Chapter 2
Print ISBN: 978-93-5547-666-1, eBook ISBN: 978-93-5547-667-8

Antidiabetic Effects of Metal Nanoparticles in Rodents

Marjan Assefi [a], Nadeem Kizilbash [b*], Naila Mahmood [c], Sohila Nankali [d], A. Nankali [e] and Gholamreza Abdi [f]

DOI: 10.9734/bpi/capr/v6/3473B

ABSTRACT

Many people suffer from Diabetes Mellitus all over the world. It is a metabolic disorder that results in high blood Glucose level and is a multi-factorial problem marked by hyperglycemia due to decreased Insulin production or increased Insulin resistance. The restorative effect of Zinc Oxide and Silver nanoparticles on Streptozotocin-induced diabetic rodents has been investigated by numerous studies. The metal nanoparticles play an important role in clinical and natural applications. Although, Silver is an important metal used by many metabolic processes, very little information is available about the effect of Silver or Silver nanoparticles (SNPs) on Glucose metabolism. The reported results by various studies reveal a decrease in blood Glucose level of diabetic rodents treated with ZnONPs, Silver nanoparticles (SNPs) and Insulin.

Keywords: Diabetes mellitus; silver nanoparticles; glycogenesis; metabolism.

1. INTRODUCTION

A number of studies have shown the effect of metal nanoparticles on Glucose metabolism and diabetes. Vanadium [1], Chromium [2], Magnesium [3], and Zinc [4] are known to play a role in Glucose metabolism and have been used for treatment of diabetes. Zinc, a fundamental metal, is an activator for hundreds of enzymes in the body [5]. It assumes a key part in various metabolic pathways including Glucose digestion. Zinc accelerates hepatic Glycogenesis through its activities on the Insulin pathways and along these lines further develops glucose usage [6]. Zinc is also known to play a role in Insulin biosynthesis, storage and

[a] *University of North Carolina at Greensboro, Greensboro, NC 27403, USA.*
[b] *Department of Chemistry, Faculty of Physical Sciences, Quaid-i-Azam University, Islamabad-45320, Pakistan.*
[c] *Molecular Immunology Laboratory, Atta-ur-Rehman School of Applied Biosciences, National University of Science and Technology, Islamabad, Pakistan.*
[d] *Northcentral University, San Diego, CA, USA.*
[e] *Kermanshah University of Medical Sciences, Kermanshah, Iran.*
[f] *Department of Biotechnology, Persian Gulf Research Institute, Bushehr, 75169, Iran.*
**Corresponding author: E-mail: fsd707@gmail.com;*

synthesis [4,7]. There are various Zinc transporters in pancreatic β-cells [8] such as the Zinc Carrier 8 that plays an important role in Insulin production [9]. Moreover, the level of Zinc can influence Insulin receptor phosphorylation by PI3K and inhibition of Glycogen Synthase Kinase-3 activity [6]. The advantages of using Zinc for treating diabetes has been proven by investigations about Zinc supplements in diabetic rodents [7,10].

The gastrointestinal enzymes, α-Glucosidase and α-Amylase, play a key role in Glucose metabolism. A fundamental antidiabetic approach is to decrease the post-prandial blood Glucose level by inhibiting the α-Glucosidase and α-Amylase enzymes. The *In vitro* anti-diabetic activity was assessed after the biosynthesis of Silver nanoparticles from the marine red alga, *Halymenia poryphyroides*. An investigation about the effect of Silver nanoparticles has revealed their inhibitory effect on α–Amylase protein at doses of 0.2 mg/ml. An Insulin resistance was observed at a dose level of 1.0 mg/ml. Similarly, an increase in inhibitory activity against α-Glucosidase protein was observed at lower doses of 0.2 mg/ml and Insulin resistance at a higher dose of 1.0 mg/ml was observed [11,12].

2. SYNTHESIS OF SILVER NANOPARTICLES

Silver nanoparticles, employed by these studies, are typically synthesized by the green union procedure where Silver Nitrate is added as a precursor to marine Red Alga, *Halymenia poryphyroides*. Silver nanoparticles are consequently formed by the decrease of Ag^+ ion concentration during the reaction at 60°C with a change in color from light yellow to brown that demonstrates the production of Silver nanoparticles.

3. CHARACTERIZATION OF SILVER NANOPARTICLES

The morphology of Silver nanoparticles has been investigated by the use of UV–Nanophotometer, FT-IR, SEM and XRD [11-13]. The UV-Nanophotometer has been used to characterize the biosynthesized silver nanoparticles obtained from the concentrate of the marine red alga *H. poryphyroides* [11]. The appearance of Silver Surface Plasmon Resonance band is observed at 420 nm. The recurrence and width of the Surface Plasmon Resonance band depends on the size and shape of the metal nanoparticles.

The FTIR analysis of silver nanoparticles has shown the conversion of Silver particles to Silver nanoparticles [11,12]. The natural products such as metabolites assume a significant role in the production of the metal nanoparticles [11,13]. The SEM characterization of Silver nanoparticles has revealed the colloidal structure of the SNPs (Fig. 1). There is an effect of shape in algal-produced Silver nanoparticles. The symmetric circularly shaped and isotropic nanoparticles increase the activities of many biomolecules. In the electron micrographs, the Silver nanoparticles appear to be covered with the cell divider polysaccharide on the micrograph. It is observed that the morphology of the metal nanoparticles changes their optical and electronic properties.

4. DISCUSSION

Numerous nanoparticles have been investigated for uses in therapy [12]. Some nanoparticles, such as Zinc, Silver, Iron and Gold, play important roles in clinical applications [14-16]. The results show a decrease in blood Glucose level in diabetic groups treated with ZnONPs (Fig. 2), SNPs and Insulin (75.8%, 68.2% and 84.2%) [6]. Various studies have revealed that ZnONPs and SNPs can increase serum Insulin level in diabetic subjects (79.4% and 3% respectively). The results demonstrate that ZnONPs cause greater Insulin release than the SNPs [17]. Moreover, the mRNA transcription level of Insulin quality seemed to increase in ZnONPs and insulin-treated groups when compared with the diabetic non-treated groups. Certain studies have shown that ZnONPs can increase Insulin production by pancreatic islets removed from rodents [7,18]. Umrani and Paknikar [19] have shown that ZnONPs also avoid the danger of causing hypoglycemia in subjects. In contrast, SNPs increase the Insulin level at an extremely low rate (3%) when compared to ZnONPs. This might be due to aggregation of ZnONPs in the secretory vesicles of β-cells containing the Zinc transporters [9,20]. Zinc transporters are present in both fat and liver cells [21] that control Glucose metabolism.

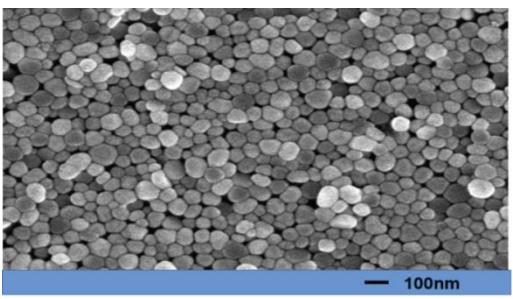


Fig. 1. Electron micrograph showing the morphology of Silver nanoparticles

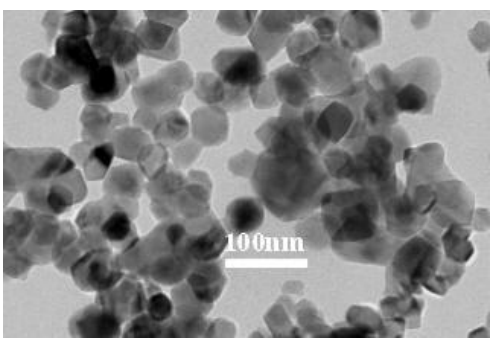


Fig. 2. Electron micrograph showing the morphology of zinc oxide nanoparticles

Glucokinase (GK) activity in the liver is not fixed in rodents. GK catalyzes the initial step of Glucose metabolism in the liver and it has a high affinity for Glucose in the blood [22]. It is important to note that the activity of GK decreases in diabetic rat [23]. There is an increase in the activity of GK in ZnONPs, SNPs and Insulin-treated cells (52.5%, 25.8% and 44.7% respectively) when compared to diabetic non-treated groups. There is also evidence that the ZnONPs-treated subjects exhibit the greatest therapeutic improvement among the various treated groups.

The activity level of GLUT-2 is not fixed in hepatic tissue either. Decreased GLUT-2 activity is found in diabetes [24]. Excess 2 is a membrane-bound protein and has a high Michaelis Constant (K_m) for Glucose transport into the liver [25,26]. The adjusted activity of GLUT-2 can be correlated with the pathogenesis of diabetes.

5. CONCLUSIONS

Various studies have shown that ZnONPs and SNPs can increase the activity level of GLUT-2 in hepatic tissues which can lead to an increase in the uptake of glucose from hepatocytes. The results have shown the extraordinary antidiabetic action of these nanoparticles. The ZnONPs display greater potency than SNPs since Zinc has a powerful impact on hepatic Glycogenesis. As the ZnONPs are more potent in their effect than Silver nanoparticles, they lead to a decrease in the blood Glucose level, increased Insulin level and an increased GK translocation and activity as well as an increase in the activity level of IRA and GLUT-2 in diabetic rodents.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Thompson KH, Lichter J, LeBel C, Scaife MC, McNeill JH, Orvig CJJoib. Vanadium treatment of type 2 diabetes: A view to the future. 2009;103(4):554-8.
2. Wang ZQ, Cefalu WTJCdr. Current concepts about chromium supplementation in type 2 diabetes and insulin resistance. 2010;10(2):145-51.
3. Wells ICJCjop, pharmacology. Evidence that the etiology of the syndrome containing type 2 diabetes mellitus results from abnormal magnesium metabolism. 2008;86(1-2):16-24.
4. Chausmer ABJJotACoN. Zinc, insulin and diabetes. 1998;17(2):109-15.
5. Haase H, Overbeck S, Rink LJEg. Zinc supplementation for the treatment or prevention of disease: current status and future perspectives. 2008;43(5):394-408.
6. Jansen J, Karges W, Rink LJTJonb. Zinc and diabetes—clinical links and molecular mechanisms. 2009;20(6):399-417.

7. Alkaladi A, Abdelazim AM, Afifi MJIjoms. Antidiabetic activity of zinc oxide and silver nanoparticles on streptozotocin-induced diabetic rats. 2014;15(2):2015-23.
8. Smidt K, Jessen N, Petersen AB, Larsen A, Magnusson N, Jeppesen JB, et al. SLC30A3 responds to glucose-and zinc variations in ß-cells and Is critical for insulin production and in vivo glucose-metabolism during ß-cell stress. 2009;4(5):e5684.
9. Rungby JJD. Zinc, zinc transporters and diabetes. 2010;53(8):1549-51.
10. Uyoyo Ukperoro J, Offiah N, Idris T, Awogoke DJMJoN, Metabolism. antioxidant effect of zinc, selenium and their combination on the liver and kidney of alloxan-induced diabetes in rats. 2010;3(1):25-30.
11. Manam D, Kiran V, Murugesan SJJoC, Research P. Biogenic silver nanoparticles by Halymenia poryphyroides and its in vitro anti-diabetic efficacy. 2013;5(12):1001-8.
12. Febles C, Arias A, Gil-Rodriguez M, Hardisson A, Sierra Lopez AJAdIdEC. *In vitro* study of antimicrobial activity in algae (Chlorophyta, Phaeophyta and Rhodophyta) collected from the coast of Tenerife. 1995;34(2):181-92.
13. Bottini N, Vang T, Cucca F, Mustelin T, editors. Role of PTPN22 in type 1 diabetes and other autoimmune diseases. Seminars in immunology; Elsevier; 2006.
14. Hirst SM, Karakoti AS, Tyler RD, Sriranganathan N, Seal S, Reilly CMJS. Anti-inflammatory properties of cerium oxide nanoparticles. 2009;5(24):2848-56.
15. Venkatachalam M, Govindaraju K, Mohamed Sadiq A, Tamilselvan S, Ganesh Kumar V, Singaravelu G. Functionalization of gold nanoparticles as antidiabetic nanomaterial. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2013;116:331-8.
16. Mahmoudi F, Mahmoudi F, Gollo KH, Amini MM. Biosynthesis of novel silver nanoparticles using eryngium thyrsoideum boiss extract and comparison of their antidiabetic activity with chemical synthesized silver nanoparticles in diabetic rats. Biological Trace Element Research. 2021;199(5):1967-78.
17. Nazarizadeh A, Asri-Rezaie S. Comparative study of antidiabetic activity and oxidative stress induced by zinc oxide nanoparticles and zinc sulfate in diabetic rats. AAPS PharmSciTech. 2016;17(4):834-43.
18. Richards-Williams C, Contreras JL, Berecek KH, Schwiebert EMJPs. Extracellular ATP and zinc are co-secreted with insulin and activate multiple P2X purinergic receptor channels expressed by islet beta-cells to potentiate insulin secretion. 2008;4(4):393-405.
19. Umrani RD, Paknikar KMJN. Zinc oxide nanoparticles show antidiabetic activity in streptozotocin-induced Type 1 and 2 diabetic rats. 2014;9(1):89-104.
20. Wijesekara N, Dai FF, Hardy AB, Giglou PR, Bhattacharjee A, Koshkin V, et al. Beta cell-specific Znt8 deletion in mice causes marked defects in insulin processing, crystallisation and secretion. Diabetologia. 2010;53(8):1656-68.

21. Mocchegiani E, Giacconi R, Malavolta M. Zinc signalling and subcellular distribution: emerging targets in type 2 diabetes. Trends in Molecular Medicine. 2008;14(10):419-28.
22. Matschinsky FM, Magnuson MA, Zelent D, Jetton TL, Doliba N, Han Y, et al. The network of glucokinase-expressing cells in glucose homeostasis and the potential of glucokinase activators for diabetes therapy. Diabetes. 2006;55(1):1-12.
23. Tahrani AA, Piya MK, Kennedy A, Barnett AH. Glycaemic control in type 2 diabetes: Targets and new therapies. Pharmacology & Therapeutics. 2010;125(2):328-61.
24. Orci L, Unger RH, Ravazzola M, Ogawa A, Komiya I, Baetens D, et al. Reduced beta-cell glucose transporter in new onset diabetic BB rats. 1990;86 5:1615-22.
25. Van Schaftingen E, da-Cunha MV, Niculescu L. The regulatory protein of glucokinase. Biochemical Society Transactions. 1997;25(1):136-40.
26. Alkaladi A, Abdelazim AM, Afifi M. Antidiabetic activity of zinc oxide and silver nanoparticles on streptozotocin-induced diabetic rats. 2014; 15(2):2015-23.

Biography of author(s)

Dr. Marjan Assefi
University of North Carolina at Greensboro, Greensboro, NC 27403, USA.

Research and Academic Experience: She is an American biologist, researcher, and writer. She has a Ph.D. in Nanobiology, and Doctorate in Healthcare Administration, and she is a fellow researcher, international speaker, and author. She has Experience on Nano Science, Nanoengineering, Medicine, Brain Mapping.

Research Area: Her Research Area includes Nano Science, Nanoengineering, Medicine and Brain Mapping.

Number of Published papers: She has More than 80 Published papers in national and international journals.

Any other remarkable point(s): Any other remarkable point(s).

Dr. Nadeem Kizilbash
Department of Chemistry, Faculty of Physical Sciences, Quaid-i-Azam University, Islamabad-45320, Pakistan.

Research and Academic Experience: He is the Head and Assistant Professor of Biochemistry, Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, Northern Border University, Saudi Arabia. He completed PhD on Biophysics from Boston University, USA and MA on Chemistry from Washington University, USA.

Research Area: His Research Area includes Structural Biology, Nanotechnology, Biotechnology and Molecular Biology.

Number of Published Papers: He has 50 Published Papers in national and international journals.

Special Award: He has Editorial Board Membership of several journals : I*nternational Clinical Case Reports Journal* (October, 2021); *Ocean Journal of Respiratory Medicine* (September, 2021); *Journal of Clinical Epidemiology and Toxicology* (March, 2021); *Acta Scientific Microbiology* (*February, 2021*); *Journal of Stem Cell and Therapeutics* (January, 2021); *Journal of Stem Cell and Therapeutics Research* (January, 2021); *Annals of Clinical Case Studies and Reports* (December, 2020); *Cambridge Scholars Publishing*(October, 2020); *Asian Digital Library* (August, 2020); *CPQ Medicine* (August, 2020); *AS Pharmaceutical Sciences* (August, 2020); *Stem Cell Research & Therapeutics* (February, 2019); *International Journal of Diabetes and Endocrinology* (December, 2018); *Advances in Cancer Research*

& Clinical Imaging (September, 2018); *Trends in Technical & Scientific Research* (September, 2018); *Clinics of Oncology*(August, 2018); *CPQ Microbiology* (March, 2018); *International Journal of Nanoparticles & Nanotechnology* (March, 2018); *Cohesive Journal of Microbiology & Infectious Disease* (February, 2018); *Nanomedicine and Nanoscience Research*(December, 2017); *Research and Reviews on Healthcare*: *Open Access Journal* (December, 2017); *Nanotechnology & Medicine*(September, 2017); *Research & Development in Material Science* (September, 2017); *EC Pharmaceutical Science* (January, 2015); *European Journal of Biophysics* (*EJB*) (December, 2013); *MOJ Cell Science & Report* (May, 2014); *Journal of Cell Science & Report: Open Access* (April, 2014); *Journal of Teaching and Teacher Education*(February, 2014); *VRI Phytomedicine*(September, 2013); *Global Advanced Research Journal of Medicine and Medical Science* (May, 2012); *International Journal of Pharmacy and Pharmaceutical Sciences* (November, 2012).

Any other remarkable point(s):

Reviewer/Referee for Doctoral Theses

- *Ph.D*. thesis, Mansoura University (Egypt), Department of Zoology, Faculty of Science (November, 2014)
- *Ph.D*. thesis, Mansoura University (Egypt), Department of Zoology, Faculty of Science (February, 2013)

Ph.D. Supervisor Appointment

Appointment as *Ph.D*. Supervisor, Higher Education Commission, Pakistan, (November, 2004).

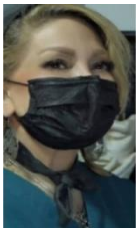
Ms. Naila Mahmood
Molecular Immunology Laboratory, Atta-ur-Rehman School of Applied Biosciences, National University of Science and Technology, Islamabad, Pakistan.

Research and Academic Experience: She is working at Molecular Immunology Laboratory, Atta-ur-Rahman school of Applied Biosciences, National University of Science and Technology, Islamabad, Pakistan. She is expert in molecular and cell culture techniques.

Research Area: Her Research Areas are Molecular Biology and Immunology.

Number of Published papers: She has some published papers in national and international journals and 2 published book chapters.

Special Award: She has MS President's Gold Medal in Academics in her credit.



Dr. Sohila Nankali
Northcentral University, San Diego, CA, USA.

Research and Academic Experience: OBGYN, Women Health, Brain Mapping.

Research Area: OBGYN, Women Health, Brain Mapping.

Number of Published papers: 60.

Any other remarkable point(s): Editor in chief of Gynaecology Journal.

Dr. A. Nankali
Kermanshah University of Medical Sciences, Kermanshah, Iran.

Research and Academic Experience: Dr. Nankali is an associate professor, and practice OBGYN for more than 24 years.
Research Area: Dr. Nankali's Research Areas are OBGYN and Medicine.
Number of Published papers: Dr. Nankali has More than 80 Published papers in national and international journals.