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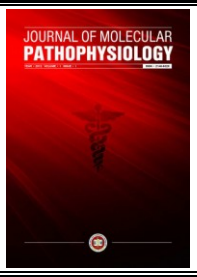

Review Article

Therapeutic potential of metals in managing diabetes mellitus: a review

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Abstract
Diabetes mellitus (DM) represents one of the greatest threats to modern global health. Diabetes mellitus is characterized by chronic elevation of blood glucose concentration as a consequence of decreased blood insulin levels or decreased action of insulin. In order to prevent or delay the onset of such complications, tight control of fasting and postprandial blood glucose levels is a central aspect of diabetes treatment. Development of new therapies that are able to improve glycemia management, cure diabetes, and can even protect from it, are of great interest. Metal compounds proposed to have the potential to elicit beneficial effect in the pathogenesis and complication of the disease. The idea of using metal ions for the treatment of diabetes originates from the report in 1899. Vanadium, chromium, copper, cobalt, tungsten and zinc were found to be effective for treating diabetes in experimental animals. Results from long-term trials are needed in order to assess the safety and beneficial role of these metals as complementary therapies in the management of diabetes. The present review includes the therapeutic potential of some metals showing promising result in the treatment of diabetes.

INTRODUCTION

Diabetes mellitus (DM), a leading non communicable disease with multiple etiologies, is considered as one of the five leading causes of death in the world. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [1]. DM is a clinically and genetically heterogeneous group of disorders, characterized by abnormally high blood glucose concentration. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Deficient supply of insulin cause abnormalities in carbohydrate, fat, and protein metabolism.These metabolic disturbances result in acute and long term diabetic complications, which are responsible for premature death and disability [2].

DM is mainly classified as either insulin-dependent Type I or non-insulin-dependent Type II. Type I is characterized by immune-mediated destruction of insulin-producing pancreatic beta cells. Type II is characterized by disorders of insulin action [3].

Under physiological conditions antioxidant defense system protects the body against adverse effects of free radical generation. In diabetes mellitus hyperglycemia may depress the natural antioxidant system. Free radicals are generated by auto-oxidation reactions of sugars and sugars adducts to proteins and by auto-oxidation of unsaturated lipids in plasma and membrane proteins which results in the consumption of antioxidant defense components. It may lead to disruption of cellular functions and oxidative damage to membranes and may enhance susceptibility to lipid per oxidation. Several reports indicate that hyperglycemia leads to oxidative stress [4-6].The level of lipid per oxidation in cell is controlled by various cellular defense mechanisms consisting of enzymatic

and nonenzymatic scavenging systems [7]. The efficiency of this defense mechanism is altered in diabetes [8] and, therefore, the ineffective scavenging of free radicals may play a crucial role in determining tissue injury.

To treat DM, which has many severe complications, several types of insulin preparations and synthetic drugs have been developed and are in clinical use. However, there are several problems concerning the insulin preparations and synthetic drugs, such as physical and mental pain due to daily insulin injections [9]. Consequently, a new class of therapeutic agents is anticipated. It has been suggested that medicinal plants may provide valuable therapeutics agents in modern medicine and in traditional system, especially in areas where the modern drugs are unavailable [10]. Though there are numerous medicinal plants traditionally reported to have hypoglycemic property. Many of them proved to be not effective in lowering glucose levels in severe diabetes and reported to have side effects including hematological disorders, metabolic coma and disturbances of liver and kidney. Therefore there is a need to search for more effective and safe drugs for diabetes [11]. Researches have been shown significant progress in utilization of metal complexes to overcome the problems of diabetes mellitus. Metals and metal complexes have played key role in the development of modern chemotherapy. A number of transitional and other metal compounds like chromium, manganese, molybdenum, copper, cobalt, zinc, tungsten and vanadium have been proposed as possible adjuncts in the treatment of diabetes mellitus *in vitro* and *in vivo* [12,13].

Metal compounds induce hypoglycemia by a wide variety of mechanisms. Possible mechanisms of their antidiabetic insulin-like effects are activation of insulin receptor signaling (chromium, mangesium), antioxidant properties (cobalt, manganese, tungstate, zinc),inhibition of phosphatases (vanadium), stimulation of glucose uptake, glycogen and lipid synthesis in muscle, adipose and hepatic tissues and inhibition of gluconeogenesis (chromium, cobalt) or stimulation of the activities of the gluconeogenic enzymes: phosphoenol pyruvate carboxykinase and glucose-6 phosphatase (manganese) [14,15].

In recent years, interest has been growing in the assessment of potential insulin mimetic metallopharmaceuticals relying on the unique and characteristic properties of metal ions. The present review update the knowledge about therapeutic potential of some selected metals (chromium, copper, cobalt, magnesium, manganese, molybdenum, tungstate, vanadium and zinc) in insulin resistance and diabetes treatment in both animal models and clinical trials.

CHROMIUM

The most stable oxidation state of chromium, Cr (III), is regarded by many nutritionists as an essential micronutrient for humans. It is an essential element required for normal carbohydrate and lipid metabolism [16].The first suggestion that a biological Cr (III) compound could act as a nutritional enhancement to glucose metabolism was traced in 1950s by Schwarz and Mertz, on the basis of experiments with nutrient-deficient rats. They suggested that brewer's yeast contained a glucose tolerance factor (GTF) that prevented diabetes in experimental animals [17]. Trivalent chromium is reported to be one of the elements essential for treating Type II diabetes as it is believed to enhance insulin action [18].

Although the use of large doses of Cr (III) supplements may lead to improvements in glucose metabolism for type II diabetics, there is a growing concern over the possible genotoxicity of these compounds, particularly of chromium Cr (Pic) [19]. Therefore Cr (III) complexes with propionate [20], L-histidinate [21, 22], D-phenylalaninato [23], and nicotinato (niacinato or 3-pyridinecarboxylato) [24] ligands as well as Cr (III)-enriched yeast [25] have been proposed as safer antidiabetics.

Yang et al. [23] evaluated the effects of a novel synthetic chromium (D-phenylalanine) 3 [Cr (DPhe) 3] complex on insulin-sensitivity, plasma lipid profile and oxidant stress in a mouse model of type II diabetes. Plasma glucose levels and Total serum cholesterol to high-density lipoprotein ratio following intraperitoneal insulin-challenge (1 U/kg) to obese ob/ob (+/+) mice treated with Cr (D-Phe) 3 (150 lg/kg/day for 6 weeks) were significantly lower compared to vehicle-control. Hepatic oxidant stress, assessed as malondialdehyde equivalents and protein-carbonyl content were significantly attenuated following Cr (DPhe) 3 treatments. The complex also inhibited lipid-per oxidation *in vitro*, in a concentration dependent manner.

Sahin et al. [26] evaluated the metabolic effects of chromium picolinate (CrPic) in a rat model of type II diabetes mellitus. Sprague-Dawley rats received a high-fat diet (HFD; 40% of calories as fat) for 2 weeks and then were intraperitoneally injected with streptozotocin (STZ, 40 mg/kg; HFD/STZ) on day 14 with addition of 80 μg CrPic per kilogram body weight per day. The addition of CrPic in the treatment lowered glucose by an average of 63%, total cholesterol by 9.7% and triglycerides by 6.6%. CrPic treatment also lowered free fatty acid levels by 24%, blood urea by 33%, and creatinine level by 25%, and reduced the severity of glomerular sclerosis. Histopathologic findings suggest that the CrPic-treated group had normal renal tubular

and hepatocyte appearance compared with the HFD/STZ-treated group. This was accompanied by a significant greater fall in fasting serum insulin in the chromium-treated group. Improvement in insulin sensitivity and lower glucose levels was suggested by Kim et al. [27] after chromium picolinate (CrPic) supplementation in Goto kakizaki (GK) rats.

Chromium supplementation significantly improves glycemia among patients with diabetes but do not show any significant effect on glucose metabolism in healthy subjects [28]. Studies of chromium supplementation (1000 micrograms of Cr daily) conducted in humans with Type II DM for 16 weeks leads in increased glucose tolerance, decreased circulating insulin, fasting glucose, cholesterol and hemoglobin [29]. Ghosh et al. [30] observed a significant greater fall in fasting serum insulin in the chromium (200 μg trivalent chromium twice daily) treated Indian subjects with type 2 diabetes mellitus.

Chromium picolinate (CrPic) may have a possible antidiabetic effect in insulin-resistant 3T3-L1 adipocytes through the involvement of p38 Mitogen-activated protein kinase (MAPK).Treatment with CrPic could partially reduce hyperglycemia and insulin-induced insulin resistance. CrPic increased the basal and insulin-stimulated glucose uptake and metabolism as well as GLUT4 translocation to plasma membrane in both the control and insulin-resistant 3T3-L1 adipocytes. CrPic also increased the basal and insulin-stimulated p38 MAPK activation [31].The antidiabetic activity can be further explained by the cholesterol lowering ability of chromium picolinate [32].

COBALT

Cobalt (Co) is considered an essential nutritional trace element and has therapeutic value in pharmacological doses. Cobalt has also been demonstrated to boost the effects of insulin and its action [33].Cobalt chloride ($CoCl_2$) decreases the glycemia of diabetic rats by augmentation of GLUT-1 gene expression. The addition of 2 mM Co(II) in the drinking water reduced the glycemia of streptozotocin-induced diabetic rats by day 3 from 32.3 +/- 2.1 to 21.0 +/- 1.9 mM (non-fasting).Treatment with 4 mM Co(II) was more effective than 2 mM Co(II) in reducing the glycemia of diabetic rats[34].

Nomura et al. [35] reported that treatment of normal rats with cobalt chloride (2mM Co (II) for 2 weeks) in drinking water did not modify blood glucose level, insulin level and liver glycogen however muscle glycogen was significantly increased. When STZ diabetic rats were treated with cobalt chloride, there was significant decline in blood glucose, no effect on plasma insulin and significant increase in liver glycogen showing no effect on muscle glycogen. Increase in liver glycogen of diabetic rats would be due to the glycogen signaling. Previously, it was demonstrated that glucose release via glycogen-induced glycogenolysis was suppressed by Co (II) in the perfused liver of normal rats without a STZ administration [36].

Vasudevan and McNeill [37] investigated the anti-hyperglycemic effects of cobalt in streptozotocin-diabetic rats. Normal and diabetic rats were provided with drinking water containing 3.5 mM cobalt chloride for three weeks followed by 4 mM for four weeks. Cobalt-treated diabetic rats demonstrated an enhanced ability to clear a glucose load compared to untreated diabetics. Chronic cobalt treatment decreases plasma glucose levels in STZ-diabetic rats and improves tolerance to glucose which suggested that cobalt modulates specific mediators and/or pathways involved in glucose metabolism.

As cobalt in its single and pure form may be toxic to patients, therefore, various cobalt complexes has been suggested which can reduce the potential toxicity of cobalt without impacting on its effectiveness. Vaidya and Choure [38] observed that Co complex with glimepiride found to be more effective in bringing down the blood glucose level. Glimepiride is a sulphonylurea drug that is used as an antihyperglycaemic agent for the oral therapy of type 2 diabetes mellitus. Streptozotocin induces diabetic rats were given 0.035gm/kg of drug and complexes orally in canulla separately and response was noted after subsequent intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 hours. The glimepiride drug and Co complexes show a decrease in the blood glucose in 9 hours. Glucosaminic acid-cobalt chelate has been reported to be effective as an antidiabetic agent. Oral administration of chelate solution 0.4 mL at various concentrations (0.32–0.4 g/mL) led to reduction in water intake by the diabetic mice after 5 days of treatment, with a subsequent reduction in glucose levels observed 2 weeks later [39].

Cobalt therapy may prove effective in improving the impaired antioxidant status during the early state of diabetes, and ascorbic acid supplementation at this dose potentiates the effectiveness of cobalt action [40-41]. Shukla et al. [42] revealed that cobalt chloride enhances the expression of glucose transporter isoforms mediated by activation of hypoxia inducible factor -1 α (HIF-1α) and decreases blood sugar in diabetic rats. It has been proposed that the glycemia-lowering was mediated by reductions in the rate of hepatic gluconeogenesis. The reduction was explained by the suppression of phosphoenolpyruvate carboxykinase (PEPCK) transcription through HIF-1α activated by Co (II) [33].

COPPER

Copper (Cu) is an 'essential' metalloelement and as such it is required for life. Copper (Cu) plays an important role in electron transfer reactions. Copper has been recognized for as a nutritional factor that improves glucose tolerance by enhancing *in vivo* insulin action. Copper intake *in vivo* has shown both pro-oxidant and antioxidant effects [43]. Copper complexes have been shown to be effective antiulcer, anticonvulsant, anticancer, and antidiabetic agents [44].

Cu deficiency results in impaired energy production, abnormal glucose and cholesterol metabolism, increased oxidative damage [45]. Walter et al. [46] hypothesized that the alterations in Cu metabolism contribute to the progression of diabetes-related pathologies. The pancreas is particularly sensitive to Cu status and changes in CuZnSOD activity can modulate the tolerance of pancreatic beta cells to oxidative stress induced diabetogenesis [47].

Various studies have been conducted to find the effect of copper (II) complexes on glucose metabolism in diabetic rats. Abdul-Ghani et al. [48] studied the effect of copper (II) complexes [bis (acetato) tetrakis (imidazole) copper (II), [Cu $(OAc)_2$ $(Im)_4$] on glucose metabolism in streptozotocin-induced diabetic rats. Intramuscular administration of various doses of Cu $(OAc)_2$ $(Im)_4$ ranging from 10 to 100 mg/kg body mass to overnight fasted rats decreased blood glucose levels in a dose-dependent manner and improved their tolerance for glucose. Yasumatsu et al.[49] proposed that copper (II)-picolinate [Cu (Pic) 2] may be a potent alternative antidiabetic agent. When Cu (Pic) 2 complexes was given to STZ induced type I-like diabetic mice by single intraperitoneal injection, it exhibited a higher hypoglycemic effect.

Copper ions are also involved in the pathogenesis of type II diabetes and copper chelating agent exerts a beneficial effect in the treatment of type II diabetes. The treatment with copper chelating agent tetrathiomolybdate decreased both serum copper ion and ROS levels and consequently ameliorate glucose and lipid metabolism in diabetic db/db mice [50].

Copper sulfate treatment can exert beneficial effects in diabetes with preservation of β-cell function by reducing free radicals or through reduction in glucose levels [51]. It also has been suggested that copper improves hyperglycemia by activating the phosphoinositide 3'-kinase (PI3-K/Akt) pathway leading to GLUT 4 translocation [52-53].

MAGNESIUM

Magnesium (Mg) is a necessary cofactor in over 300 enzymatic reactions especially in all phosphorylation processes including carbohydrate metabolism. Mg concentration is critical in the phosphorylation of the tyrosine kinase of the insulin receptor as well as all other proteinkinases, all ATP and phosphate transfer-associated enzymes, such as the Ca-ATPases in plasma membrane and endoplasmic reticulum [54].

The use of Mg supplements could be an alternative tool for the prevention of type II diabetes. Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose uptake and vascular tone. A tendency for magnesium deficiency in patients with diabetes mellitus is well-established. Barbagallo and Dominguez [55] confirmed the critical importance of Mg metabolism in regulating insulin action and sensitivity. Magnesium supplementation has been proved beneficial as it improves insulin sensitivity as well as insulin secretion in patients with type II diabetes [56-57]. Hypomagnesemia has been linked both to the acute metabolic and late chronic complication of diabetes [58]. Some metabolic studies and clinical trials suggested that magnesium supplementation might improve insulin action among nondiabetic participants or patients with type II diabetes [59].

Experimental studies have shown an adverse effect of magnesium deficiency on glucose-induced insulin secretion and insulin-mediated glucose uptake. Diminished levels of magnesium may decrease tyrosine kinase activity at insulin receptors, leading to an impairment of insulin signaling [60]. Balon et al. [61] indicated that an increased dietary Mg intake in male obese rats prevents deterioration of glucose tolerance, thus delaying the development of spontaneous non-insulin-dependent diabetes mellitus (NIDDM). The male obese Zucker diabetic fatty rat, a model of NIDDM were administered on magnesium-supplemented (Mg-S; 1% Mg) diet for 6 week beginning at 6 week of age. The rats maintained on the Mg-S diet had markedly lower fasting and fed-state blood glucose concentrations and an improved glucose disposal. Improved insulin-mediated glucose disposal and insulin secretion has been reported in magnesium supplemented experimental animals [62]. Song et al. [63] reported the protective role of higher intake of magnesium in reducing the risk of developing type II diabetes, especially in overweight women.

Recently, various clinical trials among type II diabetic subjects showed that magnesium supplementation enhance fasting plasma glucose and insulin sensitivity indices in normo-magnesemic nondiabetic overweight people [64-65]. Guerrero-Romero and Rodríguez-Morán [66] concluded that daily intake of magnesium chloride ($MgCl_2$ 2·5 g) for 3 months improves the ability of beta-cells to compensate for variations in insulin sensitivity in non-diabetic individuals with significant hypomagnesaemia.

MANGANESE

Manganese (Mn) plays an important role in a number of physiologic processes as a constituent or activator of some enzymes which are essential for the metabolism of carbohydrate, amino acid and cholesterol [67]. It is an essential component of metalloenzymes such as Se–cys containing glutathione peroxidase, Cu/Fe cytochrome C oxidase or different types of superoxide dismutases, all of them important in intra- and extra-cellular antioxidant defense [68].

Nicoloff et al. [69] showed that decreased serum manganese concentration found to be associated with microvascular complications in diabetic children. Synthetic manganese porphyrins can be used as potent therapeutic agent in diabetes. EUK-8 is a member of a new class of synthetic salen-manganese compounds with low toxicity that possess catalytic superoxide dismutase, peroxidase and catalase activity that can inactivate superoxide and nitrogen oxides (e.g. peroxynitrite and nitrogen dioxide). EUK-8 administration inhibited the adoptive transfer of type II diabetes and completely inhibited spontaneous disease progression in pre-diabetic NOD mice with established -cell autoimmunity [70].

Gluck et al. [71] observed that d-chiro-inositol (DCI) and manganese sulfate reduced hyperglycemia even more effectively (40%) as compared to control animals. They suggested that DCI and manganese are combined *in vivo* in the cell in the form of chelated insulin mediator glycans such as INS-2. In addition, both phosphoprotein phosphatases PP2C and PDHP, which activate glycogen synthesis and pyruvate oxidation, require manganese and/or magnesium for bioactivity. By these mechanisms both DCI and manganese act to restore normal physiological balance and their prolonged combined supplementation demonstrates an enhanced antihyperglycemic effect as compared to DCI alone. Binding of a divalent metal Mn (II) to an allosteric site on CDK4, a serine/ threonine kinase also activates the enzyme which is involved in signal transduction [72].

Manganese may have a common mechanism of action in raising the cellular concentration of cGMP, by eliciting a change in cyclic nucleotides, which act as a second messenger resulting in the modulation of the metabolic profiles [73]. Insulin mimetic action of manganese can be explained by the regulation of protein phosphatases, including pyruvate dehydrogenase phosphatase which activates glycogen synthesis. Manganese may also augment the activity of manganese-dependent enzymes by increasing their stability [74-75].

MOLYBDENUM

Molybdenum (Mo) represents an important trace element involved in the structure of certain enzymes catalyzing redox reactions. Different chemical forms of molybdenum have been identified as insulin mimetic and being used as anti-diabetic agents. Simple molybdenum compounds, such as sodium molybdate (Na_2MoO_4) and complex compounds such as cis-MoO_2L_2 (L ¼ maltol (3-hydroxy-2-methyl-4 pyrone)) were found to significantly reduce the levels of blood glucose and free fatty acids [76].

Molybdate exert insulin-like effects on the glycolytic pathway by increasing basal fructose 2, 6-bisphosphate (Fru (2, 6) P2) levels, counteract the effects of glucagon on Fru (2, 6) P2 concentrations and 6-phosphofructo-2-kinase (PFK-2) activity, and stimulate glycolytic flux [77]. A weak insulin-like effect of molybdate is potentiated synergistically with H_2O_2, presumably by producing peroxocompounds. The combination of 1 mM molybdate and 1 mM H_2O_2 induced striking stimulation of the uptake of 3-O-methylglucose (3-O-MG) in a synergistic manner [78]. Peroxide of molybdate mediates their effects predominantly via the insulin receptor by activating both cytosolic protein tyrosine kinase and the insulin receptor tyrosine kinase. Thus normalize blood glucose levels in streptozotocin-induced diabetic rats [79].

Molybdenum may be useful for the prevention or early treatment of diabetic mellitus by preventing oxidation of lipids and protects antioxidant systems in experimental diabetic rats. Oral administration of molybdate (100 mg/kg body weight/day) to alloxan diabetic rats for 30 days significantly reduced the levels of lipids like cholesterol, triglycerides, phospholipids and lipid peroxidation whereas the activities of antioxidants like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and reduced glutathione (GSH) were increased [80].

Oral administration of Molybdenum (174 mg/kg Mo element for 7 weeks) decreased the hyperglycemia of obese mice to the levels of lean (+/+) mice. Tolerance to oral glucose was improved. Molybdenum treatment increased hepatic Glucokinase mRNA levels and activity, and had no, or only a mild, effect on the already increased L-Pyruvate kinase variables. The level of m RNA and activity of the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase were augmented in obese mice liver which were reduced by Mo treatment. Insulin binding to partially purified receptors from liver was restored by Mo treatment. Molybdate inhibit protein phophotyrosine phosphatase and thereby stimulates cytosolic protein tyrosine kinase which activates several insulin bio effects via insulin dependent pathways [81].

Ozcelikay [82] investigated the effects of oral administration of Na_2MoO_4 for 8 weeks on carbohydrate and lipid metabolism in streptozotocin-diabetic rats. Na_2MoO_4 decreased hyperglycemia and glucosuria by 75% and corrected the elevation of plasma nonesterified fatty acids. Molybdenum mimics certain insulin actions *in vitro*. Liu et al. [83] suggested protective effect on pancreatic beta cells that may contribute to their antihyperglycemic action. Culture of clonal BRIN BD11 cells for 3 days with molybdate (1 mmol/L) increased cellular insulin content and enhanced basal insulin release.

Molybdenum/ascorbic acid complex showed some significant insulin-mimic and cardio protective effects. Streptozocin induced diabetic rats were treated with the molybdenum/ascorbic acid complex or sodium ascorbate to the drinking water for 6 weeks. Blood glucose levels and blood lipid levels were significantly lowered in animals treated with the complex than in other diabetic animals [84].

TUNGSTEN

The antidiabetic properties of sodium tungstate have been widely reported. Sodium tungstate has shown a remarkable normoglycemic effect in several animal models of diabetes and low toxicity in diabetic and healthy animals [85- 86].

Barbera et al. [87] observed that oral administration of tungstate (2 mg/ml sodium tungstate in 0.9% NaCI) for 16 days normalize glycemia and glucose hepatic metabolism in streptozotocin-induced diabetic rats. Heidari et al. [88] suggested that sodium tungstate protects pancreatic beta cells from STZ-induced cell damage. Rats were supplemented with 1–1.75 mg/ml sodium tungstate at 1 week after STZ injection for 5 weeks. Islets volume density, mean islets volume, and mass of beta cells, islets, and pancreas were significantly higher in sodium tungstate treated STZ-induced diabetic rats.

Yaghmaei et al. [89] suggested that pre-treatment with sodium tungstate leads to amelioration of diabetic complications. STZ induced diabetic rats treated by sodium tungstate from 1 week before STZ injection showed significant decrease in fasting glucose levels and oral glucose tolerance test, less elevation of glucose in diabetic-induced rats.

Munoz et al. [85] observed that tungstate administration to Zucker diabetic fatty (ZDF) rats causes a considerable reduction of glycemia, mainly through a partial restoration of hepatic glucose metabolism and a decrease in lipotoxicity. Tungstate treatment of these rats induced a 42% decrease in serum levels of triglycerides and normalized hepatic glucose-6-phosphate concentrations, glycogen phosphorylase *a* activity, and phosphoenolpyruvate carboxykinase levels.

Kawasaki et al. [90] indicated that tungstate regenerated pancreatic beta-cells population in neonatal STZ rats, a type II diabetes model. Tungstate administration enhances the insulin activity rather than increased insulin levels. Male Wistar rats were made STZ-diabetic and then treated with tungstate in their drinking water for 9 weeks. Tungstate-treated STZ-diabetic rats showed a significant reduction in fluid and food intake, plasma glucose, triglycerides, and free fatty acid levels, and improved tolerance to glucose [91].

Fernandez-Alvarez et al. [92] indicated that tungstate treatment regenerate a stable, functional pancreatic beta-cell population which maintains normoglycaemia.Tungstate treatment increases extra-islet β-cell replication without modifying intra islet β-cell replication rates. PDX-1 gene expression studies revealed that the treatment induces an increase in insulin-positive cells located close to ducts, as well as PDX-1 positive cells scattered in the exocrine tissue, suggesting active neogenesis. Tungstate is able to increase the phosphorylation state of PDX-1 through the activation of p38.

Dominguez et al. [93] identified the first set of molecular targets through which sodium tungstate may exert its antidiabetic action. In primary cultured hepatocytes, extra cellular signal-regulated kinases 1 and 2 (ERK1/2) was stimulated by tungstate treatment which contributes to tungstate-induced glycogen synthase (GS) activation and glycogen deposition in liver.

Nakhaee et al. [94] indicated that sodium tungstate can ameliorate brain oxidative stress in STZ-induced diabetic rats, probably by reducing of the high glucose-induced oxidative stress and/or increasing of the antioxidant defense mechanisms. Diabetes was induced with an intraperitoneal STZ injection (65 mg/kg body weight), and sodium tungstate with concentration of 2 g/L was added to drinking water of treated animals for 4 weeks. Sodium tungstate reduced the hyperglycemia and restored the diabetes induced changes in all mentioned markers of oxidative stress. However, catalase activity was not significantly affected by diabetes, while sodium tungstate caused a significant increase in enzyme activity of treated animals.

STZ diabetic rats were treated orally with tungstate for five weeks. Treated STZ diabetic rats showed a partial recovery of exocrine and endocrine function, with lower glycemia, increased insulinemia and amylasemia, and increased beta cell mass achieved by reducing beta cell apoptosis and raising beta cell proliferation.

Tungstate improves pancreatic function through a combination of hyperglycemia-independent pathways and through its own direct and indirect effects, whereas the MAPK pathway has a key role in the tungstate-induced increase of beta cell proliferation [95].

Sodium tungstate ameliorates hyperglycemia by showing insulin-like properties [96], by pancreatic regeneration which leads to restoration of beta-cell mass [90], by protecting the beta cells from streptozotocin-induced damages [88], by increasing the total amount and translocation of glucose transporter (GLUT-4) in muscle [97], and by reducing the glucose-6-phosphatase activity, an enzyme that hydrolysis glucose-6-phosphate liberating glucose into the bloodstream [98]. Tungstate treatment also restored pyruvate kinase activity and fructose 2, 6 bisphosphate concentrations. Alterations in the hepatic glucose metabolism due to diabetes were almost completely counteracted by tungstate treatment [99].

VANADIUM:

Vanadium (V) is arguably the most efficacious insulin-enhancing transition metal. Vanadium compounds mimics action of insulin through alternative signaling pathways which involve the inhibition of phosphotyrosine phosphatases , leading to increased phosphorylation of Insulin receptor substrate 1 (IRS-1), protein kinase B (PKB), Glycogen synthase kinase 3 (GSK3) and Forkhead box protein O1 (FOXO1) and the interplay between two non-insulin receptor tyrosine kinases. The insulin-like potential of vanadium has been demonstrated *in vitro* and *in vivo* in rodents (where the oxidation states IV and V were found to be equipotent) and more recently in human diabetic subjects [100-103]. The earliest documented evidence of the insulin-like effects of the inorganic vanadium salt, sodium orthovanadate (Na_3VO_4) was published by Lyonnet et al. [104]. It was observed that oral Na_3VO_4 administration decreased glucosuria in 2 out of 3 diabetic patients.

Vanadyl sulphate is widely used in both type I and type II diabetic animal models, where it acts as an insulin-mimetic drug. It is well known as a complex to activate or inhibit many enzymes involved in carbohydrate metabolism inducing glucose transport, glucose transporter translocation, glycolysis and glycogen synthesis.or lipid metabolic pathways [105-107].Cam et al. [108] administered vanadyl sulphate in the drinking water (0.75 mg/ml) from 3, 10 and 17 days after the streptozotocin injection for 5 months. Glucose tolerance and adipose tissue function was normalized in vanadyl treated diabetic rats, supporting the concept that vanadyl sulphate acts as an insulin-mimetic.

Tolman et al. [109] showed that several inorganic vanadium compounds, similar to insulin, stimulated glucose transport and oxidation in adipocytes, increased glycogen synthesis in the rat diaphragm and hepatocytes, and inhibited gluconeogenesis in liver cells. Meyerovitch et al. [110] demonstrated that chronic sodium metavanadate administration also lowered plasma glucose levels and enhanced basal hexose transport in both liver and muscle.

Administration of vanadyl sulphate (100 mg/kg b.wt./day for 60 days) in streptozotocin induced diabetic rats caused significant lowering of serum total cholesterol, LDL-cholesterol, triglycerides, phospholipids, blood glucose, non enzymatic glycosylation and lipid peroxidation and improvement in GSH level in spleen and gastrointestinal tract [111]. Similarly in a clinical study by Jacques-Camarena et al. [112] revealed that administration of vanadyl sulfate (50 mg p.o. twice daily for 4 weeks) in diabetic patients increased triglyceride concentrations without changes in insulin sensitivity.

A wide variety of vanadium containing complexes has also been tested as anti-diabetic treatments [113]. Vanadium complexes with organic ligands have proved to be less toxic, with improved solubility and lipophilicity. Vanadium complexes show insulin like effects by activation of several key components of insulin signaling pathways [114]. Bis (maltolato) oxovanadium [BMOV] have shown long-term in vivo insulin mimetic effects [115], Ammonium dipicolinatooxovanadium (V) [115] and arylalkylamine derivatives [117] have been used as a hypoglycemic agent in naturally occurring diabetes mellitus in cats and in other animal models.

Cohen et al. [118] evaluated the effects of vanadyl sulphate (100 mg/day) for 3 weeks in type- II diabetic patients. A reduction in fasting plasma glucose and glycosylated hemoglobin (HbA1c) without changes in plasma insulin levels was noticed. The beneficial effects on insulin sensitivity persisted for up to 2 weeks following cessation of treatment. Vanadyl sulfate improves hepatic and muscle insulin sensitivity in type II diabetes mellitus. The glucose-lowering effect of vanadyl sulfate correlated well with the reduction in endogenous glucose production, but not with insulin-mediated glucose disposal, suggesting that liver is the primary target of vanadyl sulfate action at therapeutic doses in type II diabetes mellitus [119].

ZINC:

Zinc (Zn) plays an important role in the synthesis, storage, and secretion of insulin as well as conformational integrity of insulin in the hexameric form. Zinc was considered as a component of insulin crystals as earliest since 1934 [120].

Zinc supplementation can ameliorate glycemic condition in type I and II diabetes. Zinc seems to exert insulin-like effects by affecting the insulin signaling pathway at several levels, inducing phosphorylation of the β subunit of the insulin receptor as well as of Akt and leading to inhibition of GSK-3β probably as a consequence of Akt phosphorylation and by reducing the production of cytokines, which lead to beta-cell death during the inflammatory process in the pancreas in the course of the disease [121].

Zinc supplementation produced a significant improvement in glucose disposal. Zinc seems to exert insulin-like effects by supporting the signal transduction of insulin and by reducing the production of cytokines, which lead to beta-cell death during the inflammatory process in the pancreas [121]. The action of zinc seemed to be related to the increased activities of insulin independent glucose transporters [122]. Zinc could act also in protecting sulfhydryl groups against oxidation and participate in the inhibition of the free radical production. Zinc induces the translocation of GLUT to the plasma membrane, resulting in an increased uptake of glucose into tissue cells, thereby lowering the blood glucose level.

Higher zinc intake has also been associated with a slightly lower risk of type II diabetes [123]. Anderson et al. [124] suggested the potential beneficial antioxidant effects of the individual and combined supplementation of Zn and Cr in people with type II diabetes. These results are particularly important in light of the deleterious consequences of oxidative stress in people with diabetes.In a clinical trial people with type I diabetes mellitus receiving 30 mg of Zinc as Zn gluconate for three months showed decreased lipid peroxidation and an improvement in antioxidant status [125]. Further Oh and Yoon [126] also suggested that Zinc (50 mg zinc daily as zinc gluconate for 4 weeks) supplementation significantly improve fasting glucose as well as HbA1c in diabetic patients with shorter diabetic duration, poorer glycemic control, and marginal zinc status.

Zinc exerts insulin like effects on the oxidation of glucose by both pathways, glycolytic and hexose monophosphate shunt. Zinc chloride administered either by oral gavage(210 mg mL^{-1} kg^{-1}) or intraperitoneally (i.p.100 mg mL^{-1} kg^{-1}) to STZ-diabetic rats led to blood glucose lowering, by 50% and 75%, respectively, within 3 hours [127]. Zinc complexes has also been tested, both *in vitro* and *in vivo*, as ‘‘insulinomimetics’’such as Zn(II)/Carnitine Complex [128]; bis(maltolato)zinc(II) Complex [129]; zinc(II)-*N* -acetyl-L-cysteine complex [130], zinc(II) complexes with picolinamide derivatives [131].Yoshikawa et al. [132] proposed that the Di (1-oxy-2-pyridinethiolato) Zn complex Zn (opt) (2) complex with Zn(S (2) O (2)) coordination mode is a novel candidate for the treatment of type II diabetes through oral administration. Zn (opt) (2) improved the insulin and adiponectine levels in the plasma.

Duzguner and Kaya [133] supplemented diabetic rabbits administered with 150 mg/L of zinc as zinc sulfate ($ZnSO_4$) in their drinking tap water for 3 months. A significant decrease in plasma MDA concentration and significant increase in the activity of antioxidant enzymes (SOD, CAT, and GSH-Px) and GSH levels was observed.

Zinc sulfate supplementation may be a therapeutical resource to recover microvascular complications in diabetes. Treatment of 100 mg zinc sulfate for 12 weeks in diabetic patients was well tolerated, significantly reduced total cholesterol and triglyceride concentrations and increased HDL cholesterol in the bloodstream [134].

CONCLUSIONS

In this review, an overview of the various metallic compounds which have shown promising results in the treatment of diabetes has been presented. It seems that good opportunities exist to exploit metal and metal based drugs in the discovery and development of alternative tool for the prevention of diabetes. Further, understanding of the mechanism of action, cellular target and toxicological studies are required for their therapeutic applications. This area should be essentially explored in adequate clinical trials so that diabetes related problems can be resolved.

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