

Lower Plasma Zinc Levels in Hyperglycemic People Living with HIV in the MASH cohort

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Abstract

Background: Zinc deficiency is prevalent in HIV and hyperglycemic patients. Antiretroviral therapy (ART) is a treatment to control HIV progression; however it increases the risk for hyperglycemia. The objective of this study was to assess the plasma zinc levels in hyperglycemic people living with HIV (PLWH).

Methods: Secondary analysis was conducted on the data from the Miami Adult Studies in HIV (MASH) cohort in Florida. Patients were categorized into hyperglycemic group (fasting blood glucose ≥ 100 mg/dL) and normal group (< 100 mg/dL).

Results: Plasma zinc status and CD4 levels were lower in the hyperglycemic group, however the difference was not significant. There was a greater percentage of plasma zinc deficiency in the hyperglycemic group (69%) compared to the normoglycemic group (64%).

Discussion: Although not statistically significant, related biomarkers such as plasma zinc levels and CD4 levels were lower in the hyperglycemic group. This may be due to the role zinc plays in the immune system. Due to the fact that there was a higher percentage of plasma zinc deficiency in the hyperglycemic group (69%) compared to the normoglycemic group (64%), it is important to monitor and manage blood glucose levels to minimize complications. Our findings along with previous findings suggest that zinc supplementation may benefit hyperglycemic PLWH.

Keywords: HIV; Antiretroviral therapy (ART); Zinc; Glucose; Hyperglycemia; Viral load; CD4 count

Introduction

Zinc deficiency is prevalent among people living with the human immunodeficiency virus (PLWH) [1-4]. This may be due to the preferential use of zinc by human immunodeficiency virus (HIV) for viral replication, altered zinc metabolism and/or inadequate dietary zinc intake [1-3]. Low plasma zinc levels directly affect the immune system because zinc is an important co-factor in the maturation of CD4 cells, which are part of the T-cell system of the immune system [5]. In addition, zinc is important for many catalytic enzymatic activity and protein/DNA synthesis [6]. Due to its importance and pervasiveness in all tissues, zinc deficiency has many adverse effects such as impairing the reconstitution of the immune function in PLWH.

In 1996, antiretroviral therapy (ART) was first used to successfully control the HIV viral load [7] and become the standard of treatment for HIV [8]. The treatment, however, has been associated with hyperglycemia and type 2 diabetes [4,9,10]. As a result, PLWH are at a higher risk of developing type 2 diabetes and subsequently cardiovascular disease after initiation of ART [9,11].

While HIV infection is associated with numerous micronutrient deficiencies, ART has been shown to normalize plasma levels of some micronutrients after initiation [8]. However, micronutrients such as zinc, selenium and vitamin A have not been shown to increase after ART initiation [8]. Like HIV-infection, type 2 diabetes is also characterized with low plasma zinc levels [12,13]. This may be attributed to altered mineral metabolism and hyperzincuria [12-14]. Due to HIV infection and the association of ART to hyperglycemia and type 2 diabetes [9,10], PLWH may be at higher risk of developing severe zinc deficiency.

Several studies have assessed zinc status in PLWH and in people with hyperglycemia, but not zinc status in people when both

conditions are present [1-3,12-14]. Currently, research investigating the relationship of zinc status with hyperglycemia/diabetes in PLWH is lacking. The purpose of this study is to examine the relationship of plasma zinc levels and fasting blood glucose (FBG) in PLWH who are hyperglycemic/diabetic. We present data from PLWH who manifest hyperglycemic (prediabetic)/diabetic conditions and their respective zinc levels along with other related variables.

Method

A convenience sample from the Miami Adult Studies on HIV (MASH) cohort was used. The inclusion criteria were being an adult between 18-60 years of age, who had body mass index (BMI) > 18 kg/m² to ensure adequate nutritional status at the beginning of the study. Participants were excluded if they were pregnant, had Hepatitis B or C, End Stage Liver Disease or any chronic inflammatory diseases such as uncontrolled diabetes. Uncontrolled diabetes is defined as FBG ≥ 140 mg/dl [15]. A total of 271 participants were eligible to be included in this study for analyses.

Only the baseline values of FBG, plasma zinc levels, CD4 cell count, HIV viral load, liver fibrosis and zinc intake were included in

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the analysis. The eligible PLWH ($n=271$) were divided into 2 categories: hyperglycemic ($n=60$) and normoglycemic ($n=211$). Criteria for hyperglycemia or normal were based on the guidelines from the American Diabetes Association, which states that FBG < 100 mg/dL is considered to be normal and ≥ 100 mg/dL is considered to be hyperglycemic [16].

The variables FBG, plasma zinc levels, CD4 cell count and HIV viral load were analyzed from the blood that was drawn for the parent studies. Zinc intake was obtained from a validated 24-hour food recall which was then entered into a nutrition analyses database that provided the amount of individual nutritional components, such as zinc and total calories consumed.

Liver fibrosis is measured by FIB-4, an inexpensive and accurate tool to calculate and predict the existence of liver fibrosis. FIB-4 utilizes other variables such as age and platelet count to calculate an index that predicts the extent of liver fibrosis. FIB-4 values <1.45 is known to have a negative predictive value of liver fibrosis and is indicative of a healthy and normal functioning liver; however, FIB-4 values above 3.25 has a positive predictive value of significant liver fibrosis [17].

Due to the fact that alcohol consumption inhibits intestinal zinc absorption, alcohol consumption was included in the analyses. Alcohol consumption is measured by the Alcohol Use Disorders Identification Test (AUDIT) [18] to assess any difference of alcohol consumption in the two study arms. AUDIT is a validated tool developed by the World Health Organization (WHO) to measure and assess alcohol consumption.

Statistical analysis

Descriptive statistics were used to characterize the mean and standard deviations of the continuous variables, and percent was calculated for the categorical variables. Student Independent t-test

was used to determine any significant differences between the two study groups: normoglycemic (<100 mg/dL) and hyperglycemic (≥ 100 mg/dL). One-way ANOVA was used to determine any significant differences between the ethnicities/races. Finally, Pearson Correlation was used to determine any correlations between zinc intake/plasma zinc levels. P values ≤ 0.05 were considered significant.

Results

Our sample population had more males than females (67%), was generally overweight (average BMI=27.6), mostly African American (70%) and were receiving ART medication (80%). Of these characteristics, the only significant different between the 2 groups was BMI, with the hyperglycemic group having a significantly higher BMI (29.2) than the normal group (27.4) (Table 1).

Although not significant, markers of zinc deficiency (<0.75 $\mu\text{g/dL}$) [2], and disease progression (CD4 cell count) were lower in the hyperglycemic group (Table 2). In addition, the percentage of zinc deficiency was higher in the hyperglycemic group (69%) compared to the normoglycemic group (64%), which is equivalent to the entire sample population percentage (64%).

The difference in liver fibrosis as measured by FIB-4 was higher in the hyperglycemic group, however, this difference was not significant ($P=0.099$). FIB-4 values between 1.45 and 3.25 are indicative of liver fibrosis and >3.25 is considered to be severe liver fibrosis [17]. In our sample population, the hyperglycemic group had an average FIB-4 value of 1.44 ± 1.7 , which is approaching the parameters for liver fibrosis, while the normoglycemic group had a normal average of FIB-4 values (1.21 ± 0.6), indicative of no liver fibrosis.

Zinc intake was significantly higher in the hyperglycemic participants (12.6 ± 16.2 vs. 8.5 ± 7.1 , $P=0.005$), compared to the normoglycemic participants, but lost significance when adjusted

Characteristics	Total ($n=271$)	Hyperglycemic ($n=60$)	Normoglycemic ($n=211$)	P-value
Age (years)	45.3 ± 7.9	46.1 ± 7.2	44.6 ± 8.3	0.208
Male %	67%	62%	66%	0.503
Ethnicity %				
African American	70%	65%	53%	0.415
White	6%	8.3%	5.3%	0.388
Hispanic	18%	18.3%	17.4%	0.867
Others	6%	8.4%	24.3%	---
BMI (kg/m^2)	27.6 ± 5.25	29.2 ± 5.7	27.4 ± 5.2	0.037*
ART (Y/N) %	80%	88%	82%	0.235

$p < 0.05$ is considered significant and denoted by *.

Table 1: Population characteristics.

Characteristics	Total ($n=271$)	Hyperglycemic ($n=60$)	Normoglycemic ($n=211$)	P-value
Caloric intake (kcal)	2171 ± 1451	2608 ± 2452	2089 ± 1019	0.091
Zinc Intake (mg)	9.4 ± 9.6	12.6 ± 16.2	8.5 ± 7.1	0.005*
Zinc intake/ 1000kcal	4.41 ± 3.20	4.61 ± 2.98	4.25 ± 3.02	0.673
Plasma zinc level ($\mu\text{g/dL}$)	0.73 ± 0.3	0.70 ± 0.2	0.74 ± 0.3	0.360
Zinc deficient (%)	64%	69%	64%	----
CD4 cell count (cells/mL^3)	497.3 ± 357.01	417.8 ± 439.40	436.8 ± 344.70	0.693
Viral load (\log_{10})	2.70 ± 1.3	2.72 ± 1.3	2.73 ± 1.2	0.959
Albumin (mg/dL)	4.25 ± 0.3	4.3 ± 0.4	4.23 ± 0.3	0.179
FIB-4	1.32 ± 1.1	1.44 ± 1.7	1.21 ± 0.6	0.099
AUDIT Score	9.45 ± 10.1	9.61 ± 10.2	9.8 ± 10.1	0.900

$p < 0.05$ is considered significant and denoted by *.

Table 2: Results.

by intake in g/1000 kcal. A Pearson correlation showed a negative correlation ($r = -0.87$; $p = 0.140$) between zinc intake and plasma zinc levels in the sample population. There was a positive correlation in the hyperglycemic group ($r = 0.24$; $p = 0.861$) and a negative correlation in the normoglycemic group ($r = -0.117$; $p = 0.076$) between zinc intake and plasma zinc levels.

Discussion

The results obtained in this secondary analysis of data confirm findings from previous studies on the prevalence of zinc deficiency in HIV and hyperglycemic/diabetic populations [2,13]. Findings are also consistent with the literature on obesity that shows that higher BMI is a risk factor for both hyperglycemia and liver fibrosis [19,20]. Both study groups were zinc deficient ($<0.75 \mu\text{g/dL}$) with the hyperglycemic group being more deficient ($0.70 \pm 0.2 \mu\text{g/dL}$). While this difference was not significant, it is important to understand that uncontrolled diabetes was excluded in the original data repository, thus preventing access to a large portion of hyperglycemic/diabetic participants. As a result, the hyperglycemic sample used in the secondary analysis is not necessarily representative of the HIV hyperglycemic population, and certainly not of the most at-risk population.

The lack of correlation between zinc intake and plasma zinc levels confirms that there are probably more than one factor affecting zinc absorption, utilization and metabolism. Previous studies have shown variable absorption rates related to zinc status and zinc intake. This might signify that the body compensates for inadequate zinc status and intake [7,21,22]. Considering that this population had more men than women (67%), they should be consuming zinc at the recommended dietary allowances (RDA) levels, which is 11 mg/day for men and 8 mg/day for women [23]. We observed that the hyperglycemic group consumed adequate amounts of zinc ($\sim 12 \text{ mg}$), however the normoglycemics reported a mean zinc intake that was inadequate ($\sim 8 \text{ mg}$) but their plasma levels were higher. The negative correlation between zinc intake and status confirms previous studies suggesting compensation in bioavailability for inadequate zinc intake [7,21,22].

Although the difference is not significant, CD4 levels were lower in the hyperglycemic group (417.8) compared to the normal group (436.8). This is in conjunction with lower plasma zinc levels (0.70 ± 0.2) and a higher proportion of zinc deficient subjects (69%) in the hyperglycemic group. This is important to consider because zinc is a necessary cofactor for the maturation of CD4 T cells which play a vital role in the immune system. When cell counts drop to $<200 \text{ cells/mm}^3$, it is considered to be immunological failure [2] and a diagnosis of Acquired Immunodeficiency Syndrome (AIDS) [24]. A study conducted by Baum et al. [2] found that supplementation of zinc to HIV-infected adults for 18 months resulted in a 4-fold decrease in the likelihood of developing immunological failure. As a result, they are less susceptible to opportunistic infections and have a decreased risk of mortality [2].

The importance of maintaining adequate plasma zinc levels for immune function is evident especially in PLWH, due to the observed deficiency of zinc in this particular population [2,25]. Zinc deficiency is also observed in hyperglycemic conditions such as diabetes [12,13], which may be worsened when co-occurring with HIV infection. Due to the fact that ART medication increases the risk of developing diabetes in PLWH, type 2 diabetes is prevalent in the HIV population and may pose an additional risk for disease progression and complications. Our results have not found significant difference in plasma zinc levels

between the hyperglycemic and normoglycemic groups, but this may be due to the small sample size and the fact that uncontrolled diabetes was excluded from our data repository. Although our findings do not show significance, it is noteworthy to mention that the plasma zinc levels were lower in the hyperglycemic group despite adequate zinc intake. In addition, there was a higher percentage of zinc deficiency in the hyperglycemic group (69%) compared to the normoglycemic group (64%).

Limitations

The sample size is limited by the availability of the data repository, and the direction and effect size of the analyses indicate that a larger sample size will be needed to assess the relationship between hyperglycemia and zinc status.

This was a secondary analysis of data collected for other purposes, which limits the availability of other variables, such as acute phase reaction, which is needed to adjust the relationship between intake and plasma zinc levels. In addition, uncontrolled diabetics were excluded from the parent study, thus reducing our sample size and the ability to observe the effects of extreme hyperglycemic values. We presume that our findings would approach significance if our sample size was larger and cases of uncontrolled diabetes were included in our analyses.

We utilized 24-hour food recalls to estimate zinc intake, which is dependent on the memory and accuracy of the participants providing the information. Finally, acute phase reactants, such as C-reactive protein, were not measured and they may be an important covariate since zinc is sequestered in all cells under acute inflammation producing a temporary false deficiency status.

Conclusions

Previous studies have shown altered glucose and lipid metabolism in HIV patients taking ART. This has resulted in increased levels of FBG and increased cardiovascular risk factors such as diabetes [4,10,11]. While ART has been shown to normalize other micronutrient plasma levels, zinc levels remains deficient [8]. Our findings confirm that plasma zinc is deficient in HIV infection and hyperglycemia and it is slightly more deficient when both conditions are present, but the difference is not significant. We also found a higher percentage of plasma zinc deficient subjects in the hyperglycemic group (69%) compared to the normoglycemic group (64%). Moreover, CD4 cells were slightly lower in the hyperglycemic group but the difference was not significant. Further research in this particular field is warranted to minimize the complications associated with HIV and ART associated-hyperglycemia. PLWH are encouraged to monitor their FBG and plasma zinc status after initiating ART to prevent complications associated with these conditions.

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Conflicts of Interest

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