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To study the effect of age and blood sugar on the levels of magnesium and glycated hemoglobin in Bundelkhand region: A case control analysis

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Abstract
In Type 2 Diabetes Mellitus (T2DM) loss of minerals may lead to decrease in its bodily content and might affect the concentrations of minerals. The aims of this study were to compare the plasma glucose, glycated hemoglobin (HbA1c), and Magnesium (Mg) concentrations of patients with T2DM and healthy controls (Non-diabetic) in Bundelkhand region and also to know the association of blood glucose and HbA1c with Mg in respective groups. This study has shown altered Fasting Blood Sugar (FBS), HbA1c, and Mg in T2DM group subjects when compared with healthy control group subjects. The statistical significance was observed to be at $p<0.05$. Insignificant difference was observed in the age parameter when compared between the two groups. In the present study pertaining to T2DM group subjects, an inverse correlation between Age and FBS; Age and HbA1c were established. In conclusion, we observed lower Mg levels in T2DM individuals in the Bundelkhand region. As Mg depletion aggravates insulin resistance and may result in increased loss through urine, therefore, it may be advisable to periodically monitor Mg concentrations in T2DM subjects. Moreover, further research is imminent to understand the deeper insights into the association of Mg with T2DM which is, prior to the initiation or after initiation of T2DM.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder in which there is insulin resistance, and it is experienced by insulin dependent tissues and for the same insulin is needed for the uptake of glucose[1]. The classical symptoms of T2DM include increased thirst, frequent urination, and unexplained weight loss[2]. Long-term persistent hyperglycemia leads to a number of secondary complications due to glucose toxicity namely cardio-vascular diseases, cerebral strokes, diabetic nephropathy, peripheral neuropathy and diabetic retinopathy which can result in loss of vision[3,4].

There are many etiologic hypotheses for hyperglycemia in T2DM, such as genetic defect [5], loss of insulin sensitivity[3], High Density Lipoprotein (HDL) defect[6], oxidative stress[4], glucose toxicity[3,4], low concentrations of chromium[7,8], zinc[9], and melatonin[10,11]. It is possible that several of these hypotheses, e.g., trace element deficiencies[7-9], mitochondrial defect[12], and oxidative stress[3], may interact as pathogenetic mechanisms for insulin resistance in T2DM. Bioavailability of minerals is hampered in hyperglycemia due to change of oxidation state of minerals for their vulnerability towards free

radicals[13]. Loss of minerals may lead to decrease in its bodily content and might affect the concentrations of minerals like Magnesium (Mg).

Mg is a necessary co-factor for several enzymes that play a vital role in glucose metabolism[14]. Studies have demonstrated hypomagnesemia as a common feature in patients with T2DM[15], though diabetes can induce lower Mg levels, in addition, Mg deficiency has been proposed as a risk factor for T2DM[16]. Studies on models demonstrated that Mg has a negative effect on the signaling process of insulin[17,18]. However, some studies [19,20] revealed that Mg administration has a beneficial effect on insulin action and glucose metabolism. In a study[21-23], found an inverse correlation between Mg intake and risk of T2DM. Moreover, Mg depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with T2DM[24,25], as well as on the evolution of complications such as retinopathy, thrombosis and hypertension[26,27]. Interestingly, a study showed lower serum Mg is a strong independent predictor of the development of T2DM[28]. In a country it has been shown that nearly 40% outpatient diabetics have low concentrations of serum Mg[29], and several studies have shown lower serum Mg concentrations in T2DM compared to healthy controls[30,32]. However, there is no clear indication or hypothesis to trace whether Mg deficiency occurs first or after development of T2DM.

Although low serum Mg concentrations in diabetics have also been found in several studies [14–32], there are no reported data for diabetics living in Bundelkhand region. Therefore, the aims of this study were to compare the plasma glucose, glycated hemoglobin, and Mg concentrations of patients with T2DM and healthy controls in Bundelkhand region and also to know the association of blood glucose and HbA1c with Mg in respective groups.

Materials & Methods

The study was conducted in the Department of Biochemistry, Maharani Laxmi Bai Medical college (MLBMC), Jhansi. Age & sex matched fifty human individuals having a normal glycaemic status were taken into healthy control group. Fifty T2DM subject, on treatment were included in T2DM group. The diagnosis of T2DM was made according to the norms laid by American Diabetes Association 2018. The diagnosis of T2DM group subjects was done by the consultants of General Medicine department of MLBMC. Exclusion criteria were type 1 diabetes individuals, less than five years of known duration of T2DM, and with complications. Inclusion criteria for healthy controls were non-diabetic, not taking supplementations, and having no other complications. Fasting venous blood (5ml) were drawn into EDTA and plane vials, after informed written consent from all the study group subjects with a disposable syringe & needle, under all aseptic conditions. Serum was separated by centrifuging the blood at 3000 rpm for 20 minutes. Samples were stored in aliquots at -20^{o} C until assayed. Plasma glucose was estimated by using the method Glucose Oxidase and Peroxidase (DPEC – GOD/POD) purchased from Transasia Biomedicals. HbA1C was estimated by using the ClinRep complete kit on the BioRad HbA1c analyzers Diamat and Variant. Serum Mg was estimated by using the method of Calmagite purchased from Beacon Coral Clinical Systems.

Statistical Analysis

Unpaired ‘t’ test was performed to compare the means of variables between T2DM group and healthy control group subjects. Scattered plots were used to know the regression equation of variables taken in the present study and were considered to understand the association between two variables. P <0.05 was considered significant.

Results

The figures 1 and 2 show altered FBS and HbA1c, and Mg in T2DM group subjects when compared

with healthy control group subjects. The statistical significance was observed to be at $p<0.05$. Insignificant significant was observed in the age parameter when compared between the two groups.

Insignificant differences were reported in the age (53.9±7.2) and (53.06±4.7) and in the distribution of subjects in the age groups of 41-50, 51-60, 61-70, and above 70 years when compared between the Type 2 Diabetes Mellitus (T2DM) subjects and healthy controls of the present study (Figs. 3 & 4). Only one subject was included above 70 years of age as per our criteria.

In the present study pertaining to T2DM group subjects, an inverse correlation between Age (x axis) with FBS; Age and HbA1c were established as evident from the graph shown in the figure 3. In addition (figure 4), we also observed an inverse correlation between serum magnesium (Mg; x axis) and HbA1c (y axis). Out of the three trend lines in Fig. 5 & 6, the order of decline is in the order as follows $y=-100x+8.815$ ($R^2=0.001$), $y=-0.098x+12.78$ ($R^2=0.082$), and $y=-0.018x+2.070$ ($R^2=0.043$). The overall p value demonstrated significant result at $p<0.05$ between T2DM group subjects and healthy control group subjects when compared the means of FBS, HbA1c, and Mg except that of age.

In the present study pertaining to healthy control group subjects Figure 5, an inverse correlation between age (x axis) with HbA1c (y axis); age (x axis) and Mg (y axis) were established as evident from the graph shown. Out of the two trend lines in Fig. 7, the order of decline is in the order as follows $y=-0.01+6.733$ ($R^2=0.012$) and $y=-0.033x+3.75$ ($R^2=0.073$).

Figure 1: Mean values of Age and FBS in control and T2DM subjects

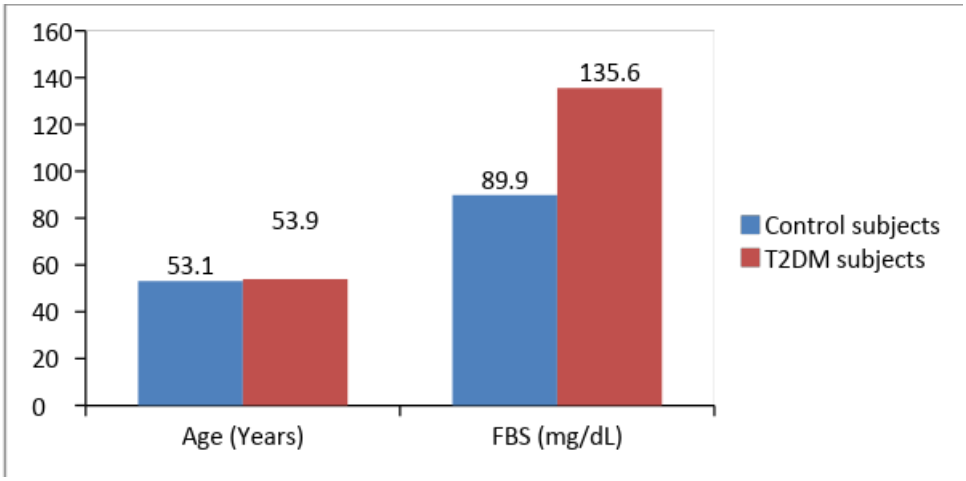


Figure 2: Mean values of HbA1c and Mg in control and T2DM subjects

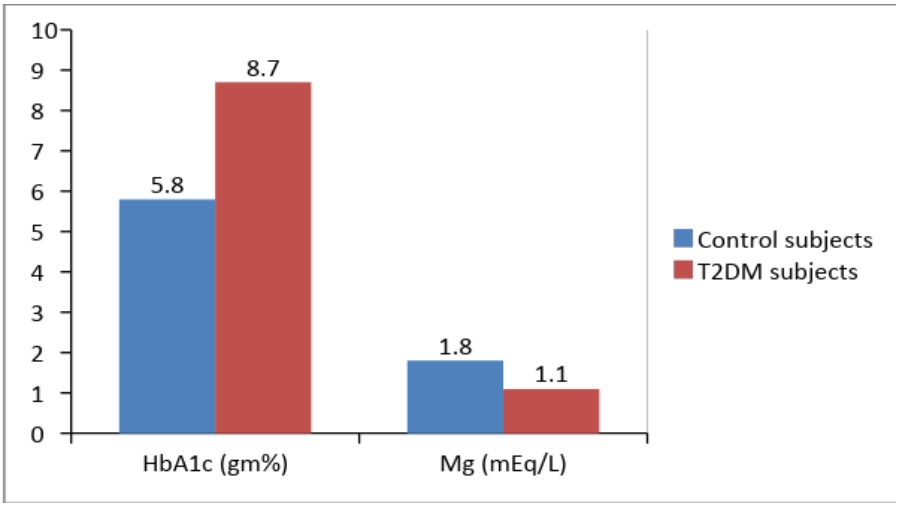


Figure 3: Scatter diagram showing relationships between Age with FBS and Mg in T2DM group

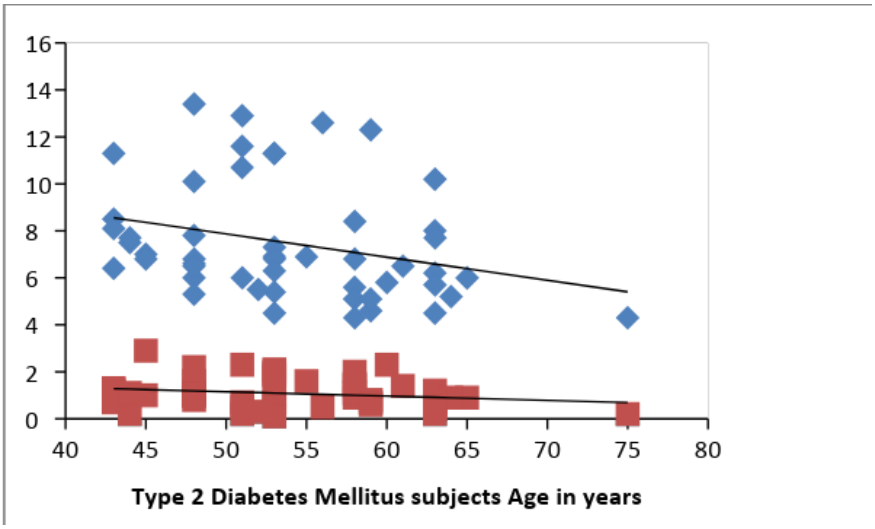


Figure 4: Scatter diagram showing relationships between Mg and HbA1c in T2DM group

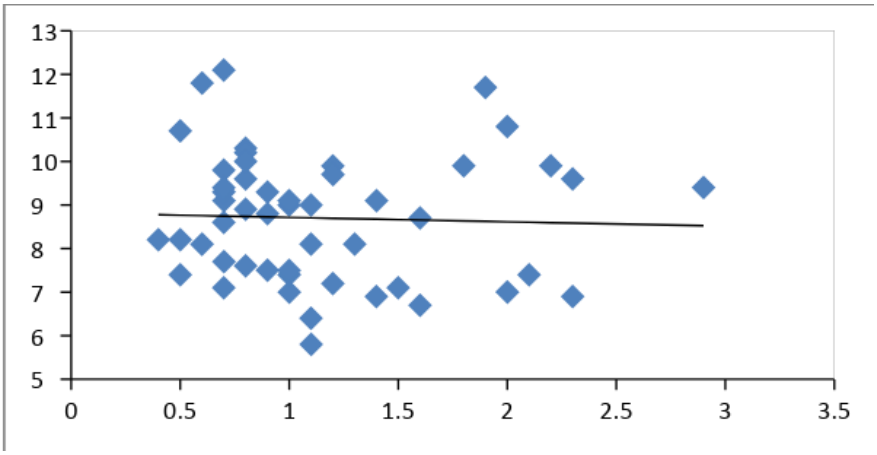
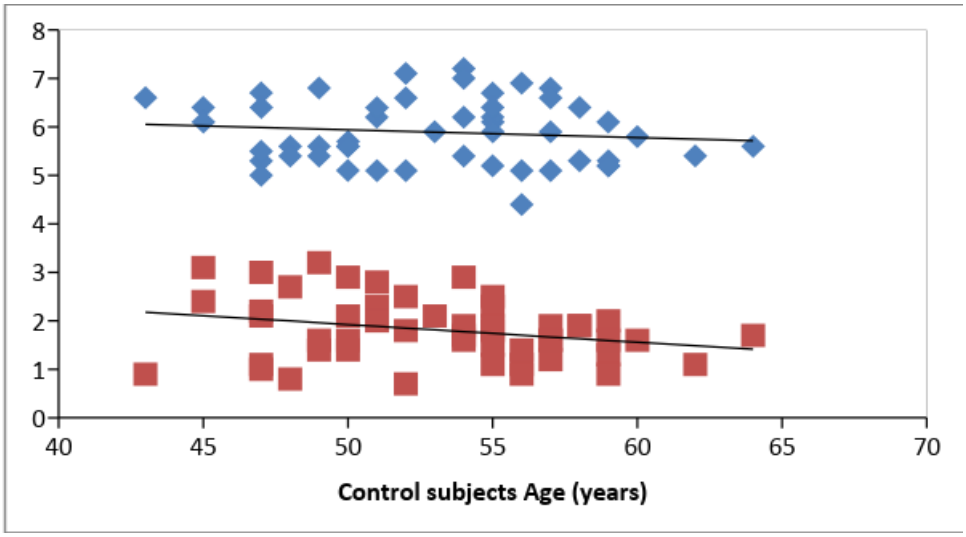


Figure 5: Scatter diagram showing relationships between Mg and HbA1c in T2DM group



Discussion

Questions that are asked in this study were to compare the plasma glucose, glycated hemoglobin, and Mg concentrations of patients with T2DM and healthy controls in Bundelkhand region and also to know the association of blood glucose and HbA1c with Mg in respective groups.

The T2DM group subjects showed altered FBS, HbA1c, and Mg when compared with healthy control group subjects. Insignificant difference was observed in the age parameter when compared between the two groups.

In the present study pertaining to T2DM group subjects, an inverse correlation between age and FBS was observed, but not in healthy controls. This finding suggests that increased blood sugar in T2DM group may be caused by increase age in the subjects[33,34]. Literature related to T2DM reveals that T2DM is one of the aging diseases in the present world and our finding also infers the concerns with age in T2DM subjects[35,36]. Studies reported that individuals above 40 years of age are more susceptible to develop T2DM[37,38]. Interesting point is that no correlation was observed in the control group when compared between age and blood sugar, however, we observed insignificant difference in age when compared between T2DM and controls. Keeping in view of this finding, we suggest that individuals, who have predisposition to T2DM, are prominently driven towards the initiation of the disease rather than the individuals who has fewer predispositions. Therefore it is not coincidental to report that older adults have the highest prevalence of diabetes, and such individuals have traditionally not been included in some studies that involve research on diabetes [33,34].

It is interesting that a correlation between age and HbA1c was negative in the T2DM group and also control group. At first it seems contradictory, but possible explanation could be that the oxidative stress increases with age and increase in HbA1c is compensatory to the increase in age and the free radical production. Many studies have shown that people with T2DM tend to have higher oxidative stress compared to healthy controls compared with same age group individuals[1,3,4]. Though the present did not estimate free radicals but it is evident through the literature that oxidative stress is increased in T2DM patients and also in aged controls[39-40].

We observed significant lower Mg levels in T2DM group subjects when compared to control group subjects and an inverse correlation between serum Mg and HbA1c in T2DM group. The lower level was due to hyperglycemia present in T2DM subjects. Osmotic diuresis is seen in T2DM subjects, and frequent urination causes loss of Mg as suggested by the studies[41-44]. In addition, re-absorption of Mg in the tubules needs insulin sensitivity, but resistance of the tubules towards insulin because of insulin resistance may hamper the re-absorption of Mg and subsequently Mg is not reabsorbed but excreted in the urine[13,45]. Similar finding has been shown in studies performed with T2DM subjects[13,45].

The other fact is that free radicals change the oxidation state of the Mg which hinders the bioavailability of the Mg in the body [46-48]. This fact can be explained with the finding of the present study of inverse correlation between age and Mg in the control group. As discussed earlier that free radicals are increased as the age progresses. These free radicals can alter the oxidation state of the minerals and thus lost from the body without getting used. Studies have shown the justification of this fact[7,8]. This could imply that the administration of Mg may be therapeutically beneficial.

Conclusion

In conclusion, we observed lower Mg levels in T2DM individuals in the Bundelkhand region. As Mg depletion aggravates insulin resistance and may result in increased loss through urine, it may be advisable to periodically monitor Mg concentrations in T2DM subjects. Moreover, further research is imminent to understand the deeper insights into the association of Mg with T2DM prior to the initiation or after initiation of T2DM.

Conflict of interest: None declared.

References

1. Ernst, M. C., & Sinal, C. J. (2010). Chemerin: at the crossroads of inflammation and obesity. Trends in Endocrinology & Metabolism, 21(11), 660-667
2. American Diabetes Association. (2015). 2. Classification and diagnosis of diabetes. Diabetes care, 38(Supplement 1), S8-S16
3. Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. Circulation research, 107(9), 1058-1070
4. Rains, J. L., & Jain, S. K. (2011). Oxidative stress, insulin signaling, and diabetes. Free Radical Biology and Medicine, 50(5), 567-575
5. Martin BC, Warram JH, Krolewski AS, Soeldner JS, Kahn CR, Bergman RN. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. The Lancet. 1992 Oct 17;340(8825):925-9.
6. Kontush A, Chapman MJ. Why is HDL functionally deficient in type 2 diabetes?. Current diabetes reports. 2008 Feb 1;8(1):51-9.
7. Anderson, R. A., Cheng, N., Bryden, N. A., Polansky, M. M., Cheng, N., Chi, J., & Feng, J. (1997). Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes.Diabetes, 46(11), 1786-1791.
8. Doddigarla Z, Ahmad J, Parwez I. Effect of chromium picolinate and melatonin either in single or in a combination in high carbohydrate diet-fed male Wistar rats. Biofactors. 2016 Jan;42(1):106-14.
9. Kinlaw WB, Levine AS, Morley JE, Silvis SE, McClain CJ. Abnormal zinc metabolism in type II diabetes mellitus. The American journal of medicine. 1983 Aug 1;75(2):273-7.
10. Peschke E, Stumpf I, Bazwinsky I, Litvak L, Dralle H, Mühlbauer E. Melatonin and type 2 diabetes–a possible link?. Journal of pineal research. 2007 May;42(4):350-8.
11. Doddigarla Z, Parwez I, Abidi S, Ahmad J. Effect of Melatonin and Chromium Picolinate Administration to High Carbohydrate Diet-Fed Male Wistar Rats. Journal of Molecular and Genetic Medicine. 2017;11:1-7.
12. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. Science. 2005 Jan 21;307(5708):384-7.
13. Nsonwu AC, Usoro CA, Etukudo MH, Usoro IN. Serum and urine levels of chromium and magnesium in type 2 diabetics in Calabar, Nigeria. Malaysian Journal of Nutrition. 2005;11(2):133-42.
14. Dzúrik R, Stefíková K, Spustová V, Fetkovská N. The role of magnesium deficiency in insulin resistance: an in vitro study. Journal of hypertension. 1991 Jan 1;9:S314.
15. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Journal of clinical epidemiology. 1995 Jul 1;48(7):927-40.
16. Tosiello L. Hypomagnesemia and diabetes mellitus: a review of clinical implications. Archives of internal medicine. 1996 Jun 10;156(11):1143-8.
17. Suarez A, Pulido N, Casla A, Casanova B, Arrieta FJ, Rovira A. Impaired tyrosine-kinase activity of muscle insulin receptors from hypomagnesaemic rats. Diabetologia. 1995 Nov 1;38(11):1262-70.
18. Fincham SC, Drobatz KJ, Gillespie TN, Hess RS. Evaluation of plasma-ionized magnesium concentration in 122 dogs with diabetes mellitus: a retrospective study. Journal of veterinary internal medicine. 2004 Sep 1;18(5):612-7.

19. Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesauro P, Varricchio M, d'Onofrio F. Daily magnesium supplements improve glucose handling in elderly subjects. The American journal of clinical nutrition. 1992 Jun 1;55(6):1161-7.
20. Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes care. 1997 Apr 1;20(4):545-50.
21. Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of clinical diabetes in women. The American Journal of Clinical Nutrition. 1992 May 1;55(5):1018-23.
22. Meyer KA, Kushi LH, Jacobs Jr DR, Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. The American journal of clinical nutrition. 2000 Apr 1;71(4):921-30.
23. Kao WL, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Archives of Internal Medicine. 1999 Oct 11;159(18):2151-9.
24. Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. Archives of biochemistry and biophysics. 2007 Feb 1;458(1):40-7.
25. Sales CH, Pedrosa LD. Magnesium and diabetes mellitus: their relation. Clinical nutrition. 2006 Aug 1;25(4):554-62.
26. Viktorínová A, Tošerová E, Križko M, Ďuračková Z. Altered metabolism of copper, zinc, and magnesium is associated with increased levels of glycated hemoglobin in patients with diabetes mellitus. Metabolism. 2009 Oct 1;58(10):1477-82.
27. Kundu D, Osta M, Mandal T, Bandyopadhyay U, Ray D, Gautam D. Serum magnesium levels in patients with diabetic retinopathy. Journal of natural science, biology, and medicine. 2013 Jan;4(1):113.
28. Walter RM, Uriu-Hare JY, Olin KL, Oster MH, Anawalt BD, Critchfield JW, Keen CL. Copper, zinc, manganese, and magnesium status and complications of diabetes mellitus. Diabetes care. 1991 Nov 1;14(11):1050-6.
29. Keane WF, Brenner BM, De Zeeuw D, Grunfeld JP, McGill J, Mitch WE, Ribeiro AB, Shahinfar S, Simpson RL, Snapinn SM, Toto R. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. Kidney international. 2003 Apr 1;63(4):1499-507.
30. Ritz E, Rychlík I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. American journal of kidney diseases. 1999 Nov 1;34(5):795-808.
31. Agrawal P, Arora S, Singh B, Manamalli A, Dolia PB. Association of macrovascular complications of type 2 diabetes mellitus with serum magnesium levels. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2011 Jan 1;5(1):41-4.
32. Koenig W, Khuseyinova N, Baumert J, Meisinger C, Löwel H. Serum concentrations of adiponectin and risk of type 2 diabetes mellitus and coronary heart disease in apparently healthy middle-aged men: results from the 18-year follow-up of a large cohort from southern Germany. Journal of the American College of Cardiology. 2006 Oct 3;48(7):1369-77.
33. Hebert PL, Geiss LS, Tierney EF, Engelgau MM, Yawn BP, McBean AM. Identifying persons with diabetes using Medicare claims data. American Journal of Medical Quality. 1999 Nov;14(6):270-7.
34. Katon W, Von Korff M, Ciechanowski P, Russo J, Lin E, Simon G, Ludman E, Walker E, Bush T, Young B. Behavioral

and clinical factors associated with depression among individuals with diabetes. Diabetes care. 2004 Apr 1;27(4):914-20.
35. Reaven GM, Reaven EP. Age, Glucose Intolerance, and Non—Insulin-dependent Diabetes Mellitus. Journal of the American Geriatrics Society. 1985 Apr;33(4):286-90.
36. Moore PA, Zgibor JC, Dasanayake AP. Diabetes: a growing epidemic of all ages. The Journal of the American Dental Association. 2003 Oct 1;134:11S-5S.
37. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature reviews endocrinology. 2012 Apr;8(4):228.
38. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. JAMA internal medicine. 2014 Feb 1;174(2):251-8.
39. Wolff SP. Diabetes mellitus and free radicals: free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. British medical bulletin. 1993 Jan 1;49(3):642-52.
40. Memısoğullari R, Taysı S, Bakan E, Capoglu I. Antioxidant status and lipid peroxidation in type II diabetes mellitus. Cell Biochemistry and Function: Cellular biochemistry and its modulation by active agents or disease. 2003 Sep;21(3):291-6.
41. Aydın A, Orhan H, Sayal A, Özata M, Şahin G, Işımer A. Oxidative stress and nitric oxide related parameters in type II diabetes mellitus: effects of glycemic control. Clinical biochemistry. 2001 Feb 1;34(1):65-70.
42. Viktorínová A, Tošerová E, Križko M, Ďuračková Z. Altered metabolism of copper, zinc, and magnesium is associated with increased levels of glycated hemoglobin in patients with diabetes mellitus. Metabolism. 2009 Oct 1;58(10):1477-82.
43. Turner RC, Cull CA, Frighi V, Holman RR, UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). Jama. 1999 Jun 2;281(21):2005-12.
44. Navarro JF, Mora C, Macıéa M, Garcıéa J. Inflammatory parameters are independently associated with urinary albumin in type 2 diabetes mellitus. American Journal of Kidney Diseases. 2003 Jul 1;42(1):53-61.
45. Lin CC, Huang YL. Chromium, zinc and magnesium status in type 1 diabetes. Current Opinion in Clinical Nutrition & Metabolic Care. 2015 Nov 1;18(6):588-92.
46. Nasli-Esfahani E, Faridbod F, Larijani B, Ganjali MR, Norouzi P. Trace element analysis of hair, nail, serum and urine of diabetes mellitus patients by inductively coupled plasma atomic emission spectroscopy. Journal of Diabetes & Metabolic Disorders. 2011;10:1.
47. Ekmekcioglu C, Prohaska C, Pomazal K, Steffan I, Schernthaner G, Marktl W. Concentrations of seven trace elements in different hematological matrices in patients with type 2 diabetes as compared to healthy controls. Biological Trace Element Research. 2001 Mar 1;79(3):205-19.
48. Zargar AH, Bashir MI, Masoodi SR, Laway BA, Wani AI, Khan AR, Dar FA. Copper, zinc and magnesium levels in type-1 diabetes mellitus. Saudi medical journal. 2002;23(5):539-42.