Minerals and insulin dependent diabetes in children: A review article

Khaled Abdalla Abdelbaseer\textsuperscript{a}, Zienab Mohammad Mohey EL-Deen\textsuperscript{b}, Mohammed H. Hassan\textsuperscript{c}, Fatma El-Zahraa Mostafa Abo EL-Magd\textsuperscript{a*}, Eman Ahmed Abd-Elmawgood\textsuperscript{a}

\textsuperscript{a}Department of Pediatrics, Faculty of Medicine, South Valley University, Qena, Egypt.
\textsuperscript{b}Department of Pediatrics, Faculty of Medicine, Assiut University, Assiut, Egypt.
\textsuperscript{c}Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, South Valley University, Qena, Egypt.

Abstract

Background: The human body contains trace levels of minerals and other micronutrients. Particularly advantageous for physiologic processes, a wide range of biochemical processes, stabilizing proteins and enzymes, and serving as cofactors for different enzymes. These essential micronutrients have a major physiological effect and are significantly associated with diabetes. Cobalt, boron, chromium, copper, Sulphur, iodine, fluoride, selenium, manganese, zinc, and molybdenum are examples of trace elements. Sodium, potassium, calcium, phosphorus, magnesium, and iron related to macro elements. The main focus of this review is the effect of particular minerals and trace elements on childhood insulin-dependent diabetes.

Objective: Our understanding of how minerals and trace elements affect insulin-dependent diabetes in children will be improved as a result of this review, which is its main goal.

Conclusion: The interaction, development, and outcomes of insulin-dependent diabetes in children are significantly influenced by minerals and trace elements.

Keywords: Macro, micro minerals, insulin dependent DM.

*Correspondence: f.mostafa4242@gmail.com

DOI: 10.21608/SVUIJM.2022.158921.1397

Received: 1 September, 2022.
Revised: 14 September, 2022.
Accepted: 26 October, 2022.
Published: 16 May, 2024

1. Introduction
Insulin-dependent diabetes mellitus, often known as type one diabetes mellitus (T1DM), affects 5–10% of diabetics (American Diabetes Association, 2014). The quantity of b-cells and insulin production decrease as a result of the autoimmune destruction of b-cells in the islet of Langerhans. A few instances of how autoimmune manifests in T1DM include islet autoantibodies, insulin autoantibodies, tyrosine phosphatase IA2 and IA-2b autoantibodies, and glutamic acid decarboxylase isoform-65 (GAD65) autoantibodies. The latter is typically discovered when T1DM at the early stage of hyperglycemia (American Diabetes Association, 2015). Despite the fact that T1DM can manifest at any age, including in old age, it is more prevalent in childhood and adolescence (American Diabetes Association, 2014).

When we talk about type 1 diabetes, we're talking about the process of beta-cell degeneration that can result in it, when "insulin is essential for survival" to avoid ketoacidosis, coma, and death (World Health Organization, 2013).

Micronutrients such as minerals and trace elements, which are essential for human health but are only present in tiny levels, a sufficient number of stable cell structures are maintained by micronutrients, which have a dual effect for promoting health and preventing disease (Uurlu et al., 2016).

Micronutrients and trace elements have a substantial impact on the links between pathogenic variables and the onset of diabetes. Compared to people without diabetes, diabetics may have a higher concentration of bound minerals, such as copper, manganese, and iron, in their body fluids and tissues (Wankhede et al., 2021).

Healthful growth, development, and physiology depend on trace elements, thus experts recommend ingesting 1 to 100 mg of these minerals daily (Tako et al., 2019).

In contrast to macro elements like calcium, phosphorus, magnesium, sodium, potassium, and iron, trace elements include cobalt, boron, chromium, copper, Sulphur, iodine, fluoride, selenium, manganese, zinc, and molybdenum (Siddiqui et al., 2014).

2. A. Macronutrients' impact on insulin sensitivity DM
2. A.1. Calcium

Numerous biological functions, such as bone formation, blood clotting, hormone responses, cardiovascular balance, and cell division and development, depend on calcium (Koeppen et al., 2010).

The ranges for total plasma calcium must be maintained since only one percent of calcium is distributed in intracellular fluid (ICF) and extracellular (ECF) and 99 percent of calcium is stored in bone. These levels are from 8.5 to 10.5 mg/dL for total calcium and 4.65 to 5.25 for ionized calcium (Favus et al., 2008).

The overall amount of calcium in the body must be balanced with the calcium that is taken in by the stomach and the calcium that is excreted by the kidneys in order to maintain healthy calcium homeostasis (Koeppen et al., 2010).

In order to boost insulin production, calcium and cyclic AMP are required. A higher concentration of cytosolic ionized particles, Calcium ions directly control the Langerhans islet's ability to produce insulin in rats, and any changes in calcium flow can negatively impact the beta-cell secretory function (Kratz et al., 2004).

For intracellular insulin-regulated functions in insulin-responsive tissues including skeletal muscle and adipose tissue, calcium is necessary and any decrease in calcium may cause peripheral insulin resistance by impairing the performance of the glucose transporter 4 (GLUT4) and the insulin
signal's ability to communicate (Pittas et al., 2007). Chronic hyperglycemia causes a reduction in calcium outflow from cells. Increased calcium input and decreased calcium outflow maintain an increase in cytosolic calcium concentrations above the starting level (Siddiqui et al., 2014). Glucose is taken in by glucose transporters and metabolized in the beta-cell through glycolysis and the tricarboxylic acid (TCA) cycle to increase ATP generation (Henquin et al., 2009). At this point, glucose stimulation causes the calcium levels in the endoplasmic reticulum (ER) and mitochondria to rise, which causes the cytosolic calcium to fall. There is a significant calcium influx and the start of insulin synthesis after potassium channels (KATP-channels) that are ATP-sensitive are shut down by the following rise in the ATP-to-ADP ratio. After this first peak, the second phase reaction continues as long as blood glucose levels are high, accelerating the release of calcium and insulin (Jensen et al., 2008). The trajectories of glucose-stimulated calcium (GSCa) and glucose-stimulated insulin secretion (GSIS) are comparable because calcium is a strong exocytosis stimulator (Ramadan et al., 2011). These findings imply that aberrations in the latency, direction, and amplitude of the diphasic GSCa response may be a reflection of issues with the stimulus-secretion coupling or other aspects of islet dysfunction. The pathways and amplification mechanisms of the Consensus Model link glucose uptake and metabolism to insulin exocytosis (Jensen et al., 2008).

2. A.2. Iron
Iron is crucial for several physiological processes, such as redox equilibrium, inflammation, energy metabolism, and environmental sensing. Diabetes and hyperglycemia are two conditions that have been researched in both human and animal models and have both been associated to disturbances in iron homeostasis (Wang et al., 2014). Diabetes risk is elevated by specific iron homeostasis-related genetic variations (Cooksey et al., 2004). Through altering the synthesis of adenosine triphosphate (ATP), the stability of hypoxia-inducible factor-1 (HIF-1), and the production of reactive oxygen species (ROS), iron overload in pancreatic islets decreases cell survival and function. Reduced adiponectin levels, macrophage-mediated inflammation, and ROS-mediated activation of liver kinase B1/adenosine monophosphate-activated protein kinase (LKB1/AMPK) are additional factors that cause insulin resistance brought on by iron overload (Zhuang et al., 2014).

Although the exact process by which iron promotes diabetes is uncertain, three basic pathways are thought to be in operation. The greatest method to comprehend the pathogenic mechanisms underlying iron-induced diabetes is to comprehend hemochromatosis in animal models, where it manifests as 1) an insulin deficit, 2) insulin resistance, and 3) hepatic dysfunction (Targher et al., 2007). Diabetic people is frequently associated with excess amounts of non-transferrin-bound iron (NTBI), the iron form most susceptible to redox activity, even though elevated ferritin may not reflect elevated body iron stores or an intracellular labile iron pool that contributes to oxidant injury. These people make for 59–92% of those with elevated ferritin levels (Jehn et al., 2007). We may infer from research in cell culture, animal models, and functional human subjects that iron plays a key role in the onset of vascular disease (vascular reactivity). NTBI boosts the production of adhesion molecules on the surfaces of human endothelial cells and monocyte
attachment to the endothelium reticulum in cell culture models (Kartikasari et al., 2004).
Iron may be pathogenic for diabetes and its side effects, including microangiopathy and atherosclerosis, according to circumstantial evidence. To precisely gauge the amount of free/catalytic iron that causes oxidative damage, sensitive and trustworthy measurement techniques must be created (Targher et al., 2007).

2. A.3. Potassium and Sodium
Numerous body functions, including pH balance, neuronal signaling, blood clotting, and muscular contraction, depend on electrolytes (Siddiqui et al., 2014). Electrolyte abnormalities brought on by dehydration, fever, vomiting, renal failure, and other endocrine problems have been connected to diabetic complications and other endocrine disorders (Husain et al., 2009).

The gradients in sodium and potassium concentrations across membranes are maintained by the constant Na+/K+-ATPase pump. A number of DM issues could arise as a result of changes to this transportation infrastructure (Siddiqui et al., 2014). The American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) propose measuring the blood potassium content prior to beginning insulin therapy in their consensus statements on the management of diabetic ketoacidosis (DKA) (Wolfsdorf et al., 2014).

With severe hypokalemia potentially interfering with insulin administration, the suggestions are intended to reduce the risk of iatrogenic morbidity and mortality (Liamis et al., 2013). Pretreatment blood potassium levels are typically adequate due to the intracellular shift of potassium that occurs with metabolic acidosis and insulin insufficiency, even though a potassium deficit of 3-6mmol/kg is anticipated at the outset of DKA (Bialo et al., 2015).

Due to equilibrium between the osmotic diuresis brought on by glycosuria, which tends to raise serum sodium levels, and the hyperglycemia-induced movement of water from the intracellular to extracellular compartment, which tends to lower serum sodium levels, a person with DKA experiences fluctuating serum sodium levels (Liamis et al., 2014).

Insulin is known to enhance sodium-potassium ATPase activity, or the "Na+/K+-pump," which turns sodium into potassium in a 3:2 ratio, in addition to this hyperosmolality-related impact. With insulin insufficiency, different sodium and potassium concentrations are found in the intracellular and extracellular fluid compartments (Beukhof et al., 2007). Insulin has a crucial role in controlling plasma potassium levels as it controls Na+/K+-ATPase activity and muscle potassium absorption (Onyiriuka et al., 2018).

2. A.4. Magnesium
Magnesium deficiency is one of the micronutrient deficiencies most frequently associated with diabetes (O'Connell, 2001). Over 300 enzymes, including those involved in glycolysis, oxidative energy metabolism, biosynthesis, bone metabolism, neuromuscular function, electrolyte balance, and cell membrane integrity, all depend on magnesium to function properly. Additionally, all energy-based transportation methods require it (Valk, 1999).

Green leafy vegetables, legumes, whole grains, nuts, seeds, milk, and meat all contain magnesium (Veronese et al., 2016). Magnesium is essential for the normal metabolism of macronutrients, cellular transport mechanisms, intracellular signaling networks, platelet aggregation, tone and contractility of vascular smooth muscle, electrolyte homeostasis, and...
phosphorylation/dephosphorylation reactions, which is proof that these effects are multifactorial. There has been evidence that in people with type 1 diabetes, measurements of glycemic control and plasma magnesium levels are at odds with one another (Siddiqui et al., 2014). Recent research found reduced magnesium levels in type-1 diabetics with inadequate glycemic control. Contrary to other studies, the current investigation discovered that type-1 DM patients with microalbuminuria and clinical proteinuria did not exhibit severe hypomagnesemia or intracellular magnesium depletion (Alghobashy et al., 2018).

Mg status and/or consumption are typically reduced in diabetic patients, Mg deficiency is intimately linked to insulin resistance, and Mg-dependent protein kinases are involved in both the insulin signaling cascade and the production of insulin (Sales et al., 2011). Children with type 1 diabetes, particularly those with poor glycemic control, exhibited low serum magnesium levels. This led to recommendations for efficient glycemic control, the monitoring of serum trace element concentrations in juvenile diabetic patients, and additional research into other trace elements and their connections with oxidative stress markers (Alghobashy et al., 2018).

2. A.5. Phosphorus

Phosphorus is an element that plays an essential role in the metabolic process. When diabetes first makes its appearance, tissue hypoxia and low levels of high-energy phosphate may be the outcome of a paradoxical metabolic imbalance in inorganic phosphate (Pi) (Dalili et al., 2020). Phosphorus is an essential element for metabolism because of the significant roles that phosphorus-containing substances play in cellular structure, including the cell membrane and nucleic acids; cellular metabolism, including the production of ATP; the regulation of subcellular processes, including the phosphorylation of essential enzymes; and acid-base homeostasis, including urinary buffering (Amanzadeh et al., 2006).

Although organic phosphates are also present in plasma, only the inorganic variety can be isolated at this time. The rate of oxygen consumption, as well as the behavior and metabolism of enterocytes, renal tubular cells, mitochondria, and muscle cells, are all influenced by pi concentration (Ditzel et al., 2010). Patients with diabetes may experience lower levels of high-energy phosphate as well as tissue hypoxia as a result of a paradoxical metabolic imbalance in Pi (Vorum et al., 2014).

Hypophosphaturia is caused by diabetes because it depolarizes the brush border membrane, which is essential for Pi reabsorption. This results in hypophosphaturia. Tissue hypoxia, muscle weakness, neurological issues, malfunctioning erythrocytes and leukocytes, and poor cardiac performance are all signs of low and high plasma inorganic phosphate levels. This is in contrast to the low and high levels of unregulated blood sugar, which are more difficult to detect (Nansel et al., 2013).

Table 1. Summary of rules of macro minerals in insulin dependent DM in children

<table>
<thead>
<tr>
<th>Element</th>
<th>Role</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>-Changes in calcium flow can impair beta-cell secretory activity and disrupt normal insulin release.</td>
<td>(Pittas et al., 2007)</td>
</tr>
<tr>
<td>Iron</td>
<td>Elevated iron reserves can</td>
<td>(Wilson et al., 2003)</td>
</tr>
</tbody>
</table>
cause pancreatic beta-cell oxidative damage, impaired hepatic insulin extraction, and insulin's inability to control hepatic glucose production.

<table>
<thead>
<tr>
<th>Sodium &amp; Potassium</th>
<th>Na+/K+ ATPase maintain sodium and potassium transmembrane gradients. Diabetes-related disorders are linked to this transport pathway.</th>
<th>(Totan et al., 2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium</td>
<td>- involved in insulin secretion, binding, and activity. - Cofactor for glucose-metabolizing enzymes. - Increase insulin sensitivity.</td>
<td>(Volpe et al., 2008)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>- Hypophosphaturia is caused by a depolarization of the brush border membrane, which is responsible for Pi reabsorption.</td>
<td>(Nansel et al., 2013)</td>
</tr>
</tbody>
</table>

2. B. Role of micro minerals in insulin dependent DM in children

2. B.1 Chromium
Normal glucose metabolism requires trivalent chromium (Cr+3). Glucose tolerance is increased when experimental chromium deprivation is coupled with chromium supplementation (O'Connell, 2001).

It could be difficult to identify a chromium deficiency. Studies on the effects of chromium on glycemic control, dyslipidemia, weight loss, body composition, and bone density have been conducted (Sarubin A, 2000).

By increasing the number of insulin receptors, the binding of insulin to the receptor, and the activation of the receptor in the presence of insulin, chromium helps diabetics with dyslipidemia (O'Connell, 2001).

2. B.2. Vandium

There has never been any indication that humans are lacking in vanadium (Sarubin et al., 2000).

The biological effects of vanadium could be affected by its similarity to phosphorus. It alters the function of phosphatases, phosphotransferases, and ATPase’s, indicating that it is a phosphate analogue (Cam et al., 2000).

Although daily insulin doses decreased, vanadium had no effect on type 1 diabetes patients' insulin sensitivity. The supplement increased kinase activity while lowering cholesterol, HbA1c, and blood sugar (O'Connell, 2001).

2. B.3. Copper

The trace element copper is essential for the proper operation of mitochondrial cytochrome oxidase. Its absence causes metabolically active tissues, such as hepatocytes and pancreatic acinar cells, to exhibit mitochondrial hypertrophy (Alghobashy et al., 2018).
In T1D, copper deficiency may be a therapeutic target because it may be associated with inflammation (Squitti et al., 2019). A copper deficit causes increased glucose sensitivity, glucose intolerance, and impaired insulin sensitivity (Kazi et al., 2008).

2. B.4. Zinc

Is necessary for many human metabolic enzymes and for the storage of insulin in ß-cells (Alghobashy et al., 2018). Zn is the second most common trace metal after iron and is necessary for 300 enzymes and 1,000 transcription factors (Cherasse et al. 2017).

In order to produce insulin, secrete it, incorporate zinc into the insulin granules, and co-secrete it, transporter 8 of zinc (ZnT8) is required (Davidson et al., 2014). Autoantibodies to ZnT8 are present in patients with type 1 diabetes who also have beta cells that generate insulin. So Zn deficiency is considered as a cause of diabetes (Fukunaka et al 2018). Despite the fact that zinc and zinc transporter 8 are known to play a critical role in type 1 diabetes, it is essential to study if the connections we found are substantial (Wessels et al., 2020). Some studies reported that Insulin-treated type 1 diabetics have higher zinc levels (Alghobashy et al., 2018).

2. B.5. Selenium

By triggering the endoplasmic reticulum stress and insulin signaling pathways, selenium compounds can be used to develop novel diabetes treatments. To reduce blood sugar levels and liver damage, selenium compounds function as molecules similar to insulin so blood sugar level and liver damage reduced (Ozenc et al., 2015).

There is a correlation between diabetes and a lower plasma Selenium level (Laclaustra et al., 2010).

Defective antioxidant system, alterations in the activity of the pancreatic antioxidant enzymes, and prolonged exposure to low selenium levels are all factors that have the potential to contribute to the loss of pancreatic B cells and the development of diabetes (Kostolanska et al., 2009). It is possible for adolescents with type 1 diabetes to have lower Se levels if they have increased antioxidant activity, which in turn reduces both free radicals and oxidative stress (Ozenc et al., 2015).

A recent study came to the conclusion that getting diet containing selenium on a daily basis might not be enough to protect human health (Praveena et al., 2013).

2. B.6. Boron

Often known as vitamin B6, is a trace element that may be found in many different foods and is vital for proper metabolic function (Uluisik et al., 2018).

Boron facilitates the production of sexual hormones, as well as bone growth and regeneration, the metabolism of vitamin D, the absorption of calcium and magnesium, and the healing of wounds, also plays a role in wound healing (Khaliq et al., 2018). According to the findings of research, the levels of insulin in plasma can be affected by dietary boron (Uluisik et al., 2018).

Bakken and colleagues discovered that rats lacking boron had significantly elevated levels of plasma insulin (Bakken, 2003). Boron therapy lowered abiogenesis-related genes and proteins by acting on the -catenin, AKT, and ERK signaling pathways to bring about the desired result (Dogan et al., 2017).

Boron therapy protected diabetic rats' pancreatic beta cells by reducing the oxidative damage caused by the disease (Coban et al., 2014).

2. B.7. Iodine

Iodine deficiency inhibits the generation of thyroid hormones, increasing TSH and promoting thyroid gland development.
Impaired thyroid function may have an impact on diabetics' ability to control their blood glucose because of its impact on energy metabolism, also diabetes increase risk of thyroid disease (Nederstigt et al., 2016).

### Table 2. Summary of roles of micro minerals in insulin dependent DM in children

<table>
<thead>
<tr>
<th>Element</th>
<th>Role</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium</td>
<td>A crucial cofactor for insulin's activity and a component of the glucose tolerance factor (GTF), which is responsible for preserving glucose homeostasis.</td>
<td>(Siddiqui et al., 2014).</td>
</tr>
<tr>
<td>Vanadium</td>
<td>- Has an impact on the transport of glucose, glycolysis, glucose oxidation, and glycogen formation, among other aspects of carbohydrate metabolism. - Principally serves as an insulin mimicking substance.</td>
<td>(Cam et al., 2000).</td>
</tr>
<tr>
<td>Copper</td>
<td>A copper deficit causes increased glucose sensitivity, glucose intolerance, and impaired insulin sensitivity. Atherosclerosis and excessive cholesterol are linked to this condition. Copper promotes lipogenesis and has properties comparable to insulin.</td>
<td>(Kazi et al., 2008).</td>
</tr>
<tr>
<td>Zinc</td>
<td>It is essential to the process of how glucose is metabolized. Cofactor for intracellular enzymes involved in the metabolism of carbohydrates, lipids, and proteins. - involved in the formation of insulin receptors and the control of the signal transduction pathway started by insulin receptors.</td>
<td>(Siddiqui et al., 2014).</td>
</tr>
<tr>
<td>Selenium</td>
<td>Important as an antioxidant which inhibit diabetic comorbidities. - regulates the production and</td>
<td>(Bleys et al., 2007).</td>
</tr>
</tbody>
</table>
signaling of insulin receptors.

<table>
<thead>
<tr>
<th>Boron</th>
<th>Diabetes patients’ oxidative stress is reduced, and insulin plasma concentrations are adjusted.</th>
<th>(Coban et al., 2014).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine</td>
<td>With regard to insulin resistance and beta-cell activity, thyroid stimulating hormone has a negative correlation. This is due to an increase in thyroid stimulating hormone and the insulin-opposing actions of thyroid hormones (TSH).</td>
<td>(Chen et al., 2010).</td>
</tr>
</tbody>
</table>

**Conclusion**

The macro elements are the most crucial minerals for the body. Life requires trace elements to exist. They are necessary both as enzyme activators and as enzyme components. For the onset of diabetes and its harmful interactions, certain micronutrients and trace minerals are crucial. Nutritional management aims to improve health by lowering the risk of diabetic complications by keeping blood glucose levels normal. Diabetes mellitus alters the concentrations of trace elements, which can alter the state of a biological function. We need to exercise, eat well, and practice meditation because diabetes is on the rise as a result of our bad lifestyle.

**References**


Abdelbaseer et al. (2024)


Abdelbaseer et al. (2024) endocrine & metabolic disorders, 16(1):15–23.


