosis. *Diabetes Res ClinPract.* **2019**, *150*, 57–63.
80. Lee JH, Kang YE, Kim JM, Choung S, Joung KH, Kim HJ, Ku BJ. Serum Meteorin-like protein levels decreased in patients newly diagnosed with type 2 diabetes. *Diabetes Res ClinPract.* **2018**, *135*, 7–10.
81. Zhang SL, Li ZY, Wang DS, Xu TY, Fan MB, Cheng MH, Miao CY. Aggravated ulcerative colitis caused by intestinal Metrnl deficiency is associated with reduced autophagy in epithelial cells. *ActaPharmacol Sin.* **2020**, *41*, 763–770.
82. Qi Q, Hu WJ, Zheng SL, Zhang SL, Le YY, Li ZY, Miao CY. Metrnl deficiency decreases blood HDL cholesterol and increases blood triglyceride. *ActaPharmacol Sin.* **2020**, *41*, 1568–1575.
83. Ochieng J, Nangami G, Sakwe A, Moye C, Alvarez J, Whalen D, Thomas P, Lammers P. Impact of Fetuin-A (AHSG) on Tumor Progression and Type 2 Diabetes. *Int J Mol Sci.* **2018**, *19*, 2211.
84. Artunc F, Schleicher E, Weigert C, Fritsche A, Stefan N, Häring HU. The impact of insulin resistance on the kidney and vasculature. *Nat Rev Nephrol.* **2016**, *12*, 721–737.
85. Miura Y, Iwazu Y, Shiizaki K, Akimoto T, Kotani K, Kurabayashi M, Kurosu H, Kuro-O M. Identification and quantification of plasma calciprotein particles with distinct physical properties in patients with chronic kidney disease. *Sci Rep.* **2018**, *8*, 1256.
86. Goustin AS, Abou-Samra AB. The "thrifty" gene encoding Ahsg/Fetuin-A meets the insulin receptor: Insights into the mechanism of insulin resistance. *Cell Signal.* **2011**, *23*, 980–90.
87. Gerst F, Wagner R, Kaiser G, Panse M, Heni M, Machann J, Bongers MN, Sartorius T, Sipos B, Fend F, Thiel C, Nadalin S, Königsrainer A, Stefan N, Fritsche A, Häring HU, Ullrich S, Siegel-Axel D. Metabolic crosstalk between fatty pancreas and fatty liver: effects on local inflammation and insulin secretion. *Diabetologia.* **2017**, *60*, 2240–2251.
88. Ochieng J, Nangami G, Sakwe A, Moye C, Alvarez J, Whalen D, Thomas P, Lammers P. Impact of Fetuin-A (AHSG) on Tumor Progression and Type 2 Diabetes. *Int J Mol Sci.* **2018**, *19*, 2211.
89. Sujana C, Huth C, Zierer A, Meesters S, Sudduth-Klinger J, Koenig W, Herder C, Peters A, Thorand B. Association of fetuin-A with incident type 2 diabetes: results from the MONICA/KORA Augsburg study and a systematic meta-analysis. Eur J Endocrinol. **2018**, *178*, 389–398.
90. Guo VY, Cao B, Cai C, Cheng KK, Cheung BMY. Fetuin-A levels and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. ActaDiabetol. **2018**, *55*, 87–98.
91. Lanthier N, Lebrun V, Molendi-Coste O, van Rooijen N, Leclercq IA. Liver Fetuin-A at Initiation of Insulin Resistance. *Metabolites.* **2022**, *12*, 1023.
92. Sun Q, Cornelis MC, Manson JE, Hu FB. Plasma levels of fetuin-A and hepatic enzymes and risk of type 2 diabetes in women in the U.S. Diabetes. **2013**, *62*, 49–55.
93. Trepanowski JF, Mey J, Varady KA. Fetuin-A: a novel link between obesity and related complications. *Int J Obes (Lond).* **2015**, *39*, 734–41.
94. Wang C, Zhang R, Wei X, Lv M, Jiang Z. Metalloimmunology: The metal ion-controlled immunity. *AdvImmunol.* **2020**, *145*, 187–241.
95. Venter C, Eyerich S, Sarin T, Klatt KC. Nutrition and the Immune System: A Complicated Tango. *Nutrients.* **2020**, *12*, 818.
96. Mayer AB, Trenchard L, Rayns F. Historical changes in the mineral content of fruit and vegetables in the UK from 1940 to 2019: a concern for human nutrition and agriculture. *Int J Food Sci Nutr.* **2022**, *73*, 315–326.
97. Erisman, J.W. Nature-based agriculture for an adequate human microbiome. *Org. Agr.* **2021**, *11*, 225–230.
98. Oghbaei, M. & Prakash J. Effect of primary processing of cereals and legumes on its nutritional quality: a comprehensive review. *Cogent Food Agric.* **2016**, *2*, 1136015.
99. Whitfield KC, Smith TJ, Rohner F, Wieringa FT, Green TJ. Thiamine fortification strategies in low- and middle-income settings: a review. *Ann N Y Acad Sci.* **2021**, *1498*, 29–45.
100. Maharaj PP, Prasad S, Devi R, Gopalan R. Folate content and retention in commonly consumed vegetables in the South Pacific. *Food Chem.* **2015**, *182*, 327–32.

101. Alghamdi M, Gutierrez J, Komarnytsky S. Essential Minerals and Metabolic Adaptation of Immune Cells. *Nutrients.* **2022**, *15*, 123.
102. Fiorentini D, Cappadone C, Farruggia G, Prata C. Magnesium: Biochemistry, Nutrition, Detection, and Social Impact of Diseases Linked to Its Deficiency. *Nutrients.* **2021**, *13*, 1136.
103. Ashique S, Kumar S, Hussain A, Mishra N, Garg A, Gowda BHJ, Farid A, Gupta G, Dua K, Taghizadeh-Hesary F. A narrative review on the role of magnesium in immune regulation, inflammation, infectious diseases, and cancer. *J Health PopulNutr.* **2023**, *42*, 74.
104. Chu N, Chan TY, Chu YK, Ling J, He J, Leung K, Ma RCW, Chan JCN, Chow E. Higher dietary magnesium and potassium intake are associated with lower body fat in people with impaired glucose tolerance. *Front Nutr.* **2023**, *10*, 1169705.
105. Pelczyńska M, Moszak M, Bogdański P. The Role of Magnesium in the Pathogenesis of Metabolic Disorders. *Nutrients.* **2022**, *14*, 1714.
106. Weyh C, Krüger K, Peeling P, Castell L. The Role of Minerals in the Optimal Functioning of the Immune System. *Nutrients.* **2022**, *14*, 644.
107. Dubey P, Thakur V, Chattopadhyay M. Role of Minerals and Trace Elements in Diabetes and Insulin Resistance. *Nutrients.* **2020**, *12*, 1864.
108. Kheriji N, Boukhalfa W, Mahjoub F, Hechmi M, Dakhlaoui T, Mrad M, Hadj SalahBahlous A, Ben Amor N, Jamoussi H, Kefi R. The Role of Dietary Intake in Type 2 Diabetes Mellitus: Importance of Macro and Micronutrients in Glucose Homeostasis. *Nutrients.* **2022**, *14*, 2132.
109. Feng J, Wang H, Jing Z, Wang Y, Cheng Y, Wang W, Sun W. Role of Magnesium in Type 2 Diabetes Mellitus. *Biol Trace Elem Res.* **2020**, *196*, 74–85.
110. Liu M, Jeong EM, Liu H, Xie A, So EY, Shi G, Jeong GE, Zhou A, Dudley SC Jr. Magnesium supplementation improves diabetic mitochondrial and cardiac diastolic function. *JCI Insight.* **2019**, *4*, e123182.
111. Rooney MR, Pankow JS, Sibley SD, Selvin E, Reis JP, Michos ED, Lutsey PL. Serum calcium and incident type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Am J ClinNutr.* **2016**, *104*, 1023–1029.
112. Humbert A, Lefebvre R, Nawrot M, Caussy C, Rieusset J. Calcium signalling in hepatic metabolism: Health and diseases. *Cell Calcium.* **2023**, *114*, 102780.
113. Arruda AP, Hotamisligil GS. Calcium Homeostasis and Organelle Function in the Pathogenesis of Obesity and Diabetes. *Cell Metab.* **2015**, *22*, 381–97.
114. Kim KN, Oh SY, Hong YC. Associations of serum calcium levels and dietary calcium intake with incident type 2 diabetes over 10 years: the Korean Genome and Epidemiology Study (KoGES). DiabetolMetabSyndr. **2018**, *10*, 50.
115. Park YJ, Yoo SA, Kim M, Kim WU. The Role of Calcium-Calcineurin-NFAT Signaling Pathway in Health and Autoimmune Diseases. *Front Immunol.* **2020**, *11*, 195.
116. Wongdee K, Krishnamra N, Charoenphandhu N. Derangement of calcium metabolism in diabetes mellitus: negative outcome from the synergy between impaired bone turnover and intestinal calcium absorption. *J Physiol Sci.* **2017**, *67*, 71–81.
117. Yanni AE, Kartsioti K, Karathanos VT. The role of yoghurt consumption in the management of type II diabetes. *Food Funct.* **2020**, *11*, 10306–10316.
118. Tan M, He FJ, Wang C, MacGregor GA. Twenty-Four-Hour Urinary Sodium and Potassium Excretion in China: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* **2019**, *8*, e012923.
119. Stone MS, Martyn L, Weaver CM. Potassium Intake, Bioavailability, Hypertension, and Glucose Control. *Nutrients.* **2016**, *8*, 444.
120. Weir MR, Espaillat R. Clinical perspectives on the rationale for potassium supplementation. *Postgrad Med.* **2015**, *127*, 539–48.
121. Ekmekcioglu C, Elmadfa I, Meyer AL, Moeslinger T. The role of dietary potassium in hypertension and diabetes. *J Physiol Biochem.* **2016**, *72*, 93–106.
122. Do EA, Gries CM. Beyond Homeostasis: Potassium and Pathogenesis during Bacterial Infections. *Infect Immun.* **2021**, *89*, e0076620.
123. Chatterjee, R.; Biggs, M.L.; de Boer, I.H.; Brancati, F.L.; Svetkey, L.P.; Barzilay, J.; Djoussé, L.; Ix, J.H.; Kizer, J.R.; Siscovick, D.S.; et al. Potassium and Glucose Measures in Older Adults: The Cardiovascular Health Study. *J. Gerontol. A Biol. Sci. Med. Sci.***2015**, *70*, 255–261.
124. Brandão-Lima PN, Carvalho GB, Santos RKF, Santos BDC, Dias-Vasconcelos NL, Rocha VS, Barbosa KBF, Pires LV. Intakes of Zinc, Potassium, Calcium, and Magnesium of Individuals with Type 2 Diabetes Mellitus and the Relationship with Glycemic Control. *Nutrients.* **2018**, *10*, 1948.
125. Wang X, Ma H, Kou M, Tang R, Xue Q, Li X, Harlan TS, Heianza Y, Qi L. Dietary Sodium Intake and Risk of Incident Type 2 Diabetes. *Mayo Clin Proc.* 2023 :S0025-6196(23)00118-0.
126. Ming L, Wang D, Zhu Y. Association of sodium intake with diabetes in adults without hypertension: evidence from the National Health and Nutrition Examination Survey 2009-2018. *Front Public Health.* **2023**, *11*, 1118364.

127. Schatz V, Neubert P, Schröder A, Binger K, Gebhard M, Müller DN, Luft FC, Titze J, Jantsch J. Elementary immunology: Na+ as a regulator of immunity. *PediatrNephrol.* **2017**, *32*, 201–210.
128. Suckling RJ, He FJ, Markandu ND, MacGregor GA. Modest Salt Reduction Lowers Blood Pressure and Albumin Excretion in Impaired Glucose Tolerance and Type 2 Diabetes Mellitus: A Randomized Double-Blind Trial. *Hypertension.* **2016**, *67*, 1189–95.
129. Calvo MS, Uribarri J. Public health impact of dietary phosphorus excess on bone and cardiovascular health in the general population. *Am J ClinNutr.* **2013**, *98*, 6–15.
130. Mancini FR, Affret A, Dow C, Balkau B, Clavel-Chapelon F, Bonnet F, Boutron-Ruault MC, Fagherazzi G. High dietary phosphorus intake is associated with an increased risk of type 2 diabetes in the large prospective E3N cohort study. *ClinNutr.* **2018**, *37*, 1625–1630.
131. Hill CR, Shafaei A, Balmer L, Lewis JR, Hodgson JM, Millar AH, Blekkenhorst LC. Sulfur compounds: From plants to humans and their role in chronic disease prevention. *Crit Rev Food Sci Nutr.* **2023**, *63*, 8616–8638.
132. Dong Z, Richie JP Jr, Gao X, Al-Shaar L, Nichenametla SN, Shen B, Orentreich D. Cumulative Consumption of Sulfur Amino Acids and Risk of Diabetes: A Prospective Cohort Study. *J Nutr.* **2022**, *152*, 2419–2428.
133. Ke Q, Chen C, He F, Ye Y, Bai X, Cai L, Xia M. Association between dietary protein intake and type 2 diabetes varies by dietary pattern. *DiabetolMetabSyndr.* **2018**, *10*, 48.
134. Tesseraud S, MetayerCoustard S, Collin A, Seiliez I Role of sulfur amino acids in controlling nutrient metabolism and cell functions: implications for nutrition. *Br J Nutr* **2009**, *101*, 1132–1139
135. Dong Z, Gao X, Chinchilli VM, Sinha R, Muscat J, Winkels RM, Richie JP Jr. Association of sulfur amino acid consumption with cardiometabolic risk factors: Cross-sectional findings from NHANES III. *EClinicalMedicine.* **2020**, *19*, 100248.
136. Dubey P, Thakur V, Chattopadhyay M. Role of Minerals and Trace Elements in Diabetes and Insulin Resistance. *Nutrients.* **2020**, *12*, 1864.
137. Maywald M, Rink L. Zinc in Human Health and Infectious Diseases. *Biomolecules.* **2022**, *12*, 1748
138. Davidson HW, Wenzlau JM, O'Brien RM. Zinc transporter 8 (ZnT8) and β cell function. *Trends Endocrinol Metab.* **2014**, *25*, 415–24.
139. Skalny AV, Aschner M, Tinkov AA. *Zinc. Adv Food Nutr Res.* **2021**, *96*, 251–310.
140. Wijesekara N, Dai FF, Hardy AB, Giglou PR, Bhattacharjee A, Koshkin V, Chimienti F, Gaisano HY, Rutter GA, Wheeler MB. Beta cell-specific Znt8 deletion in mice causes marked defects in insulin processing, crystallisation and secretion. *Diabetologia.* **2010**, *53*, 1656–68.
141. Adulcikas J, Sonda S, Norouzi S, Sohal SS, Myers S. Targeting the Zinc Transporter ZIP7 in the Treatment of Insulin Resistance and Type 2 Diabetes. *Nutrients.* **2019**, *11*, 408.
142. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients.* **2020**, *12*, 236.
143. Zhang F, Li X, Wei Y. Selenium and Selenoproteins in Health. *Biomolecules.* **2023**, *13*, 799.
144. Steinbrenner H, Duntas LH, Rayman MP. The role of selenium in type-2 diabetes mellitus and its metabolic comorbidities. *Redox Biol.* **2022**, *50*, 102236.
145. Kim J, Chung HS, Choi MK, Roh YK, Yoo HJ, Park JH, Kim DS, Yu JM, Moon S. Association between Serum Selenium Level and the Presence of Diabetes Mellitus: A Meta-Analysis of Observational Studies. *Diabetes Metab J.* **2019**, *43*, 447–460. doi: 10.4093/dmj.2018.0123. Epub 2019 . PMID: 30688047; PMCID: PMC6712224.
146. Zhou J, Huang K, Lei XG. Selenium and diabetes-evidence from animal studies. *Free RadicBiol Med.* **2013**, *65*, 1548–1556.
147. McClung JP, Roneker CA, Mu W, Lisk DJ, Langlais P, Liu F, Lei XG. Development of insulin resistance and obesity in mice overexpressing cellular glutathione peroxidase. *Proc Natl Acad Sci U S A.* **2004**, *101*, 8852–7.
148. Weyh C, Krüger K, Peeling P, Castell L. The Role of Minerals in the Optimal Functioning of the Immune System. *Nutrients.* **2022**, *14*, 644.
149. Ni S, Yuan Y, Kuang Y, Li X. Iron Metabolism and Immune Regulation. *Front Immunol.* **2022**, *13*, 816282.
150. Frost JN, Tan TK, Abbas M, Wideman SK, Bonadonna M, Stoffel NU, Wray K, Kronsteiner B, Smits G, Campagna DR, Duarte TL, Lopes JM, Shah A, Armitage AE, Arezes J, Lim PJ, Preston AE, Ahern D, Teh M, Naylor C, Salio M, Gileadi U, Andrews SC, Dunachie SJ, Zimmermann MB, van der Klis FRM, Cerundolo V, Bannard O, Draper SJ, Townsend ARM, Galy B, Fleming MD, Lewis MC, Drakesmith H. Hepcidin-Mediated Hypoferremia Disrupts Immune Responses to Vaccination and Infection. *Med.* **2021**, *2*, 164-179.e12.
151. Jabara HH, Boyden SE, Chou J, Ramesh N, Massaad MJ, Benson H, Bainter W, Fraulino D, Rahimov F, Sieff C, Liu ZJ, Alshemmari SH, Al-Ramadi BK, Al-Dhekri H, Arnaout R, Abu-Shukair M, Vatsayan A, Silver E, Ahuja S, Davies EG, Sola-Visner M, Ohsumi TK, Andrews NC, Notarangelo LD, Fleming MD, Al-Herz W, Kunkel LM, Geha RS. A missense mutation in TFRC, encoding transferrin receptor 1, causes combined immunodeficiency. *Nat Genet.* **2016**, *48*, 74–8.
152. Harrison AV, Lorenzo FR, McClain DA. Iron and the Pathophysiology of Diabetes. *Annu Rev Physiol.* **2023**, *85*, 339–362. doi: 10.1146/annurev-physiol-022522-102832.

 doi:10.20944/preprints202402.0674.v1

153. Cooksey RC, Jouihan HA, Ajioka RS, Hazel MW, Jones DL, Kushner JP, McClain DA. Oxidative stress, beta-cell apoptosis, and decreased insulin secretory capacity in mouse models of hemochromatosis. *Endocrinology.* **2004**, *145*, 5305–12.
154. Liu J, Li Q, Yang Y, Ma L. Iron metabolism and type 2 diabetes mellitus: A meta-analysis and systematic review. *J Diabetes Investig*. **2020**, *11*, 946–955.
155. Zhuang T, Han H, Yang Z. Iron, oxidative stress and gestational diabetes. *Nutrients.* **2014**, *6*, 3968–80.
156. Basuli D, Stevens RG, Torti FM, Torti SV. Epidemiological associations between iron and cardiovascular disease and diabetes. *Front Pharmacol.* **2014**, *5*, 117.
157. Aceves C, Mendieta I, Anguiano B, Delgado-González E. Molecular Iodine Has Extrathyroidal Effects as an Antioxidant, Differentiator, and Immunomodulator. *Int J Mol Sci.* **2021**, *22*, 1228.
158. Sun Z, Wang X, Chen J, Duan P, Wang J, Liu Y, Guo H. [Effects of iodine excess on islet β cells(β-TC-6) function and the mechanism]. Wei Sheng Yan Jiu. **2017**, *46*, 610–614.
159. Al-Attas OS, Al-Daghri NM, Alkharfy KM, Alokail MS, Al-Johani NJ, Abd-Alrahman SH, Yakout SM, Draz HM, Sabico S. Urinary iodine is associated with insulin resistance in subjects with diabetes mellitus type 2. Exp Clin Endocrinol Diabetes. **2012**, *120*, 618–22.
160. Anil C, Akkurt A, Ayturk S, Kut A, Gursoy A. Impaired glucose metabolism is a risk factor for increased thyroid volume and nodule prevalence in a mild-to-moderate iodine deficient area. *Metabolism.* **2013**, *62*, 970–5.
161. Besold AN, Culbertson EM, Culotta VC. The Yin and Yang of copper during infection. *J BiolInorg Chem.* **2016**, *21*, 137–44.
162. Solomon EI, Heppner DE, Johnston EM, Ginsbach JW, Cirera J, Qayyum M, Kieber-Emmons MT, Kjaergaard CH, Hadt RG, Tian L. Copper active sites in biology. *Chem Rev.* **2014**, *114*, 3659–853.
163. Eckersall PD, Saini PK, McComb C. The acute phase response of acid soluble glycoprotein, alpha(1)-acid glycoprotein, ceruloplasmin, haptoglobin and C-reactive protein, in the pig. *Vet Immunol Immunopathol.* 1996 ;51(3-4):377-85.
164. Raha S, Mallick R, Basak S, Duttaroy AK. Is copper beneficial for COVID-19 patients? Med Hypotheses. 2020; 142:109814.
165. Eshak ES, Iso H, Maruyama K, Muraki I, Tamakoshi A. Associations between dietary intakes of iron, copper and zinc with risk of type 2 diabetes mellitus: A large population-based prospective cohort study. *Clin Nutr.* **2018**, *37*, 667–674.
166. Cui Z, Zhou H, Liu K, Wu M, Li S, Meng S, Meng H. Dietary Copper and Selenium Intakes and the Risk of Type 2 Diabetes Mellitus: Findings from the China Health and Nutrition Survey. *Nutrients.* **2022**, *14*, 2055.
167. Miyazaki T, Takenaka T, Inoue T, Sato M, Miyajima Y, Nodera M, Hanyu M, Ohno Y, Shibazaki S, Suzuki H. Lipopolysaccharide-induced overproduction of nitric oxide and overexpression of iNOS and interleukin-1β proteins in zinc-deficient rats. *Biol Trace Elem Res.* **2012**, *145*, 375–81.
168. Eljazzar S, Abu-Hijleh H, Alkhatib D, Sokary S, Ismail S, Al-Jayyousi GF, Tayyem R. The Role of Copper Intake in the Development and Management of Type 2 Diabetes: A Systematic Review. *Nutrients.* **2023**, *15*, 1655.
169. Lian S, Zhang T, Yu Y, Zhang B. Relationship of Circulating Copper Level with Gestational Diabetes Mellitus: a Meta-Analysis and Systemic Review. *Biol Trace Elem Res.* **2021**, *199*, 4396–4409.
170. Leyssens L, Vinck B, Van Der Straeten C, Wuyts F, Maes L. Cobalt toxicity in humans-A review of the potential sources and systemic health effects. *Toxicology.* **2017**, *387*, 43–56.
171. Szade A, Szade K, Nowak WN, Bukowska-Strakova K, Muchova L, Gońka M, Żukowska M, Cieśla M, Kachamakova-Trojanowska N, Rams-Baron M, Ratuszna A, Dulak J, Józkowicz A. Cobalt protoporphyrin IX increases endogenous G-CSF and mobilizes HSC and granulocytes to the blood. *EMBO Mol Med.* 2019;11, e09571.
172. Czarnek K, Terpiłowska S, Siwicki AK. Selected aspects of the action of cobalt ions in the human body. *Cent Eur J Immunol.* **2015**, *40*, 236–42.
173. Saker F, Ybarra J, Leahy P, Hanson RW, Kalhan SC, Ismail-Beigi F. Glycemia-lowering effect of cobalt chloride in the diabetic rat: role of decreased gluconeogenesis. *Am J Physiol.* 1998;274, E984-91.
174. Cao J, Vecoli C, Neglia D, Tavazzi B, Lazzarino G, Novelli M, Masiello P, Wang YT, Puri N, Paolocci N, L'abbate A, Abraham NG. Cobalt-Protoporphyrin Improves Heart Function by Blunting Oxidative Stress and Restoring NO Synthase Equilibrium in an Animal Model of Experimental Diabetes. *Front Physiol.* **2012**, *3*, 160.
175. Shrivastava R, Upreti RK, Seth PK, Chaturvedi UC. Effects of chromium on the immune system. *FEMS Immunol Med Microbiol.* **2002**, *34*, 1–7.
176. Anderson RA, Polansky MM, Bryden NA, Roginski EE, Mertz W, Glinsmann W. Chromium supplementation of human subjects: effects on glucose, insulin, and lipid variables. *Metabolism.* **1983**, *32*, 894–9.
177. Anderson RA. Nutritional factors influencing the glucose/insulin system: chromium. *J Am CollNutr.* **1997**, *16*, 404–10.

178. Rajendran K, Manikandan S, Nair LD, Karuthodiyil R, Vijayarajan N, Gnanasekar R, Kapil VV, Mohamed AS. Serum Chromium Levels in Type 2 Diabetic Patients and Its Association with Glycaemic Control. *J ClinDiagn Res.* 2015;9, OC05-8.
179. Horning KJ, Caito SW, Tipps KG, Bowman AB, Aschner M. Manganese Is Essential for Neuronal Health. *Annu Rev Nutr.* **2015**, *35*, 71–108.
180. Waldron KJ, Rutherford JC, Ford D, Robinson NJ. Metalloproteins and metal sensing. *Nature.* **2009**, *460*, 823–30.
181. Lv M, Chen M, Zhang R, Zhang W, Wang C, Zhang Y, Wei X, Guan Y, Liu J, Feng K, Jing M, Wang X, Liu YC, Mei Q, Han W, Jiang Z. Manganese is critical for antitumor immune responses via cGAS-STING and improves the efficacy of clinical immunotherapy. *Cell Res.* **2020**, *30*, 966–979.
182. Zabłocka-Słowińska K, Grajeta H. The role of manganese in etiopathogenesis and prevention of selected diseases. *PostepyHig Med Dosw (Online).* **2012**, *66*, 549–53.
183. Anetor JI, Asiribo OA, Adedapo KS, Akingbola TS, Olorunnisola OS, Adeniyi FA. Increased plasma manganese, partially reduced ascorbate, 1 and absence of mitochondrial oxidative stress in type 2 diabetes mellitus: implications for the superoxide uncoupling protein 2 (UCP-2) pathway. *Biol Trace Elem Res.* 2007 Winter;120(1-3):19-27.
184. Jomova K, Makova M, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Rhodes CJ, Valko M. Essential metals in health and disease. *Chem Biol Interact.* **2022**, *367*, 110173.
185. Mendel RR. The molybdenum cofactor. *J Biol Chem.* **2013**, *288*, 13165–72.
186. Schwarz G, Mendel RR, Ribbe MW. Molybdenum cofactors, enzymes and pathways. *Nature.* **2009**, *460*, 839–47.
187. Johannes L, Fu CY, Schwarz G. Molybdenum Cofactor Deficiency in Humans. *Molecules.* **2022**, *27*, 6896.
188. Gengelbach GP, Spears JW. Effects of dietary copper and molybdenum on copper status, cytokine production, and humoral immune response of calves. *J Dairy Sci.* **1998**, *81*, 3286–92.
189. Chen L, Liu J, Zhang Y, Zhang G, Kang Y, Chen A, Feng X, Shao L. The toxicity of silica nanoparticles to the immune system. *Nanomedicine (Lond).* **2018**, *13*, 1939–1962.
190. Mitra S, Paul S, Roy S, Sutradhar H, Bin Emran T, Nainu F, Khandaker MU, Almalki M, Wilairatana P, Mubarak MS. Exploring the Immune-Boosting Functions of Vitamins and Minerals as Nutritional Food Bioactive Compounds: A Comprehensive Review. *Molecules.* **2022**, *27*, 555.
191. Basu TK, Basualdo C. Vitamin A homeostasis and diabetes mellitus. *Nutrition.* **1997**, *13*, 804–6.
192. Mutlu A, Mutlu GY, Özsu E, Çizmecioğlu FM, Hatun Ş. Vitamin D deficiency in children and adolescents with type 1 diabetes. *J Clin Res Pediatr Endocrinol.* **2011**, *3*, 179–83.
193. Gupta S, Sharma TK, Kaushik GG, Shekhawat VP. Vitamin E supplementation may ameliorate oxidative stress in type 1 diabetes mellitus patients. *Clin Lab.* **2011**, *57*, 379–86.
194. Bizzaro G, Antico A, Fortunato A, Bizzaro N. Vitamin D and Autoimmune Diseases: Is Vitamin D Receptor (VDR) Polymorphism the Culprit? *Isr Med Assoc J.* **2017**, *19*, 438–443.
195. White JH. Vitamin D metabolism and signaling in the immune system. *Rev Endocr Metab Disord.* **2012**, *13*, 21–9.
196. Sîrbe C, Rednic S, Grama A, Pop TL. An Update on the Effects of Vitamin D on the Immune System and Autoimmune Diseases. *Int J Mol Sci.* **2022**, *23*, 9784.
197. Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Dal Cin E, Allavena P, Di Carlo V. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. *J Immunol.* **2000**, *164*, 4443–51.
198. Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol.* **2000**, *164*, 2405–11.
199. Bastos TSB, Braga TT, Davanso MR. Vitamin D and Omega-3 Polyunsaturated Fatty Acids in Type 1 Diabetes Modulation. *Endocr Metab Immune Disord Drug Targets.* **2022**, *22*, 815–833.
200. Habibian N, Amoli MM, Abbasi F, Rabbani A, Alipour A, Sayarifard F, Rostami P, Dizaji SP, Saadati B, Setoodeh A. Role of vitamin D and vitamin D receptor gene polymorphisms on residual beta cell function in children with type 1 diabetes mellitus. *Pharmacol Rep.* **2019**, *71*, 282–288.
201. Wu J, Atkins A, Downes M, Wei Z. Vitamin D in Diabetes: Uncovering the Sunshine Hormone's Role in Glucose Metabolism and Beyond. *Nutrients.* **2023**, *15*, 1997.
202. Yu J, Sharma P, Girgis CM, Gunton JE. Vitamin D and Beta Cells in Type 1 Diabetes: A Systematic Review. *Int J Mol Sci.* **2022**, *23*, 14434.
203. Hafez M, Musa N, Abdel Atty S, Ibrahem M, Abdel Wahab N. Effect of Vitamin D Supplementation on Lipid Profile in Vitamin D-Deficient Children with Type 1 Diabetes and Dyslipidemia. *Horm Res Paediatr.* **2019**, *91*, 311–318.
204. Sacerdote A, Dave P, Lokshin V, Bahtiyar G. Type 2 Diabetes Mellitus, Insulin Resistance, and Vitamin D. *Curr Diab Rep.* **2019**, *19*, 101.
205. Brigelius-Flohé R, Traber MG. Vitamin E: function and metabolism. *FASEB J.* **1999**, *13*, 1145–55.
206. Birringer M, Lorkowski S. Vitamin E: Regulatory role of metabolites. *IUBMB Life.* **2019**, *71*, 479–486.

 doi:10.20944/preprints202402.0674.v1

207. Jin Z, Sun J, Zhang W. Effect of Vitamin E on Diabetic Nephropathy: A Meta-Analysis. *Altern Ther Health Med*. 2024 :AT9982. Epub ahead of print.
208. Mehvari F, Imanparast F, Mohaghegh P, Alimoradian A, Khansari N, Ansari Asl B, Khosrowbeygi A. Protective effects of paraoxonase-1, vitamin E and selenium, and oxidative stress index on the susceptibility of low density lipoprotein to oxidation in diabetic patients with/without coronary artery disease. *Eur J Med Res.* **2023**, *28*, 300.
209. Carr AC, Maggini S. Vitamin C and Immune Function. *Nutrients.* **2017**, *9*, 1211.
210. Badawi A, Klip A, Haddad P, Cole DE, Bailo BG, El-Sohemy A, Karmali M. Type 2 diabetes mellitus and inflammation: Prospects for biomarkers of risk and nutritional intervention. *Diabetes Metab Syndr Obes.* **2010**, *3*, 173–86.
211. Grzebyk E, Piwowar A. Inhibitory actions of selected natural substances on formation of advanced glycation endproducts and advanced oxidation protein products. *BMC Complement Altern Med.* **2016**, *16*, 381.
212. Afkhami-Ardekani M, Shojaoddiny-Ardekani A. Effect of vitamin C on blood glucose, serum lipids & serum insulin in type 2 diabetes patients. *Indian J Med Res.* **2007**, *126*, 471–4.
213. Frank LL. Thiamin in Clinical Practice. *JPEN J Parenter Enteral Nutr.* **2015**, *39*, 503–20.
214. Muley A, Fernandez R, Green H, Muley P. Effect of thiamine supplementation on glycaemic outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. BMJ Open. **2022**, *12*, e059834.
215. Mascolo E, Vernì F. Vitamin B6 and Diabetes: Relationship and Molecular Mechanisms. *Int J Mol Sci.* **2020**, *21*, 3669.
216. Mascolo E, Vernì F. Vitamin B6 and Diabetes: Relationship and Molecular Mechanisms. *Int J Mol Sci.* **2020**, *21*, 3669.
217. Cigolini M, Iagulli MP, Miconi V, Lorenzi T, Lombardi S, Targher G. Inflammatory variables may mediate the link between low plasma vitamin B6 concentrations and cardiovascular disease in type 2 diabetes. *Nutr Metab Cardiovasc Dis.* 2006;16, e9-e10.
218. Halczuk K, Kaźmierczak-Barańska J, Karwowski BT, Karmańska A, Cieślak M. Vitamin B12-Multifaceted In Vivo Functions and In Vitro Applications. *Nutrients.* **2023**, *15*, 2734.
219. Reynolds E. Vitamin B12, folic acid, and the nervous system. *Lancet Neurol.* **2006**, *5*, 949–60.
220. Yadav A, Jyoti S, Mehta RK, Parajuli SB. Vitamin B12 Deficiency among Metformin Treated Type 2 Diabetic Mellitus Patients Visiting the Department of Medicine of a Tertiary Care Centre. *JNMA J Nepal Med Assoc.* **2023**, *61*, 861–3.
221. Tiwari A, Kumar Singh R, Satone PD, Meshram RJ. Metformin-Induced Vitamin B12 Deficiency in Patients With Type-2 Diabetes Mellitus. *Cureus.* **2023**, *15*, e47771.
222. Valdés-Ramos R, Guadarrama-López AL, Martínez-Carrillo BE, Benítez-Arciniega AD. Vitamins and type 2 diabetes mellitus. *Endocr Metab Immune Disord Drug Targets.* **2015**, *15*, 54–63.
223. Elmadfa I, Meyer AL. The Role of the Status of Selected Micronutrients in Shaping the Immune Function. *Endocr Metab Immune Disord Drug Targets.* **2019**, *19*, 1100–1115.
224. Title LM, Ur E, Giddens K, McQueen MJ, Nassar BA. Folic acid improves endothelial dysfunction in type 2 diabetes--an effect independent of homocysteine-lowering. Vasc Med. **2006**, *11*, 101–9.
225. Alian Z, Hashemipour M, Dehkordi EH, Hovsepian S, Amini M, Moadab MH, Javanmard SH. The effects of folic acid on markers of endothelial function in patients with type 1 diabetes mellitus. *Med Arh.* **2012**, *66*, 12–5.
226. Asbaghi O, Ashtary-Larky D, Bagheri R, Moosavian SP, Olyaei HP, Nazarian B, Rezaei Kelishadi M, Wong A, Candow DG, Dutheil F, Suzuki K, Alavi Naeini A. Folic Acid Supplementation Improves Glycemic Control for Diabetes Prevention and Management: A Systematic Review and Dose-Response Meta-Analysis of Randomized Controlled Trials. *Nutrients.* **2021**, *13*, 2355.
227. Fatahi S, Pezeshki M, Mousavi SM, Teymouri A, Rahmani J, Kord Varkaneh H, Ghaedi E. Effects of folic acid supplementation on C-reactive protein: A systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis.* **2019**, *29*, 432–439.
228. Brownlee, M. The Pathobiology of Diabetic Complications. *Diabetes* **2005**, *54*, 1615–1625
229. Wright, E.; Scism-Bacon, J.L.; Glass, L.C. Oxidative Stress in Type 2 Diabetes: The Role of Fasting and Postprandial Glycaemia: Oxidative Stress in Type 2 Diabetes. *Int. J. Clin. Pract.* **2006**, *60*, 308–314
230. Papachristoforou, E.; Lambadiari, V.; Maratou, E.; Makrilakis, K. Association of Glycemic Indices (Hyperglycemia, Glucose Variability, and Hypoglycemia) with Oxidative Stress and Diabetic Complications. *J. Diabetes Res.* **2020**, *2020*, 1–17,
231. Shen, Q.; Pierce, J. Supplementation of Coenzyme Q10 among Patients with Type 2 Diabetes Mellitus. *Healthcare* **2015**, *3*, 296–309
232. Renke G, Pereira MB, Renke A. Coenzyme Q10 for Diabetes and Cardiovascular Disease: Useful or Useless? Curr Diabetes Rev. 2023;19, e290422204261.
233. Weber, C.; Bysted, A.; Hølmer, G. Coenzyme Q10 in the Diet-Daily Intake and Relative Bioavailability. *Mol. Aspects Med.* **1997**, *18*, 251–254

234. Bhagavan, H.N.; Chopra, R.K. Coenzyme Q10: Absorption, Tissue Uptake, Metabolism and Pharmacokinetics. *Free Radic. Res.* **2006**, *40*, 445–453
235. El-ghoroury, E.A.; Raslan, H.M.; Badawy, E.A.; El-Saaid, G.S.; Agybi, M.H.; Siam, I.; Salem, S.I. Malondialdehyde and Coenzyme Q10 in Platelets and Serum in Type 2 Diabetes Mellitus: Correlation with Glycemic Control. Blood Coagul. *Fibrinolysis* **2009**, *20*, 248
236. Hodgson, J.; Watts, G.; Playford, D.; Burke, V.; Croft, K. Coenzyme Q10 Improves Blood Pressure and Glycaemic Control: A Controlled Trial in Subjects with Type 2 Diabetes. *Eur. J. Clin. Nutr.* **2002**, *56*, 1137–1142
237. Mehrdadi, P.; Kolahdouz Mohammadi, R.; Alipoor, E.; Eshraghian, M.; Esteghamati, A.; Hosseinzadeh-Attar, M. The Effect of Coenzyme Q10 Supplementation on Circulating Levels of Novel Adipokine Adipolin/CTRP12 in Overweight and Obese Patients with Type 2 Diabetes. *Exp. Clin. Endocrinol. Diabetes* **2016**, *125*, 156–162
238. Yen, C.-H.; Chu, Y.-J.; Lee, B.-J.; Lin, Y.-C.; Lin, P.-T. Effect of Liquid Ubiquinol Supplementation on Glucose, Lipids and Antioxidant Capacity in Type 2 Diabetes Patients: A Double-Blind, Randomised, Placebo-Controlled Trial. *Br. J. Nutr.* **2018**, *120*, 57–63
239. Liang, Y.; Zhao, D.; Ji, Q.; Liu, M.; Dai, S.; Hou, S.; Liu, Z.; Mao, Y.; Tian, Z.; Yang, Y. Effects of Coenzyme Q10 Supplementation on Glycemic Control: A GRADE-Assessed Systematic Review and Dose-Response Meta-Analysis of Randomized Controlled Trials. *eClinicalMedicine* **2022**, *52*, 101602
240. Chew, G.T.; Watts, G.F. Coenzyme Q10 and Diabetic Endotheliopathy: Oxidative Stress and the "Recoupling Hypothesis." QJM **2004**, *97*, 537–548,
241. Hamilton, S.J.; Chew, G.T.; Watts, G.F. Coenzyme Q10 Improves Endothelial Dysfunction in Statin-Treated Type 2 Diabetic Patients. *Diabetes Care* **2009**, *32*, 810–812.
242. Mortensen, S.A.; Rosenfeldt, F.; Kumar, A.; Dolliner, P.; Filipiak, K.J.; Pella, D.; Alehagen, U.; Steurer, G.; Littarru, G.P. The Effect of Coenzyme Q10 on Morbidity and Mortality in Chronic Heart Failure: Results From Q-SYMBIO: A Randomized Double-Blind Trial. *JACC Heart Fail.* **2014**, *2*, 641–649
243. Hernández-Ojeda, J.; Cardona-Muñoz, E.G.; Román-Pintos, L.M.; Troyo-Sanromán, R.; Ortiz-Lazareno, P.C.; Cárdenas-Meza, M.A.; Pascoe-González, S.; Miranda-Díaz, A.G. The Effect of Ubiquinone in Diabetic Polyneuropathy: A Randomized Double-Blind Placebo-Controlled Study. *J. Diabetes Complications* **2012**, *26*, 352–358
244. Reed, L. J., DeBusk, B. G., Gunsalus, I. C., & Hornberger Jr, C. S. (1951). Crystalline α-lipoic acid: a catalytic agent associated with pyruvate dehydrogenase. Science, 114(2952), 93-94.
245. Brookes, M. H., Golding, B. T., Howes, D. A., & Hudson, A. T. (1983). Proof that the absolute configuration of natural α-lipoic acid is R by the synthesis of its enantiomer [(S)-(–)-α-lipoic acid] from (S)-malic acid. J. Chem. Soc., Chem. Commun., (19), 1051–1053.
246. Ghibu, S., Richard, C., Vergely, C., Zeller, M., Cottin, Y., & Rochette, L. (2009). Antioxidant Properties of an Endogenous Thiol: Alpha-lipoic Acid, Useful in the Prevention of Cardiovascular Diseases. Journal of Cardiovascular Pharmacology, 54(5), 391–398.
247. Salehi B, BerkayYılmaz Y, Antika G, BoyunegmezTumer T, Fawzi Mahomoodally M, Lobine D, Akram M, Riaz M, Capanoglu E, Sharopov F, et al. Insights on the Use of α-Lipoic Acid for Therapeutic Purposes. *Biomolecules.* 2019; 9, 356.
248. Lodge JK, Youn H, Handelman G. Natural sources of lipoic acid: determination of lipoyllysine released from protease-digested tissues by high performance liquid chromatography incorporating electrochemical detection. *J Appl Nutr.* **1997**, *49*, 3–11.
249. Schupke H, Hempel R, Peter G, et al. New metabolic pathways of alpha- lipoic acid. *Drug MetabDispos.* **2001**, *29*, 855–862.
250. Gomes MB, Negrato CA. Alpha-lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. *Diabetol Metab Syndr.* **2014**, *6*, 80.
251. Golbidi S, Badran M, Laher I. Diabetes and alpha lipoic Acid. *Front Pharmacol.* **2011**, *2*, 69.
252. Brasier AR. The NF-kappaB regulatory network. *Cardiovasc Toxicol.* **2006**, *6*, 111–30.
253. Vlahopoulos SA. Aberrant control of NF-κB in cancer permits transcriptional and phenotypic plasticity, to curtail dependence on host tissue: molecular mode. *Cancer Biol Med.* **2017**, *14*, 254–270.
254. Bacher S, Schmitz ML. The NF-kappaB pathway as a potential target for autoimmune disease therapy. *Curr Pharm Des.* **2004**, *10*, 2827–37.
255. Kauppinen A, Suuronen T, Ojala J, Kaarniranta K, Salminen A. Antagonistic crosstalk between NF-κB and SIRT1 in the regulation of inflammation and metabolic disorders. *Cell Signal.* **2013**, *25*, 1939–48.
256. Bashan N, Kovsan J, Kachko I, Ovadia H, Rudich A. Positive and negative regulation of insulin signaling by reactive oxygen and nitrogen species. *Physiol Rev.* **2009**, *89*, 27–71.
257. Boullier A, Bird DA, Chang MK, Dennis EA, Friedman P, Gillotre-Taylor K, Hörkkö S, Palinski W, Quehenberger O, Shaw P, Steinberg D, Terpstra V, Witztum JL. Scavenger receptors, oxidized LDL, and atherosclerosis. *Ann N Y Acad Sci.* **2001**, *947*, 214–22.

 doi:10.20944/preprints202402.0674.v1

258. Taniyama Y, Griendling KK. Reactive oxygen species in the vasculature: molecular and cellular mechanisms. *Hypertension.* **2003**, *42*, 1075–81.
259. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE: Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest.* 2001, 108 (8): 1167-1174.
260. Kim MS, Park JY, Namkoong C, Jang PG, Ryu JW, Song HS, Yun JY, Namgoong IS, Ha J, Park IS, Lee IK, Viollet B, Youn JH, Lee HK, Lee KU. Anti-obesity effects of alpha-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase. *Nat Med.* **2004**, *10*, 727–33.
261. Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, Yin X, Xu Q. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. *Front Endocrinol (Lausanne).* **2023**, *14*, 1161521.
262. Packer L, Kraemer K, Rimbach G. Molecular aspects of lipoic acid in the prevention of diabetes complications. *Nutrition.* **2001**, *17*, 888–95.
263. Watanabe Y, Tatsuno I. Prevention of Cardiovascular Events with Omega-3 Polyunsaturated Fatty Acids and the Mechanism Involved. *J Atheroscler Thromb.* **2020**, *27*, 183–198.
264. Lorente-Cebrián S, Costa AG, Navas-Carretero S, Zabala M, Martínez JA, Moreno-Aliaga MJ. Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence. *J Physiol Biochem.* **2013**, *69*, 633–51.
265. Egalini F, Guardamagna O, Gaggero G, Varaldo E, Giannone B, Beccuti G, Benso A, Broglio F. The Effects of Omega 3 and Omega 6 Fatty Acids on Glucose Metabolism: An Updated Review. *Nutrients.* **2023**, *15*, 2672.
266. Doaei S, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F, Bagheri SE, Samipoor F, Akbari ME, Shadnoush M, Ghorat F, Mosavi Jarrahi SA, Ashouri Mirsadeghi N, Hajipour A, Joola P, Moslem A, Goodarzi MO. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. *J Transl Med.* **2021**, *19*, 128.
267. Bhaswant M, Poudyal H, Brown L. Mechanisms of enhanced insulin secretion and sensitivity with n-3 unsaturated fatty acids. *J Nutr Biochem.* **2015**, *26*, 571–84.
268. Qian F, Ardisson Korat AV, Imamura F, Marklund M, Tintle N, Virtanen JK, Zhou X, Bassett JK, Lai H, Hirakawa Y, Chien KL, Wood AC, Lankinen M, Murphy RA, Samieri C, Pertiwi K, de Mello VD, Guan W, Forouhi NG, Wareham N, Hu ICFB, Riserus U, Lind L, Harris WS, Shadyab AH, Robinson JG, Steffen LM, Hodge A, Giles GG, Ninomiya T, Uusitupa M, Tuomilehto J, Lindström J, Laakso M, Siscovick DS, Helmer C, Geleijnse JM, Wu JHY, Fretts A, Lemaitre RN, Micha R, Mozaffarian D, Sun Q; Fatty Acids and Outcomes Research Consortium (FORCE). n-3 Fatty Acid Biomarkers and Incident Type 2 Diabetes: An Individual Participant-Level Pooling Project of 20 Prospective Cohort Studies. *Diabetes Care.* **2021**, *44*, 1133–1142.
269. Zhang K, Qin W, Zheng Y, Pang J, Zhong N, Fei J, Li Y, Jian X, Hou X, Hu Z, Li C, Wang H, Chen Y. Malnutrition Contributes to Low Lymphocyte Count in Early-Stage Coronavirus Disease-2019. *Front Nutr.* **2022**, *8*, 739216.
270. Pilar Vaquero M, Martínez-Suárez M, García-Quismondo Á, Del Cañizo FJ, Sánchez-Muniz FJ. Diabesity negatively affects transferrin saturation and iron status. *The DICARIVA study. Diabetes Res Clin Pract.* **2021**, *172*, 108653.
271. Napiórkowska-Baran K, Ziętkiewicz M, Więsik-Szewczyk E, Matyja-Bednarczyk A, Tykwińska M, Alska E, Rosada T, Szynkiewicz E, Lubański J, Schmidt O, Szymczak B, Koperska K, Bartuzi Z. Points to Consider in Health Assessment of Adult Patients with Primary Antibody Deficiencies. *J Clin Med.* **2023**, *12*, 6018.