Chapter 18

Nanomedicines Utilizing Trace Elements as Targeted Intervention to Revolutionize Diabetes Treatment

Muhammad Sajid[1], Muqader Shah[5] Muhammad Azam[2], Wazir Muhammad Ikhlaq[3], Sajawal Ali[1], Abdul Mateen[2], Hussain Abbas[1], Faiza Bibi[2], Sara Khan[2] and Shahna Jabeen[2], and Ghulam Murtaza[4*]

[1]Faculty of Veterinary Sciences, University of Agriculture Faisalabad, Pakistan
[2]Department of Allied Health Professionals, Faculty of Life Sciences, Government College University Faisalabad
[3]Department of Chemistry, Faculty of Physical Science, Government College University Faisalabad
[4]Department of Anatomy, Faculty of Veterinary Sciences, University of Agriculture, Faisalabad, Pakistan
[5]College of Veterinary Sciences, The University of Agriculture, Peshawar, KPK, Pakistan
*Corresponding author: murtazakhanarman516@gmail.com

ABSTRACT

Diabetes mellitus (DM), a metabolic disease, has been rising annually all across the world based on epidemiology. An effective treatment is essential for diabetic patients to improve their quality of life and to prevent the development of chronic diseases. Microelements, also known as trace elements or nanoparticles, are small amounts of chemicals that are present in human body, and are essential for the growth, and development of the body. Over the last several years, there has been a lot of interest in nanoparticles as a novel class of nanomedicines for antidiabetic application. The nanomedicines are based on trace elements or nanoparticles that have the potential to significantly enhance the care and treatment of diabetes by controlling glucose metabolism. According to several researches, nanoparticles can prevent diabetes in various ways, including lowering blood sugar, promoting insulin secretion, reducing glucose intolerance, enhancing insulin sensitivity, modifying lipid profiles, and reducing inflammation and antioxidant stress. This chapter includes a detailed analysis of the physiological functions of nanoparticles, the pathophysiology of diabetes, the current status of diabetes therapy, and many emerging nanoparticles particularly for diabetes. To conclude, nanoparticles can be used as dietary supplements or as nanomedicines to effectively treat diabetes.

KEYWORDS
Diabetes Mellitus Pathophysiology, ZnNPs, CuNPs, MgNPs, CrNPs, FeNPs.

Received: 29-Jun-2024
Revised: 02-Jul-2024
Accepted: 07-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Sajid M, Murtaza G, Azam M, Ikhlaq WM, Ali S, Mateen A, Abbas H, Bibi F, Khan S and Jabeen S, 2024. Nanomedicines utilizing trace elements as targeted intervention to revolutionize diabetes treatment. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 155-162. https://doi.org/10.47278/book.CAM/2024.485

INTRODUCTION

DM is a metabolic disorder characterized by hyperglycemia (High blood sugar), polydipsia (excessive thirst), hyperphagia, and polyuria (excessive urination volume) (Mukhtar et al., 2020). Chronic hyperglycemia leads to the destruction and dysfunction of several organs and tissues, including the kidneys, heart, blood vessels, nerves, and eyes. Although these conditions are a substantial cause of morbidity and mortality, but these are unrelated to the disorder's direct effects. Instead, they are linked to the long-term effects of diabetes, which include neurological problems, retinal and diabetic nephropathy, coronary heart disease, peripheral artery disease (macroangiopathy), and diabetic nephropathy. Although there is no effective technique for treating DM completely, even though glycemic control drugs can impede its advancement (Teck, 2022). Trace elements are chemical elements that are required for one or more of the vital processes carried out by human bodies. Even though these microelements are just somewhat needed by the body, but their absence can seriously impair an organism's ability to survive and function (Skalnaya and Skalny, 2018). There is an evidence to support a link between the variations in the blood/serum level of trace elements, and the onset of pathoglycemia and diabetes. In an individual with diabetes, serum microelements including zinc (Zn), selenium (Se), magnesium (Mg), copper (Cu), etc. are frequently found in aberrant concentrations, or in vivo, these microelements are usually lost or reduced pathologically. Glucose homeostasis depends on the preservation of ideal trace nutrient levels. The ultimate objective of treating diabetes is believed to be modifying the way pancreatic cells function and restoring glucose homeostasis, however this is still challenging because of variations in the glucose metabolic rate but supplementation of food with microelements, particularly in the form of nanoparticles, is an emerging novel therapeutic approach for control of diabetes (Kravchenko et al., 2023). This chapter included an appropriate summary of the pathophysiology of diabetes and the

present state of therapy. It is discussed how diabetes and the physiological effect of micro elements relate to each other and also figure out the therapeutic potential of micro element nanoparticles and their underlying mechanism of action on diabetes and its complications. It is also relied to a conclusion with an overview and recommendations for the use of trace element nanoparticles for the cure and treatment of diabetes and its complications.

Diabetes Mellitus Pathophysiology

DM is a disorder of glucose metabolism that results due to inadequate production of insulin and/or a malfunction in the body's ability to produce or react to insulin, leading to an inability to maintain appropriate blood glucose level (Balaji et al., 2019). There are two main factors that contribute to the etiology and pathophysiology of DM such as genetics and environmental variables. There is an evidence of significant genetic variability for type 1 diabetes (T1DM) and type 2 diabetes (T2DM). DM is a heritable condition that affects 1/4 to 1/2 of people, and is linked to approximately 60 different genetic disorders (Cole and Florez, 2020). The pathophysiology of T1DM is linked to several DNA loci present across the whole human nucleic acid sequence, with diversiforms in the HLA genes that encode DQ and DR. Additionally, several distinct genetic mutations related to T2DM have been discovered such as abnormalities in the genes for glucokinase, insulin, insulin receptor, and mitochondria. The pathophysiology of DM is significantly influenced by environmental variables as well. One of the primary environmental factor contributing to T2DM is obesity, which is the result of overindulging and inadequate physical activity that will increases the risk of T2DM in people who are genetically predisposed to the disease.(Yasmin et al., 2021). On another hand, when a T1DM-susceptible population is infected with particular viruses, such as the parotid, rubella, or coxsackie viruses, that induced an autoimmune reaction and destroy the islet β cells (cells that release insulin) causing diabetes. About 5–10% of clinical instances of diabetes are caused by T1DM and it is mostly occurred in youngsters or teenagers. The autoimmune loss of the pancreatic islets is the primary cause of T1DM which is detected by the presence of antibodies against insulin and other islet components in the serum of patients. The existence of the antibodies is associated with a reduction in insulin secretion and typically manifests several years prior to the onset of diabetes. Approximately 90% of cases are T2DM, which is significantly more frequent than T1DM (Carey et al., 2018).

T2DM is particularly occurred in older ones, while younger patients can also be affected. Obesity due to insulin insufficiency or resistance is closely associated with T2DM because insulin resistance is a prevalent feature of T2DM in obese individuals, and their serum insulin levels are neither below nor above normal. This leads to hyperglycemia because these obese people are unable to respond to elevated blood glucose levels by producing an adequate quantity of insulin (Czech, 2017). In order to help in the metabolism of carbohydrates, healthy individuals may secrete more insulin than fat individuals. The body might produce insulin but not use it efficiently, which also results in insulin resistance. Oxidative stress in cells typically arises from overeating and inactivity. Human cells produce reactive oxidative species (ROS) during the oxygen-driven metabolism of nutrients to generate energy (Yun et al., 2022).

These free radicals emerge as excess oxygen byproducts accumulate. When these radicals interact with other biomolecules, they induce oxidative stress, which is detrimental to cellular health. Such stress can alter specific glucose transporters like GLUT4, potentially leading to insulin resistance due to enzymatic changes affecting glucose absorption in response to insulin. A mounting body of research highlights a beneficial correlation between heightened inflammation and hyperglycemia. Hyperglycemia not only escalates ROS production but also boosts the expression of inflammatory mediators. Consequently, cellular stressors such as mitochondrial oxidative stress and endoplasmic reticulum stress intertwine with metabolic inflammation. The autoimmune reaction to chronic inflammation and oxidative stress, triggered by genetic and environmental mutagenesis, underlies the physiopathology of diabetes (Lima et al., 2022). Pathophysiology of T2DM is shown in Fig. 1.

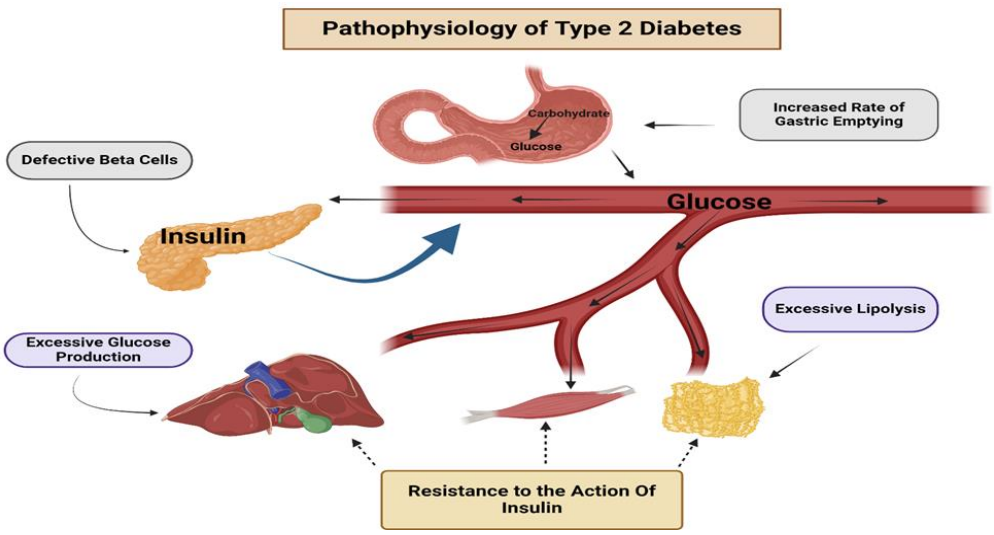

Fig. 1: Physiopathology of Type 2 DM.

Contemporary Approaches in Diabetes Management

DM is diagnosed, when blood glucose levels exceed 7 mmol/L after an overnight fast or 11.1 mmol/L during any meal period (Turner, 2023). Many individuals remain unacquainted of their diabetes until the appearance of typical symptoms like excessive urination, hyperphagia, and high blood sugar levels. Ketoacidosis, characterized by an accumulation of acids and ketones (fat-metabolizing enzymes) in the bloodstream, can result from untreated diabetes. Nausea, vomiting, and diabetic coma may occur due to the in-vivo accumulation of metabolites from lipids and saccharides. Current DM treatment focuses on maintaining nearly normal blood glucose levels, thereby enhancing diabetic patient quality of life and potentially slowing the progression of disease (Aguiar et al,, 2019).

On another hand, active therapies, including nonclinical and clinical interventions such as exercise, nutrition, insulin supplements, oral hypoglycemic medications, and insulin therapy, aim to improve the glucose utilization within the body. Diabetic patients are recommended to take high protein and low carbohydrates and lipids diet. An estimated 34% of calories are attributed to lipids, 12–16% to proteins, and the remaining portion to carbohydrate (Ludwig and Ebbeling, 2018). DM or obesity patients, are recommended to manage their daily calorie intake with 5 to 6 small meals instead of 3 large ones. Calorie restriction combined with moderate hunger can dramatically reduce hyperglycemia. Beside this, exercise in conjunction with diets can help the body to actively mobilize glucose consumption, enhancing insulin sensitivity and possibly restoring glucose homeostasis. Insulin intervention therapy is necessary for diabetic patients whose bodies are unable to produce insulin. T1DM and T2DM patients are not satisfied with oral hypoglycemic medications are the target spectators for insulin treatment (Chan et al., 2021).

Insulin therapy is known as regular subcutaneous injection of the hormone in accordance with the real state of blood glucose level. Because of significant advancements in genetically recombinant DNA technology, recombinant human insulin now fully exchanges pig and cow insulin for clinical usage. Insulin for injections, can be made from human tissue. The optimal insulin secretion schedule is most closely resembling to the standard profile, which is defined by a stimulus-responsive insulin secretion following meals but a steady amount of secretion throughout the non-eating state. A once-daily dose of both a fast-acting insulin preparation and a long-acting insulin preparation can be used to achieve target. Insulin administered subcutaneously can swiftly lower the blood sugar levels, but unlike endogenous insulin produced by pancreas, this external administered insulin does not act directly in the liver (Bolli et al., 2021). Insulin therapy has poor injectable compliance and is costly for a lifelong prescription. On the other hand, a lot of diabetic patient's favor taking oral hypoglycemic medications. Oral medications for blood glucose control fall into multiple forms, such as thiazolidinediones, and sulfonylureas. Conversely, these hypoglycemic agents bring some side effects, e.g., lower glucose level in blood, edema and nausea. The treatment for DM available today is an after-the-fact intervention that aims to reduce sign and symptoms of disease for short period of time rather than completely eradicate the disease. Dapagliflozin and empagliflozin are highly preferred as new-type hypoglycemic agents (Holtzclaw et al., 2018). They are classified as sodium-glucose co-transporter 2 (SGLT2) inhibitors, that can lower blood sugar level by preventing glucose from being reabsorbed through the tubules and reducing the insulin threshold in the kidneys, which increases glucose excretion through the urine. These medications exhibit pharmacological activities beyond the impact of hypoglycemia, such as reducing blood pressure, promoting weight loss, and lowering uric acid levels. Consequently, they may offer cardiovascular protection in addition to blood glucose control.

In recent years, new treatments for diabetes have also emerged, including implanted insulin infusion, β cell transplantation, and pancreas transplantation (Paez-Mayorga et al., 2022). Due to their complete lack of insulin secretion, patients with T1DM typically seek active intervention with novel therapeutic alternatives. The practical application of pancreas or islet transplantation is hindered by the scarcity of pancreatic tissue donors, the necessity of immunosuppressive medication, and the risk of tissue rejection. Ongoing projects involve the development of mechanical islets and the use of cell engineering to improve transplantation outcomes. Reconstructing the body's physiological processes and restoring glucose homeostasis are essential for curing DM. The current objective of DM treatment, although insufficient to meet the initial aspiration, is to control blood glucose level and help prevent long lasting problems. In reality, greater attention should be directed toward modifications in the metabolic profiles associated with diabetes, including alterations in metabolic paths and enzymes, tissue and organ damage, and loss of micro elements (Korac et al., 2021). The main physiological function of nanoparticles for human health are shown in Fig. 2.

Nanoparticles Used for DM Treatment

The types of micro element based nanoparticles utilized in DM research can be categorized into the following sections.

Zinc (ZN) Nanoparticles

Zn is present in body fluids, and almost every tissues of the human body. Zn is vital element for optimum growth of the human body, and it is an essential for approximately 300 enzymes that are necessary for various metabolic pathways. The secretory vesicles of islet β cells contain insulin crystals that assemble into hexamers, with two Zn^{2+} ions coordinating the movement of six insulin monomers. Zn influences the production, storage, secretion, structural integrity, and extending hypoglycemic potential of insulin (Pizzo et al., 2022). It is also a cofactor for enzymes that break down lipids, proteins and also used in glucose metabolism. Zn is directly involved in the energy supply system of glucose oxidation, and activates lactate dehydrogenase, glycerol 3-phosphate dehydrogenase and malate dehydrogenase. Additionally, it controls the glucose homeostasis by activating carboxypeptidase, and facilitating the proinsulin conversion into insulin. Low Zn levels decrease proinsulin conversion, lowering blood insulin levels and glucose consumption by fat and muscle cells, leading to high level of glucose in blood (Bjørklund et al., 2020).

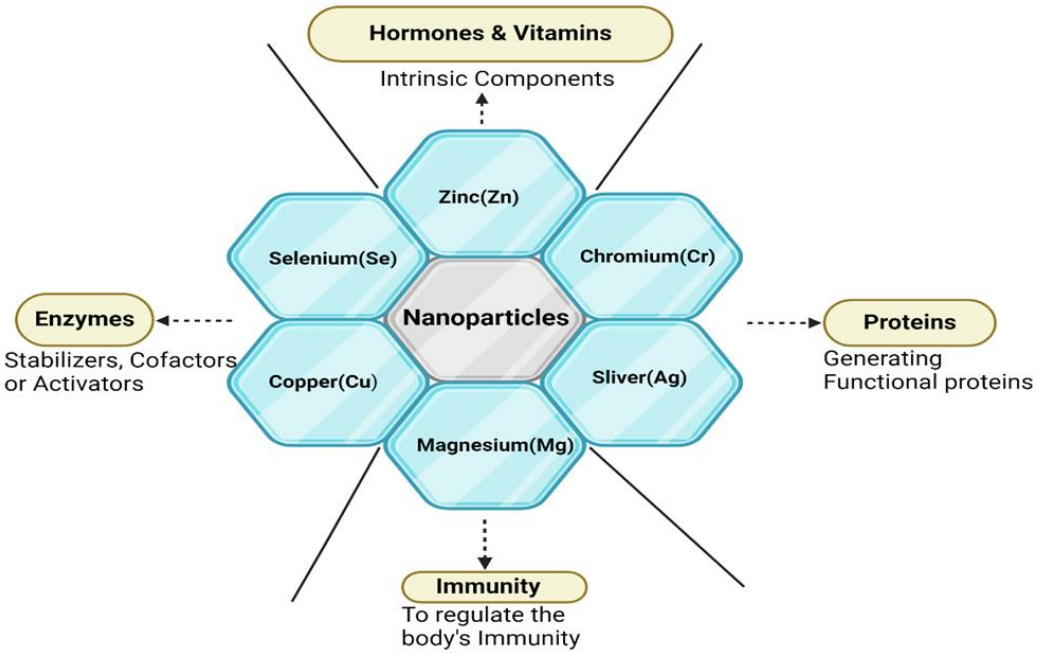

Fig. 2: The Physiological Function of Nanoparticles for Human Health

It also aids in glucose metabolism and endosomal insulin receptor trafficking, exhibiting insulin-mimetic properties and reducing insulin requirements when it is present in sufficient level. Researches reveal the prevalance of Zn shortage in diabetics, linked to reduced cellular Zn and Zn-dependent antioxidant enzymes. Zn loss through urine and decreased serum Zn concentrations are observed in hypoglycemic T2DM, suggesting major role of Zn in diabetes etiology, insulin and glucose metabolism. The growing interest in Zn supplementation or medications for diabetes treatment stems from significant Zn benefits. Zinc oxide nanoparticles (ZnONPs), discovered in 2013, notably reduce diabetes risk in both T1DM and T2DM rats. Oral ZnONPs decrease triglycerides and non-esterified fatty acids, increase serum insulin, and lower blood glucose, leading to increased Zn levels in pancreatic, liver, and adipose tissues (Jeevanandam et al., 2015). The synthesized ZnONPs exhibit outstanding anti-diabetic properties, potentially enhanced by loading docosahexaenoic acid (DHA) to boost the insulin signaling pathway. ZnONPs significantly lower blood glucose levels and prevent advanced glycated end products (AGEs) formation, showing promise in managing DM. Further research is warranted to explore therapeutic potential of ZnNPs in diabetes management.

Magnesium Nanoparticles (MgNPS)

MgNPs functions as a vital trace element necessary for numerous metabolic processes, controlling blood sugar levels, blood pressure, muscle and nerve activity (Jomova et al., 2022). The patients with T2DM often experience clinical hypomagnesemia or chronic magnesium deficit, particularly with poorly managed glycemic profiles. MgNPs is essential for control of vascular tone, insulin-mediated glucose absorption, and insulin action. The deficiency of magnesium can lead to insulin resistance, impairing glucose delivery into cells, resulting in high blood glucose levels, fatigue, increased thirst and urination, impaired vision, and other symptoms. The chronic hyperglycemia can cause severe complications over time, including cardiovascular disease, renal damage, and nerve damage (Porri et al., 2021). As a treatment for DM and its consequences, MgNPs show promising effects, and studies on animals and cells indicate that MgNPs increase insulin sensitivity, enhancing cellular response to insulin, lowering glucose level in blood, and decreasing the risk of T2DM.

In a specific investigation, diabetic rats administered naturally synthesized magnesium hydroxide nanoparticles from *Monodora myristica* showed improvements in fasting blood glucose, hepatic hexokinase activity, serum insulin, and LDH action, potentially alleviating hyperglycemia by protecting β-cells and restoring glycolytic enzyme activity. Another substance developed for anti-diabetic purposes is Magnesium oxide (MgO). Manganese oxide (MnO) and Magnesium oxide (MgO) nanoparticles were produced, and their antidiabetic and antioxidant properties were assessed. The comparing high-dose MgO (300 mg/kg/day) with the positive control group (diabetic rats) demonstrated a substantial declined in blood glucose and an increment in insulin, along with elevated serum paraoxonase levels (Shaukat et al., 2021). Subsequent investigations found that magnesium supplementation greatly improved parameters related to DM and thyroid profile, while MgO nanoparticles protected against pancreatic cell loss, maintaining pancreatic islet size and β-cell quantity. In contrast, synthesized MgO nanoparticles using *Pterocarpus marsupium* heartwood aqueous extracts, demonstrating antioxidant, antidiabetic, and anti-inflammatory properties. These studies suggest that MgNPs may serve as supplemental and alternative therapy to control diabetes.

Chromium Nanoparticles

Chromium (Cr) is an important trace mineral involved in numerous biological processes, including glucose metabolism. The insufficient Cr intake has been linked to the progression and development of DM (Lewicki et al., 2014). Cr significantly

improve insulin function, promoting cellular glucose absorption, and reducing glucose levels in blood which influences glucose metabolism. The individuals susceptible to DM often consume insufficient Cr amounts, and in diabetic's patient, supplementing with Cr can progress glycemic control and insulin sensitivity. Additionally, Cr can lower blood pressure and cholesterol levels, safeguarding diabetics from cardiovascular diseases. (Abdali et al., 2015). Micro particles, can be engineered to possess particular characteristics like enhanced bioavailability and oral absorption. According to certain studies, Cr nanoparticles outperform conventional chromium molecules improving insulin sensitivity and reducing glucose level in blood. For illustration, two-month study evaluated the effect of Cr(III) micro particles on immunological reactions and hormones in heat-stressed rats. The serological analyses revealed higher serum levels of insulin-like growth factor and immunoglobulin G in heat-stressed rats, while the control group exhibited lower insulin concentration (Ghasemi and Nari, 2020).

Subsequent investigations indicated that chromium nanoparticles might decrease serum insulin levels. Another study, suggested that chromium's physiological effect on enhancing hormone internalization into cells and increasing membrane fluidity could underlie the decrease in peripheral insulin levels. In a recent study, oral administration of Cr_2O_3 nanoparticles at a dose rate of 1 mg/kg b.w.t reestablished all genetic and biochemical factors, including hepatic and renal functions restored blood insulin, serum glucose, lipid profile, IL-6, glutathione peroxidase (GSH-Px), serum superoxide dismutase activity, γ-peroxisome proliferator-activated receptor (γ-PPAR), insulin receptor substrate-1 (IRS-1), and serum insulin to normal levels in diabetic rats. It was believed that reducing cellular DNA damage would mitigate diabetes's negative effects and protect the liver and pancreas from oxidative damage. Additionally, Cr nanoparticles may beneficial for diabetics patient through anti-inflammatory, antioxidatory, and as regulator for fat metabolism (Javanshir et al., 2020). In conclusion, Cr nanoparticles grip capacity as a potential diabetic cure, however, further study is necessary to conclude their safety and efficacy before recommending human use.

Copper Nanoparticles

Copper (Cu) is also a necessary trace element that plays an important role in human well-being. It contributes to the production of RBCs, the preservation of strong bones, and the appropriate operation of the immune system. Cu also aids in the synthesis of collagen, an essential protein for the development of connective tissues like ligaments, and skin. While the central nervous system (CNS) regulates insulin secretion from pancreatic β cells, so Cu plays a crucial role in both regular hematopoiesis and the health of the CNS. Cu is also believed to be beneficial for the production and release of insulin by the pancreas (Rajeswari and Swaminathan, 2014). So, a number of studies have linked Cu deficiency to glucose intolerance and impaired insulin secretion. The antidiabetic potential of Cu in diabetes intervention has been investigated in numerous studies that revealed a strong connection between mutative glycemic management and serum Cu level. So improving the control of diabetes, there has been requires a physiological balance level of Cu in the body. A study discovered that Cu nanoparticles (CuNPs) could suppress the activity of α-amylase, indicating possible anti-diabetic property. CuNPs have been shown in other studies to reduce inflammation and oxidative stress and to potentially enhance blood glucose regulation by blocking the actions of α-amylase and α-glucosidase (Ramasubbu et al., 2023).

Rats with Streptozotocin-induced diabetes was treated with low-dose CuNPs (1 mg/kg, p.o.). The levels of glucose in the serum of the diabetic rats were considerably lower after 4 weeks of treatment. Similarly, in Streptozotocin -induced diabetic mice, strong hypoglycemic effects of copper oxide nanoparticles (CuONPs) biosynthesized with *Bacopa monnieri* leaf extracts were noted. The resulting CuONPs, which have an usual size of 34.4 nm, were administered orally for fourteen days at a dose rate of 14 mg/kg, and this caused a 35.74% decrease in blood glucose levels (Faisal et al., 2022). According to these research findings, at the right concentrations, CuNPs have a good antidiabetic potential.

Iron Nanoparticles

Iron **(**Fe), the prevalent micro element in the human body, is involved in many physiological processes, including growth, and development of the body. Diabetes and Fe are typically perceived as two distinct illnesses that are unrelated to one another. Nonetheless, some data points to a possible connection between the onset of T2DM and iron metabolism (Backe et al., 2016). Health risks arise from both increased body iron deposition and iron deficiency. Iron overload, or excessive iron accumulation in the body, has been linked to a higher chance of developing T2DM. Conversely, low iron levels have been associated to decreased insulin sensitivity, poor glucose tolerance, and a higher chance of T2DM. When iron deficiency is identified as a contributing factor to diabetes, intervention in iron metabolism may be beneficial for managing the disease and its complications (Abbaspour et al., 2014).

For example, diabetic rats were treated through various dosages of superparamagnetic iron oxide microparticles (SPIONs) once a week for 28 days. When compared to the untreated group, SPIONs properly balanced the insulin and fasting blood glucose levels in diabetic rats. The improvement of $C_6H_{12}O_6$ detecting and active elements in the insulin nodding pathway were linked to SPIONs' antidiabetic property. Additionally, it was shown that iron micro particles might suppress the function of alpha-amylase, a protein that is essential for the breakdown of starch, glycogen, and carbohydrates. Fe2O3 nanoparticles with stem extracts from *Securidaca longipedunculata*, utilizing a green synthesis approach, and assessed their potential for antidiabetic effects. The resulting spheroidal nanoparticles had a crystallite size of 4.07 nm and a size range of 25 to 45 nm. The level of glucose in the blood of diabetic rats was reduced by 409.50 ± 5.50–199.16 ± 9.33 mg/dL by the green-synthesized iron nanoparticles (Ruan et al., 2023). According to the aforementioned research, iron nanoparticles may help to treat diabetes and prevent hyperglycemia. Table 1 shows the characteristics and anti-diabetic effects of nanoparticles that are used to treat Diabetes Mellites.

Table. 1: The Characteristics and Anti-Diabetic Effects of Nanoparticles Used to Treat DM

Type of Nanoparticles	Characteristics	Anti-Diabetic Effects	Reference
Selenium Nanoparticles	Antioxidant	Reduces blood glucose levels, enhances insulin secretion	Ruan et al., 2023
Zinc Nanoparticles	Insulin Regulator	Improves insulin function, lowers blood glucose levels	Pizzo et al., 2022
Magnesium Nanoparticles	Insulin Sensitizer	Increases insulin sensitivity, lowers blood glucose levels	Porri et al., 2021
Chromium Nanoparticles	Glucose Regulator	Enhances insulin sensitivity, reduces blood glucose levels	Ghasemi and Nari, 2020
Copper Nanoparticles	Enzyme Inhibitor	Suppresses α-amylase activity, lowers blood glucose levels	Ramasubbu et al., 2023
Iron Nanoparticles	Insulin Stabilizer	Balances insulin and blood glucose levels	Backe et al., 2016

Other Microelement Nanoparticles

A wide range of additional nanoparticles have been investigated for DM interference, in addition to the trace element nanoparticles covered above. Insulin sensitivity and glucose metabolism are enhanced in diabetic animal or cell models by these trace element nanoparticles, which include titanium (Ti), cerium (Ce), and vanadium (V). These specifically engineered microelement nanoparticles have demonstrated strong antioxidant and anti-inflammatory properties, in addition to their ability to regulate blood sugar, which may help against issues related to diabetes (Singh et al., 2021).

Prospects and Recommendations

Nanomedicine is a microscale medical way that combines biomaterial, micro technology, and medicinal molecules to treat complex and long-term illnesses. Because of their programmable features and nanoscale effect, medications based on nanoparticles offer more therapeutic options, targeted distribution, and sustained/controlled release than conventional pharmaceuticals. Because of their good intestinal absorption, micro elements in the formula of nanoparticles have superior oral bioavailability. They also have decreased systemic toxicity because of their minimal surge experience to the body and long-lasting regulatory effects because of their constant trace element release. These qualities make micro element nanoparticles very useful for diabetic treatments. (Zhu et al., 2021). The determination of trace element levels in the serum and the correlation between diabetes and an element deficiency are prerequisites for the utilization of nanoparticles in the treatment of diabetes. The quantity of nanoparticles given, in vivo buildup, and long-term harmfulness are further clinical considerations. Nanomedicine may herald a new era in diabetes treatment once these concerns are resolved. To completely comprehend the functions of nanoparticles in the cause of DM, more study is necessary (Collins et al., 2016).

It is crucial to remember that consuming too many trace elements can be hazardous and poisonous. It has been demonstrated that the release of dissolved ions and the dosage of trace element nanoparticles are related to their toxicity. High doses and ionization often result in increased production of reactive oxygen species, which stresses cells and tissues oxidatively. Because of their zero-valence condition, trace elements that are formed into nanomedicines show less toxicity than other chemical modalities because they are more stable in vivo. However, more research in superior populations is warranted to determine the efficacy of using trace element nanoparticles for diabetes treatments. Consuming microelements like Zn and Se through diet may help prevent the development of T2DM and insulin resistance. No doubt, it is essential to complement the trace element in the correct form (such as nanoparticles) when the pathophysiology of diabetes points to a micronutrient abnormality. Eating a nutritious diet is always the best method to ensure that your intake of microelements is balanced (Godswill et al., 2020). Additionally, before beginning any new supplement regimen or making big dietary adjustments, people with diabetes should get advice from their healthcare providers. Some of the nanoparticles used for various useful application in the body are shown in Fig. 3.

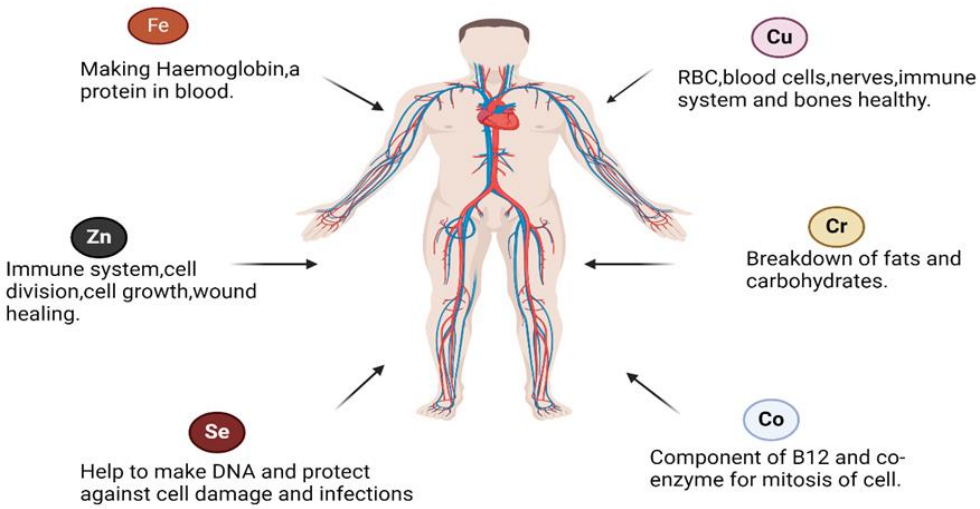

Fig. 3: Application of Nanoparticles for Various Useful Application in the Body

Conclusions

This retrospective study indicates that trace elements play a crucial role in various biological processes, particularly in glucose homeostasis. Among these elements, Se, Zn, and Mg stand out as outstanding microelements for the development of diabetes-combatting nanomedicines. These trace element nanoparticles may possess anti-diabetic properties through direct or indirect reduction of blood glucose levels, enhanced insulin tolerance, and augmented insulin secretion, improved activity of saccharide metabolism enzymes, increased glucose utilization, and restoration of islet β cell function. Moreover, it has been observed that microelement-based nanoparticles can mitigate diabetes-induced chronic microangiopathy, including diabetic nephropathy and retinopathy, by modulating immune responses, reducing inflammation, and ameliorating oxidative stress. In summary, trace element nanoparticles demonstrate promising anti-diabetic characteristics as nanomedicines.

REFERENCES

Abbaspour, N., Hurrell, R., and Kelishadi, R. (2014). Review on iron and its importance for human health. *Journal of research in medical sciences: the official Journal of Isfahan University of Medical Sciences, 19*(2), 164.

Abdali, D., Samson, S. E., and Grover, A. K. (2015). How effective are antioxidant supplements in obesity and diabetes? *Medical Principles and Practice, 24*(3), 201-215.

Aguiar, C., Duarte, R., and Carvalho, D. (2019). New approach to diabetes care: from blood glucose to cardiovascular disease. *Revista Portuguesa de Cardiologia (English Edition), 38*(1), 53-63.

Backe, M. B., Moen, I. W., Ellervik, C., Hansen, J. B., and Mandrup-Poulsen, T. (2016). Iron regulation of pancreatic beta-cell functions and oxidative stress. *Annual Review of Nutrition, 36*, 241-273.

Balaji, R., Duraisamy, R., and Kumar, M. P. (2019). Complications of diabetes mellitus: A review. *Drug Invention Today, 12*(1).

Bjørklund, G., Dadar, M., Pivina, L., Doşa, M. D., Semenova, Y., and Aaseth, J. (2020). The role of zinc and copper in insulin resistance and diabetes mellitus. *Current Medicinal Chemistry, 27*(39), 6643-6657.

Bolli, G. B., Porcellati, F., Lucidi, P., and Fanelli, C. G. (2021). The physiological basis of insulin therapy in people with diabetes mellitus. *Diabetes Research and Clinical Practice, 175*, 108839.

Carey, I. M., Critchley, J. A., DeWilde, S., Harris, T., Hosking, F. J., and Cook, D. G. (2018). Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. *Diabetes care, 41*(3), 513-521.

Chan, J. C. N., Gagliardino, J. J., Ilkova, H., Lavalle, F., Ramachandran, A., Mbanya, J. C., and Aschner, P. (2021). One in seven insulin-treated patients in developing countries reported poor persistence with insulin therapy: Real world evidence from the cross-sectional International Diabetes Management Practices Study (IDMPS). *Advances in Therapy, 38*(6), 3281-3298.

Cole, J. B., and Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nature Reviews Nephrology, 16*(7), 377-390.

Collins, K. G., Fitzgerald, G. F., Stanton, C., and Ross, R. P. (2016). Looking beyond the terrestrial: The potential of seaweed derived bioactives to treat non-communicable diseases. *Marine Drugs, 14*(3), 60.

Czech, M. P. (2017). Insulin action and resistance in obesity and type 2 diabetes. *Nature Medicine, 23*(7), 804-814.

Faisal, S., Jan, H., Abdullah, Alam, I., Rizwan, M., Hussain, Z., and Uddin, M. N. (2022). In vivo analgesic, anti-inflammatory, and anti-diabetic screening of Bacopa monnieri-synthesized copper oxide nanoparticles. *ACS Omega, 7*(5), 4071-4082.

Ghasemi, H. A., and Nari, N. (2020). Effect of supplementary betaine on growth performance, blood biochemical profile, and immune response in heat-stressed broilers fed different dietary protein levels. *Journal of Applied Poultry Research, 29*(2), 301-313.

Godswill, A. G., Somtochukwu, I. V., Ikechukwu, A. O., and Kate, E. C. (2020). Health benefits of micronutrients (vitamins and minerals) and their associated deficiency diseases: A systematic review. *International Journal of Food Sciences, 3*(1), 1-32.

Holtzclaw, B., Kenner, C., and Walden, M. (2018). *Grant writing handbook for nurses and health professionals*: Springer Publishing Company.

Javanshir, R., Honarmand, M., Hosseini, M., and Hemmati, M. (2020). Anti-dyslipidemic properties of green gold nanoparticle: Improvement in oxidative antioxidative balance and associated atherogenicity and insulin resistance. *Clinical Phytoscience, 6*, 1-10.

Jeevanandam, J., K Danquah, M., Debnath, S., S Meka, V., and S Chan, Y. (2015). Opportunities for nano-formulations in type 2 diabetes mellitus treatments. *Current Pharmaceutical Biotechnology, 16*(10), 853-870.

Jomova, K., Makova, M., Alomar, S. Y., Alwasel, S. H., Nepovimova, E., Kuca, K., and Valko, M. (2022). Essential metals in health and disease. *Chemico-biological Interactions*, 110173.

Korac, B., Kalezic, A., Pekovic-Vaughan, V., Korac, A., and Jankovic, A. (2021). Redox changes in obesity, metabolic syndrome, and diabetes. *Redox Biology, 42*, 101887.

Kravchenko, V., Ivaskiva, K. Y., Andrusyshyna, I. M., Pankiv, V. I., Khalangot, M. D., Orlenko, V. L., and Vasiuk, V. L. (2023). Assessment of serum calcium, magnesium and zinc levels in patients with type 2 diabetes mellitus in the Ukrainian population. *International Journal of Endocrinology (Ukraine), 19*(7), 505-509.

Lewicki, S., Zdanowski, R., Krzyzowska, M., Lewicka, A., Debski, B., Niemcewicz, M., and Goniewicz, M. (2014). The role of

Chromium III in the organism and its possible use in diabetes and obesity treatment. *Annals of Agricultural and Environmental Medicine, 21*(2).

Lima, J. E. B. F., Moreira, N. C. S., and Sakamoto-Hojo, E. T. (2022). Mechanisms underlying the pathophysiology of type 2 diabetes: From risk factors to oxidative stress, metabolic dysfunction, and hyperglycemia. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 874*, 503437.

Ludwig, D. S., and Ebbeling, C. B. (2018). The carbohydrate-insulin model of obesity: beyond "calories in, calories out". *Jama Internal Medicine, 178*(8), 1098-1103.

Mukhtar, Y., Galalain, A., and Yunusa, U. (2020). A modern overview on diabetes mellitus: a chronic endocrine disorder. *European Journal of Biology, 5*(2), 1-14.

Paez-Mayorga, J., Lukin, I., Emerich, D., de Vos, P., Orive, G., and Grattoni, A. (2022). Emerging strategies for beta cell transplantation to treat diabetes. *Trends in Pharmacological Sciences, 43*(3), 221-233.

Pizzo, F., Mangione, M. R., Librizzi, F., Manno, M., Martorana, V., Noto, R., and Vilasi, S. (2022). The Possible Role of the Type I Chaperonins in Human Insulin Self-Association. *Life, 12*(3), 448.

Porri, D., Biesalski, H. K., Limitone, A., Bertuzzo, L., and Cena, H. (2021). Effect of magnesium supplementation on women's health and well-being. *NFS Journal, 23*, 30-36.

Rajeswari, S., and Swaminathan, S. (2014). Role of copper in health and diseases. *Internationa Journal Current Science, 10*, 94-107.

Ramasubbu, K., Padmanabhan, S., Al-Ghanim, K. A., Nicoletti, M., Govindarajan, M., Sachivkina, N., and Rajeswari, V. D. (2023). Green Synthesis of Copper Oxide Nanoparticles Using Sesbania grandiflora Leaf Extract and Their Evaluation of Anti-Diabetic, Cytotoxic, Anti-Microbial, and Anti-Inflammatory Properties in an In-Vitro Approach. *Fermentation, 9*(4), 332.

Ruan, S., Guo, X., Ren, Y., Cao, G., Xing, H., and Zhang, X. (2023). Nanomedicines based on trace elements for intervention of diabetes mellitus. *Biomedicine and Pharmacotherapy, 168*, 115684.

Shaukat, A., Anwar, H., Mahmood, A., Hussain, G., Rasul, A., Ijaz, M. U., and Ali, A. (2021). Synthesis cum characterization of MgO and MnO nanoparticles and their assessment as antidiabetic and antioxidative agents in diabetic rat model. *Physica B: Condensed Matter, 602*, 412570.

Singh, K. R. B., Nayak, V., Singh, J., Singh, A. K., and Singh, R. P. (2021). Potentialities of bioinspired metal and metal oxide nanoparticles in biomedical sciences. *RSC Advances, 11*(40), 24722-24746.

Skalnaya, M. G., and Skalny, A. V. (2018). Essential trace elements in human health: a physician's view. *Tomsk: Publishing House of Tomsk State University, 224*, 1-222.

Teck, J. (2022). Diabetes-associated comorbidities. *Primary Care: Clinics in Office Practice, 49*(2), 275-286.

Turner, L. V. (2023). The Timing of Walking and Post-Meal Blood Sugar Levels in Adults with Type 1 Diabetes.

Yasmin, I., Khan, W. A., Naz, S., Iqbal, M. W., Awuchi, C. G., Egbuna, C., and Uche, C. Z. (2021). Etiology of obesity, cancer, and diabetes. *Dietary Phytochemicals: A Source of Novel Bioactive Compounds for the Treatment of Obesity, Cancer and Diabetes*, 1-27.

Yun, B., King, M., Draz, M. S., Kline, T., and Rodriguez-Palacios, A. (2022). Oxidative reactivity across kingdoms in the gut: Host immunity, stressed microbiota and oxidized foods. *Free Radical Biology and Medicine, 178*, 97-110.

Zhu, W., Wei, Z., Han, C., and Weng, X. (2021). Nanomaterials as promising theranostic tools in nanomedicine and their applications in clinical disease diagnosis and treatment. *Nanomaterials, 11*(12), 3346.