REVIEW ARTICLE

European Journal of Medical and Health Sciences
www.ejmed.org

Level of Micronutrients Affects Pathophysiology of Diabetes Mellitus: A Scoping Review

Dominic Kiprotich, Nourine C. Yegon and Michael N. Walekhwa

ABSTRACT

Currently, 463 million adults across the globe are living with diabetes. If undeterred, this figure is projected to rise to 700 million by 2045. About 79% of adult diabetics live in Africa; majority of whom are undiagnosed. Several interventions are already available, but the disease prevalence seems steady on an upward trajectory. The economic cost of managing diabetes is overwhelming considering that type II cases have overly and audaciously continues to rise. This underpins the need for exploration of more feasible and relatively inexpensive interventions. We profiled the role of micronutrients in the pathophysiology of diabetes mellitus (DM). Findings from 10 studies published in highly refereed journals and indexed in Research Gate, PubMed, and Elsevier were synthesized, collated, and reported. Guidelines such as year of publication, conflict of interest, type of journal, research design among others, informed the process of study selection. The level of Selenium (Se) and Copper (Cu) was higher when HBA1C was higher. Further, the level of Mg, P, K, & Vitamin D correlated inversely with HBA1C. Some studies reported increased levels of Zinc (Zn) in DM subjects while others reported a decrease. Diabetes mellitus subjects should reduce intake of Se and Cu and increase intake of Mg, P, K, & Vitamin D.

Keywords: Diabetes, diabetes mellitus, micronutrients.

Submitted: August 20, 2021

Published: September 27, 2021

ISSN: 2593-8339

DOI: 10.24018/ejmed.2021.3.5.1019

D. Kiprotich
Department of Human Nutrition & Dietetics, School of Medicine & Health Sciences, Kabarak University, Kenya.
(e-mail: dominickiprotich4@gmail.com)
N. C. Yegon
Department of Human Nutrition & Dietetics, School of Medicine & Health Sciences, Kabarak University, Kenya.
(e-mail: chepnorryn@gmail.com)
M. N. Walekhwa*
Department of Biomedical Sciences, School of Medicine & Health Sciences, Kabarak University, Kenya.
(e-mail: walekhwam@gmail.com)

Corresponding Author

I. INTRODUCTION

Diabetes Mellitus (DM) continues to represent a significant public health concern across the world [1]. While the bigger burden of DM has for a long time been a problem among developed countries, it seems to be steadily shifting focus to Africa as well as other economically underprivileged regions. Worse still, the bulk of global mortality cases are currently occurring in the latter [2]. For instance, there are 463 million cases of diabetes in the world today. If unchecked, this figure is likely to rise to 700 million by 2045. Out of the projected increase, 63 million, 49 million and 47 million will occur in North America, South & Central America and Africa, respectively. While the capacity to diagnose is poor and non-exhaustive, the African continent is projected to represent the greatest increase of global cases at 143% [3]. These figures are enormous and epitomize a genuine cause for priority concern.

Data regarding the cumulative economic cost of managing diabetes are increasingly becoming available. Evidently, governments and individuals alike spend colossal amounts of money in an effort to improve disease prognosis and prolong life. To achieve better treatment outcomes, a diabetes patient spends in excess of $9600 every year. This amount is up to 2.3 times higher than what a non-diabetic spends on healthcare over a similar period [4]. Globally, over $727 billion is injected into management of diabetes yearly. Unfortunately, this figure is projected to rise to $776 billion by 2045 [5]. With an already emaciated economy, Africa spent $3.4 billion in 2015 and this figure will rise to $5.5 billion in 2040 as the burden of diabetes is surely on a skyrocketing trajectory [3], [6]. Excluding diabetes management, Kenya spends an average of 4.6% of her Gross Domestic Product (GDP) on healthcare [7]. With such arrangement and with the projected upsurge in the prevalence of diabetes, the risk of poverty and non-compliance is at all-time high. Interventions, feasible enough to reverse these worrying statistics must be immediately explored.

Over time, several interventions to manage diabetes have been exploited [8]. They comprise dietary intervention, consistent physical activity, health education and intake of medication [9]. While medication constitutes the most important intervention, patient purchasing power has remained a significant hindrance [10]. Consequently, the case fatality rate has become higher especially for subjects living in low- and middle-income countries. One would wonder why people in these regions have yet to consider deliberate physical activity as it represents an easy to perform, likely effective and relatively affordable alternative. However, the lack of and costs necessary to accessing modern and safe training stadia and gymnasia could be prohibitive. As such, dietary management though inadequately explored seems to be the most promising and viable way forward. Wide-ranging paucity of data regarding the role of macro nutrients in the dynamics of diabetes is a fundamental setback to effective management [11]. Of greater importance is the lack of adequate knowledge on the role of micronutrients in the pathogenesis of diabetes [12].

Against this background, we reviewed published articles in order to provide clear information on the role of micronutrients in the kinetics of DM.

II. Methodology

A. Protocol and Registration

This review was carried out according to guidelines by Vrabel [13].

B. Eligibility Criteria

Several eligibility criteria regarding selection of systematic review articles were considered. All articles included satisfied the following rationale:

i. Published after January, 2012;
ii. Involves role of micronutrients in management of diabetes;
iii. Published in English language or has a current valid translation and;
iv. Published in highly refereed and peer reviewed journals.

C. Information Sources

Three medical databases were searched for articles that meet the set criteria. They include Research Gate, PubMed and Elsevier. The databases were accessed between 28th June 2021 and 26th July 2021. Corresponding authors were contacted to clarify any information that appeared vague to the study review team.

D. Search Criteria

Relevant medical subject headings were used to search for articles in the selected databases using Google Scholar as the search engine. This included the following:

Diabetes Mellitus;

1. Micronutrients;
    - Selenium
    - Potassium
    - Phosphorus
    - Magnesium
    - Bromide
    - Zinc
    - Copper
2. Diabetes and Micronutrients and;
3. Micronutrients and Diabetes

E. Selection of Studies

Several considerations informed the process of study selection. They include:

1. Conflict of interest;
2. Affiliation of the author;
3. Research design of the study;
4. The duration since the article was last published;
5. Type of the journal;
6. The language used and;
7. Any article that failed to satisfy the outlined threshold was excluded.

F. Data Collection Process & Synthesis of Results

The process of data collection was done as follows:

1. Each member of the review team individually synthesized results for each of the selected articles.
2. The entire team jointly analyzed synthesized results from each team member.
3. Congruent results were represented in a matrix table (Table I).

G. Data Items

Synthesis of results from the selected articles was guided by the following items:

1. The title of the study;
2. Research design and implementation;
3. Objectives of the study;
4. Results obtained;
5. Discussion;
6. Sources of funding and;
7. The institutional affiliation of the author

H. Risk of Bias in Individual Studies

The study methodology for the selected articles reviewed was assessed to guarantee that the design used does not in any way introduce a possibility of bias. Only results that entailed collection & analysis of empirical data were assessed.

I. Risk of Bias Across all Studies

The GRADE system of imprecision/bias analysis according to [14] was used. This GRADE system recommended that findings be summarized in brief, transparent and enlightening tables that showed quality of evidence and the degree of relative and absolute influence for each key outcome.

J. Prisma Table

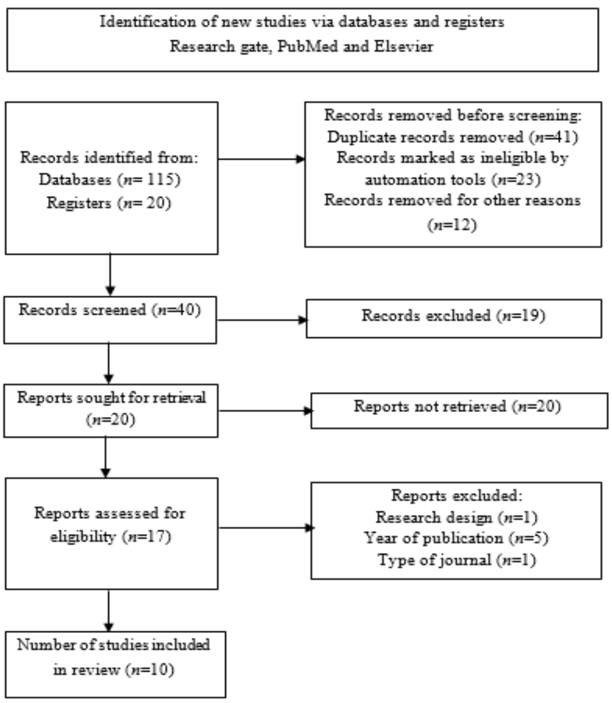

Fig. 1. Article selection criteria.

TABLE I: REVIEW RESULTS

No:	Author	Title	Major outcomes

1.	[15]	Alteration of Serum Trace Elements in Patients with Type 2 Diabetes	o Cross- sectional study design was used
			o The total number of study participants was 1837 (637 males and1200 females)
			o 510 participants had type II diabetes while;
			o 1327 were non-diabetics;
			
			o A total of 19 trace elements were assessed
			
			Levels of trace elements among the studied subjects either increased or decreased as follows:
			o Trace elements that significantly increased among type II diabetic patients include:
			    o Copper (Cu:(p<0.01);
			    o Zinc (Zn:(p<0.001) and;
			    o Selenium (Se:(p<0.001)
			    o Trace elements that reduced among type II diabetic patients include:
			    o Magnesium (Mg: p < 0.05)
			o The level of the remaining trace elements (TE) was not affected in both diabetes type II as well as non-diabetic subjects;
			o Several factors were found to be associated with the increase of Zn, Cu and Se. They include:
			    o Age;
			    o Body Mass Index (BMI);
			    o Systolic & Diastolic Blood Pressure and;
			    o Serum Insulin
			o Blood glucose levels within 2 hours after food consumption or OGTT was significantly associated with selected TEs at 0.99 CI as follows:
			    o Mg (r:-0.393) decreased and;
			    o Zn, Se and Cu significantly increased
			o Fasting Blood Glucose (FBG) was found to be significantly correlated with selected TEs as follows:
			    o Mg (r:-0.399) decreased and;
			    o Cu, Zn & Se increased
			o HbA1C was further categorized into 3 subgroups so as to be able to test for the relationship with selected TEs as follows:
			    o HbA1C < 6%;
			    o HbA1C between 6% and 7% and:
			    o HbA1C>7%
			o The results were as follows:
			    o Mg significantly decreased in HbA1C > 7% group and there was no difference when HbA1C < 7%
			    o Cu and Zn significantly increased HbA1C > 7% group compared with the other two groups
			    o Se significantly increased in HbA1C >6% groups

2.	[16]	Effect of Chromium Supplementation on Blood Glucose, Hemoglobin A1c, Lipid Profile and Lipid Peroxidation in Type 2 Diabetic Patients	o Experimental study design was used
			o The study comprised of 100 type 2 diabetic subjects. subjects were randomly divided into study and placebo groups;
			o Out of the 50 cases, 43 subjects completed the study, the seven subjects did not complete the study due to the following reasons:
			    o Four subjects had uncontrolled hyperglycemia and other complications and they were placed on insulin management
			    o Three subjects had personal issues and wished not to continue with the study
			o The age of the study subjects ranged from 40-70 years
			o The study group received 200µg of chromium picolinate capsule two times a day for 12 weeks
			o The placebo group received capsule without chromium for 12 weeks
			o Consumption of chromium picolinate by type 2 diabetic patients significantly reduced:
			    o Fasting blood glucose (p≤ 0.01) and;
			    o HbA1C (p<0.001);

3.	[17]	Glycemic Control, Micronutrients and some Metabolic Enzyme Activity in Type 2 Diabetes	o Case control study design was used; o The study had a total of 100 subjects; o Fifty type 2 diabetic patients known for a period of 1 year preceding the study (32 males, 24 females) and; o Fifty non diabetic subjects (28 males and 16 females) o There was a significant increase in levels of Ca, Fe and vitamin C among type 2 diabetic patients (p<0.05); o Phosphorus levels were reduced among type 2 diabetic patients compared to non-diabetic subjects (p<0.05); o Although reduced, phosphorus levels were higher in male compared to female subjects (p<0.05); o Ca levels increased with increasing age in all subjects of the study (p<0.05);

European Journal of Medical and Health Sciences
www.ejmed.org

TABLE I: REVIEW RESULTS

			o Phosphorus levels decreased with increasing age in all subjects of the study ($p<0.05$); o Increased Ca activity was detected in diabetics with poor metabolic control compared to those with good control ($p<0.05$) and; o Subjects who had had diabetes for a period of ≥5 years prior to the study had significantly increased vitamin C levels compared to those who had had diabetes for a period of ≤ 5 years ($p<0.05$)

4.	[18]	Higher Plasma Selenium Concentrations are Associated with Increased Odds of Prevalent Type 2 Diabetes	o The study subjects included type 2 diabetic patients and non-diabetic subjects distributed as follows:
			    o 172 type 2 diabetic patients and;
			    o 1555 non-diabetic subjects
			o Subjects were stratified by tertile of baseline plasma selenium concentrations as follows:
			    o 113.5 ± 9.7 ng/mL (n = 572)
			    o 135.4 ± 5.9 ng/mL (n = 571)
			    o 168.7 ± 23.4 ng/mL (n = 571)
			o Diabetic subjects were slightly older, more likely to be male and had a BMI >30kg/m^2;
			o Type 2 diabetic patients had a higher consumption of energy and other macronutrients;
			o Participants in the highest tertile of baseline selenium were more likely to be male and had a higher percentage of BMI of 25 to <30 kg/m^2 or BMI≥30 kg/m^2 when compared to those in the lowest tertile;
			o Participants in the highest tertile of baseline selenium concentrations had highest odds of prevalent type 2 diabetes (OR: 1.77; 95% CI: 1.16, 2.71);
			    o Participants aged <63 years had baseline selenium value either in the second or third tertile which was significantly associated with higher odds of type 2 diabetes (P-trend = 0.01) and;
			    o There were increased odds of prevalent type 2 diabetes with increasing tertile of selenium for men (P-trend = 0.01)

5.	[19]	Intakes of Zinc, Potassium, Calcium, and Magnesium of Individuals with Type 2 Diabetes Mellitus and the Relationship with Glycemic Control	o Cross-sectional study design was employed in the study;
			o The study involved participants with type 2 diabetes mellitus;
			o The study had a total of 95 participants and 69.5% of the participants were female;
			o Micronutrients assessed included: zinc, potassium, magnesium and calcium;
			o The participants were divided into groups according to their micronutrient intake:
			    o Group 1 – lower intake of micronutrients and;
			    o Group 2 – higher intake of micronutrients
			o The group with lower intake of micronutrients presented a significantly higher percentage of:
			    o HbA1C (p = 0.006) and;
			    o Triglyceride concentrations (p = 0.01)
			    o There was association between increased % HbA1C with:
			    o Lower intake of micronutrients (OR = 3.041, 95% CI =1.131; 8.175) and:
			    o Time taken to diagnose type 2 diabetes (OR= 1.155, 95% CI = 1.043; 1.278)
			
			o There was a decrease in %HbA1C for every:
			    o 1g of potassium ingested (1% decrease in %HbA1C) and;
			    o 100mg of magnesium ingested (0.7% decrease in %HbA1C)

6.	[20]	Role of Vitamin D on Glycemic Control and Oxidative Stress in Type 2 Diabetes Mellitus	o Case-control study design was used;
			o The study comprised of only male subjects aged 36-53 years;
			o The total number of subjects were 50 and distributed as follows:
			    o Thirty males with type 2 diabetes mellitus as cases and;
			    o Twenty healthy males as controls
			o Type 2 diabetic patients had a significantly lower vitamin D levels (P = 0.015);
			o Vitamin D had a negative correlation as follows:
			    o With HbA1c: (P = 0.016) and;
			    o With Postprandial blood sugar: (P = 0.018)
			    o Vitamin D had no correlation with:
			    o Fasting Blood Sugar
			    o Glutathione peroxidase
			o Glutathione peroxidase (GPx) activity in patients with type 2 diabetes was a significantly lower *(P = 0.048)*

7.	[21]	The Association Between Dietary Selenium Intake and Diabetes: A Cross-Sectional Study among Middle-Aged and Older Adults	o Cross-sectional study design was used;
			o The study had a total of 5443 subjects, aged ≥40 years and distributed as follows:
			    o 2882 males and;
			    o 2541 females
			o Four categories were formed according to selenium intake categories on the basis of quartile distribution in the study:
			    o ≤29.56 μg/day,
			    o 29.57–40.14 μg/day,
			    o 40.15–52.20 μg/day and
			    o ≥52.21 μg/day

TABLE I: REVIEW RESULTS

			o There was significant difference observed across all groups in terms of: o Age; o Sex; o Education level; o Employment; o BMI; o Activity level; o Waist circumference; o Alcohol consumption; o Smoking status; o Nutritional supplementation; o Energy intake; o Fiber intake and; o Fasting glucose o Diabetes prevalence for the target population was 9.7%; o Significant difference between diabetic and non-diabetic participants was noted in relation to: o Age, o Sex, o BMI, o Waist circumference, o Hypertension, o Smoking status, o Energy intake, o Fiber intake, and o Selenium intake. o There was a significant positive association between selenium intake and diabetes (p for trend =0.03); o There was a significant positive association between selenium intakes and diabetes among the sub-group with BMI <25 (P for trend = 0.02); o There was minor positive association between selenium intake and diabetes among the male subgroup (P for trend = 0.09) and; o There was no significant positive association between selenium intake and diabetes in the following subgroups: o Female (P for trend = 0.35) and; o BMI ≥25 (P for trend = 0.47)
8.	[22]	Trace Elements in Diabetes Mellitus	o Case control study design was used; o The study had a total of 80 subjects, aged between 35-60 years: o Forty subjects without diabetes mellitus formed the control group and; o Forty subjects with diabetes mellitus for >5 years and not taking any TE supplement formed the case group o Zinc and magnesium levels were assessed and; o The serum levels of Magnesium and zinc were significantly lower among subjects with diabetes mellitus (p< 0.001)
9.	[23]	Trace Elements in Early Phase Type 2 Diabetes Mellitus—A Population-Based Study. The HUNT Study in Norway	o Case control study design was used; o The study had 128 subjects with type 2 diabetes and 755 subjects in control group; o A total of 26 TEs were assessed; o Waist-to-hip ratio was used to form three categories based on the tertile distribution among the controls: o ≤0.88, o >0.88–< 0.94 and o ≥0.94 o There was a significant increase in prevalence of diabetes across tertiles for the following TEs (P trend < 0.05): o Cadmium; o Chromium; o Iron; o Nickel; o Silver and; o Zinc o There was a decrease in prevalence across tertiles for bromine (P trend < 0.05)
10.	[24]	Vitamin D and Glycemic Control in Diabetes Mellitus Type 2	o Case control study design was used o The study had 120 subjects with type 2 diabetes mellitus and 120 subjects in control group; o The study subjects were of the same age (25-82years) and sex; o HbA1C and 25-hydroxyvitamin D3 (25(OH)D3) were measured; o The levels of HbA1C were increased among patients with type 2 diabetic mellitus (p < 0.001, Student's t-test); o Levels of $25(OH)D_3$ were reduced among type 2 diabetic patients than the control group (*p* < 0.001); o 17.5% of patients with type 2 diabetes mellitus had vitamin D deficiency and levels

TABLE I: REVIEW RESULTS

	$25(OH)D_3$ were ≤ 10 ng/ml compared to 5.8% in the control group (chi-squared test, p = 0.0089); o 63.3% type 2 diabetic patients had mild vitamin D deficiency and < 20 ng/ml of levels of $25(oh)D_3$ compared to 23,3% in the control group (chi-squared test, p < 0.0001) and; o 25(OH) D_3 levels were inversely associated with HbA1C levels among patients with type 2 diabetes (p = 0.008, r = 0.058, linear regression analysis).

III. Discussion

Micronutrients (MNs) play a crucial role in the kinetics of diabetes mellitus (DM). Their upsurge or decrease can either be detrimental or favorable to the prognosis of the disease. For instance, [15] reported an increase in levels of Copper (Cu), Zinc (Zn) and Selenium (Se) as well as a decrease in the level of Magnesium (Mg) among type II diabetic patients. Further, the study documented a direct correlation between the former and increased age, body mass index (BMI) greater than 30, and elevated Systolic & Diastolic Blood Pressure. According to [25], Cu contains anti-oxidant properties. As such, it plays an integral role in the elimination of free radicals which are pre-cursors for a range of conditions including diabetes and malignancies. Moreover, Cu regulates the level of cholesterol and triglycerides in the body. The two are quite fundamental in the dynamics of blood pressure and heart-rate which have a strong kinship with development of DM. Reference [26] associated Cu-water with a more efficient digestion process and nutrient absorption stature. The former and the latter constitute critical events in the management process of DM.

Interestingly, unlike [15], most other studies have reported reduced levels of Zn among DM subjects. For example, [27] attributes the decrease in levels of Zn among DM subjects to increased loss through micturition while [28] documents deficient Zn levels and consequently, poor glycemic control among DM subjects. According to [29], Zn is responsible for physiological efficiency of over 300 enzymes as well as the integrity of key immunological cells like Natural Killer cells (NK-cells) and Neutrophils. Findings of [15] regarding Zn are therefore inconsistent with most other studies including [22] and may underpin the need for further methodological interrogation. While it is a clear shift from what is expected, the position of [15] seems consistent with that of [23]. Selenium (Se) is a crucial component in the process of development of antioxidant enzymes which play a pivotal role in the prevention of cell damage. It is associated with increased production of antibodies as well as improved performance of T-helper cells (Th-cells), cytotoxic T-cells (CTLs) and NK-cells. However, Se is only needed by the body in trace amounts as increased in-take may increase the risk of heart, liver, and kidney damage [30]. The role of Se in the pathogenesis of DM is yet to be clearly profiled. Reference [21] citing [31]-[33] reported that high level of serum Se may either increase or reduce the risk of DM. Obviously, this needs to be urgently studied and the actual role of Se in DM be accurately documented. According to [18], [21], the level of Se is likely to be higher in males of increased age and BMI than in females. These points to a possibility that it may be associated with increased odds of developing or poor DM prognosis.

According to [15], [17], [19], [20], the level of Magnesium (Mg), Phosphorous (P), Potassium (K) and Vitamin D among DM subjects reduced. Reference [34], reports that Mg regulates blood sugar levels. The study further documents that hypomagnesemia is often consistent with DM subjects and it is associated with elevated insulin resistance. On the same note, [35] postulates that insulin and glucose are pivotal to efficient metabolism of Mg. Cumulatively, Mg constitutes a bedrock of multiple biochemical reactions, supports optimal physiology of the immune system, and helps maintain a steady heartbeat. Low level of Mg among DM subjects may therefore be justifiably consistent with poor disease prognosis. Phosphorus has a nexus with how the body utilizes fats and carbohydrates. Further, it optimizes the functioning of the kidney as well as help maintain a normal heartbeat. References [36], [37] associates' consumption of phosphorus (P) with a reduction in postprandial glucose and insulin at minute 60. Reference [38] correlates low level of K with reduced production of insulin. Low production of insulin is often consistent with poor glycemic control & an increased likelihood of unfavorable disease outcome. Further, Potassium (K) enhances entry of nutrients into cells and ejection of waste matter out of cells. The element also counters negative effects of Sodium (Na) on blood pressure & significantly lowers the risk of development of DM. Vitamin D enhances sensitivity of the body to insulin and accordingly diminishes chances of insulin resistance. Moreover, it plays a fundamental role in the process of metabolism; help reduce cellular damage while optimizing cell physiology. These events underpin favorable management of DM.

References [23], [24] reported a decrease in the level of 25-hydroxyvitamin D_3 (25(OH) D_3) and Bromide (Br) respectively. The former reported an inverse relationship between 25(OH) D_3 and HBA_1C while the latter directly reported low level Br in DM subjects. According to [39], Br accelerates diabetes wound healing by inhibiting inflammatory responses and reducing oxidative stress. However, in the letter to the editor, [40], reported that Br has a long half-life and may be slightly toxic (bromism).

A. Review Limitations

This review involved papers published in specific databases. It is therefore possible that further or different information may be available in study papers published elsewhere.

B. Conclusion(s)

1. Increased serum/plasma level of Se & Cu is consistent with unfavorable prognosis of DM;
2. Reduced serum/plasma level of Mg, P, K, & Vitamin D correlates with favorable prognosis of DM and;
3. The role of Zn in the pathogenesis of DM remains unclear

C. Expert Opinion(s)

Based on the results synthesized above, we recommend as follows:

1. Diabetes Mellitus patients should scale down intake/supplementation of Se & Cu;
2. Diabetes Mellitus patients should increase intake/supplementation of Mg, P, K &Vitamin D and;
3. Targeted studies should be done to reveal the role of Zn in the pathogenesis of DM.

D. Conflict of Interest

Authors declare no conflict of interest.

References

[1] F. O. O. Olabiyi, "Role of nutrition in the management of diabetes mellitus," *Forum Nutr*, *56*, 170–174, 2013. https://doi.org/10.21276/apjhs.2016.3.1.1

[2] World Health Organization. *Global report on diabetes*. file:///C:/Users/ICTSERVICES/Downloads/9789241565257_eng.pdf. 2016.

[3] International Diabetes Federation. International Diabetes Federation. In *The Lancet,* 266(6881), 2019. https://doi.org/10.1016/S0140-6736(55)92135-8.

[4] W. Yang, T. M. Dall, K. Beronjia, J. Lin, A. P. Semilla, R. Chakrabarti, P. F. Hogan, and M. P. Petersen, "Economic costs of diabetes in the U.S. in 2017," *Diabetes Care*, *41*(5), 917–928, 2018. https://doi.org/10.2337/dci18-0007.

[5] International Diabetes Federation. International Diabetes Federation. In *The Lancet*, 266(6881), 2019. https://doi.org/10.1016/S0140-6736(55)92135-8.

[6] International Diabetes Federation. *IDF DIABETES ATLAS*. https://www.diabetesatlas.org/upload/resources/previous/files/7/IDF Diabetes Atlas 7th.pdf. 2015.

[7] World Health Organization. *World Health Statistics 2009.* World Health Organization. https://www.who.int/gho/publications/world_health_statistics/EN_WHS09_Full.pdf. 2009.

[8] International Diabetes Federation. *International Diabetes Federation Anual Report*, 2016.

[9] A. D. Kurnia, A. Amatayakul, and S. Karuncharernpanit, "Predictors of diabetes self-management among type 2 diabetics in Indonesia: Application theory of the health promotion model," *International Journal of Nursing Sciences*, *4*(3), 260–265, 2017. https://doi.org/10.1016/j.ijnss.2017.06.010.

[10] World Health Organization. *Global report on diabetes*. file:///C:/Users/ICTSERVICES/Downloads/9789241565257_eng.pdf. 2016.

[11] M. J. Franz, J. P. Bantle, C. A. Beebe, J. D. Brunzell, J. Chiasson, A. Garg, L. Ann Holzmeister, B. Hoogwerf, E. Mayer-davis, A. D. Mooradian, J. Q. Purnell, and M. Wheeler, "Evidence-Based Nutrition Principles and Recommendations for the Treatment and Prevention of Diabetes and Related Complications," *Diabetes Care,* 25(1), 148-198, 2002.

[12] A. D. Mooradian, B. Hoogwerf, M. Maryniuk, and J. Wylie-Rosett, "Selected Vitamins and Minerals in Diabetes," *Diabetes Care,* 7(5), 464-479, 1994.

[13] M. Vrabel, "Preferred Reporting Items for Systematic Reviews and Meta-Analyses," *Oncology Nursing Forum*, *42*(5), 552–554, 2015. https://doi.org/10.1188/15.ONF.552-554.

[14] G. Guyatt, A. D. Oxman, E. A. Akl, R. Kunz, G. Vist, J. Brozek, S. Norris, Y. Falck-Ytter, P. Glasziou, H. Debeer, R. Jaeschke, D. Rind, J. Meerpohl, P. Dahm, and H. J. Schünemann, "GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables," *Journal of Clinical Epidemiology*, *64*(4), 383–394, 2011. https://doi.org/10.1016/j.jclinepi.2010.04.026.

[15] H. Zhang, C. Yan, Z. Yang, W. Zhang, Y. Niu, X. Li, L. Qin, and Q. Su, "Alterations of serum trace elements in patients with type 2 diabetes," *Journal of Trace Elements in Medicine and Biology*, *40*, 91–96, 2017. https://doi.org/10.1016/j.jtemb.2016.12.017.

[16] N. Parsaeyan, and H. Mozaffari–Khosravi, "Effect of Chromium Supplementation on Blood Glucose, Hemoglobin A1c, Lipid Profile and Lipid Peroxidation in Type 2 Diabetic Patients," *Iranian Journal of Diabetes and Obesity*, *4*(4), 178–184, 2012.

[17] A. Nsonwu-Anyanwu, E. Egbe, J. Offor, and C. Usoro, "Glycemic control, micronutrients and some metabolic enzyme activity in type 2 diabetes," *International Journal of Research in Medical Sciences*, 2757–2764, 2015. https://doi.org/10.18203/2320-6012.ijrms20150827.

[18] L. N. Kohler, A. Florea, C. P. Kelley, S. Chow, P. Hsu, K. Batai, K. Saboda, P. Lance, and E. T. Jacobs, "Higher plasma selenium concentrations are associated with increased odds of prevalent type 2 diabetes," *Journal of Nutrition*, *148*(8), 1333–1340, 2018. https://doi.org/10.1093/jn/nxy099.

[19] P. N. Brandão-Lima, G. B. De Carvalho, R. K. F. Santos, B. da C. Santos, N. L. Dias-Vasconcelos, V. de S. Rocha, K. B. F. Barbosa, and L. V. Pires, "Intakes of Zinc, Potassium, Calcium, and Magnesium of individuals with type 2 diabetes mellitus and the relationship with glycemic control," *Nutrients*, *10*(12), 2018. https://doi.org/10.3390/nu10121948.

[20] M. Saif-Elnasr, I. M. Ibrahim and M. M. Alkady, "Role of vitamin D on glycemic control and oxidative stress in type 2 diabetes mellitus," *Journal of Research in Medical Sciences*, *22*(1), 2017. https://doi.org/10.4103/1735-1995.200278.

[21] J. Wei, C. Zeng, Q. Y. Gong, H. B. Yang, X. X. Li, G. H. Lei, and T. B. Yang, "The association between dietary selenium intake and diabetes: A cross-sectional study among middle-aged and older adults," *Nutrition Journal*, *14*(1), 2015. https://doi.org/10.1186/s12937-015-0007-2.

[22] S. Praveeena, S. Pasula, and K. Sameera, "Trace elements in diabetes mellitus," *Journal of Clinical and Diagnostic Research*, *7*(9), 1863–1865, 2013. https://doi.org/10.7860/JCDR/2013/5464.3335.

[23] A. F. Hansen, A. Simić, B. O. Åsvold, P. R. Romundstad, K. Midthjell, T. Syversen, and T. P. Flaten, "Trace elements in early phase type 2 diabetes mellitus—A population-based study," The HUNT study in Norway. *Journal of Trace Elements in Medicine and Biology*, *40*, 46–53, 2017. https://doi.org/10.1016/j.jtemb.2016.12.008.

[24] I. Kostoglou-Athanassiou, P. Athanassiou, A. Gkountouvas, and P. Kaldrymides, "Vitamin D and glycemic control in diabetes mellitus type 2," *Therapeutic Advances in Endocrinology and Metabolism*, *4*(4), 122–128, 2013. https://doi.org/10.1177/2042018813501189.

[25] M. Ware, "Health Benefits and Risks of Copper Medical News Today," *Medical News Today*, 1–16, 2017. www.medicalnewstoday.com.

[26] New Delhi Television. *Copper Water May Be An Effective Way To Manage Diabetes Naturally*. https://www.ndtv.com/food/diabetes-management-copper-water-may-be-an-effective-way-to-manage-diabetes-naturally-1911893. Retrieved on 19 th August, 2021: 2018.

[27] J. Chehade, M. Sheikh-Ali, and A. D. Mooradian, "The role of micronutrients in managing diabetes," *Diabetes Spectrum*, *22*(4), 214–218, 2009. https://doi.org/10.2337/diaspect.22.4.214.

[28] D. Farooq, A. Alamri, B. Alwhahabi, A. Metwally, and K. Kareem, "The status of zinc in type 2 diabetic patients and its association with glycemic control," *Journal of Family and Community Medicine*, *27*(1), 29–36, 2020. https://doi.org/10.4103/jfcm.JFCM_113_19.

[29] C. Wong, K. Braun, J. Bouranis, E. Davis, T. Sharpton, and E. Ho, "Effects of Zinc Status and Aging on Age-Related Immune Dysfunction and Chronic Inflammation," Current Developments in Nutrition, 4(Supplement_2), 1854-1854.

[30] M. A. Youssef, S. A. El-Khodery and H. M. M. Ibrahim, "Effect of selenium and vitamin C on clinical outcomes, trace element status, and antioxidant enzyme activity in horses with acute and chronic lower airway disease. A randomized clinical trial," *Biological Trace Element Research*, *152*(3), 333–342, 2013. https://doi.org/10.1007/s12011-013-9636-5.

[31] J. Bleys, A. Navas-Acien, E. Guallar, "Annals of Internal Medicine Editorial Selenium and Diabetes : More Bad News for Supplements," *Annals of Internal Medicine*, *9*, 50–52, 2007.

[32] M. Navarro-Alarcón, H. López-Garcia De La Serrana, V. Pérez-Valero and C. López-Martínez, "Sevum and urine selenium concentrations in patients with cardiovascular diseases and relationship to other nutritional indexes," *Annals of Nutrition and Metabolism*, *43*(1), 30–36, 1999. https://doi.org/10.1159/000012764.

[33] M. Navarro-Alarcón, H. López-Garcia De La Serrana, V.Pérez-Valero, V., & López-Martínez, C. Sevum and urine selenium concentrations in patients with cardiovascular diseases and relationship to other nutritional indexes. *Annals of Nutrition and Metabolism*, 1999:*43*(1), 30–36. https://doi.org/10.1159/000012764.

[34] V. Higuera, "Magnesium and Diabetes : How Are They Related*?"* 1–10, 2019.

[35] M. Barbagallo, "Magnesium and type 2 diabetes," *World Journal of Diabetes*, *6*(10), 1152, 2015. https://doi.org/10.4239/wjd.v6.i10.1152.

[36] U.S National Library of Medicine. *Phosphorus in diet*. Medline Plus. http://www.nlm.nih.gov/medlineplus/ency/article/002424.htm. Retrieved on 19 th August, 2021.

[37] M. C. Khattab, Abi-Rashed, H. Ghattas, S. Hlais, and O. Obeid, "Phosphorus ingestion improves oral glucose tolerance of healthy male subjects: A crossover experiment," *Nutrition Journal*, *14*(1), 1–8, 2015. https://doi.org/10.1186/s12937-015-0101-5.
[38] Stephanie, W. The link between diabetes and potassium. *WebMD*. https://www.webmd.com/diabetes/potassium-diabetes. 2020.
[39] American Diabetics Association. Nutrition recomndations and interventions for diabetes. Diabetes Care. Jan; 31(Supplement 1): S61-S78. https://doi.org/10.2337/dc08-S061. 2008.
[40] Centers for Disease Control & Prevention. Facts about bromine. https://emergency.cdc.gov/agent/bromine/basics/facts.asp. 2018.