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GENDER AS DETERMINANT OF THE EFFECT OF YEAST SELENIUM ON CD4 T CELLS COUNT AMONG HIV 1 POSITIVE CHILDREN

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ABSTRACT

Background Sex steroid estrogens (E2) have been observed to have synergistic effect on activity of GSH-px on pre-menopausal females taking selenium. GSH-px activity is correlated to CD4 T cell count in HIV positive patients. However no study has been done to determine gender differentiated effect of yeast selenium intake on CD4 T cell count of pre-puberty male and female children. Methods In the study 25 girls and 25 boys HIV-1 positive on WHO stage three and below were given 50µg yeast selenium and blood samples taken at zero, three and six months intervals in EDTA vacuutainers. The blood samples were analyzed for CD4 T cell count by ELISA. Results: No significant CD4 T cell count change in the test group = -2.943,$p< 0.05$ compared to the matched controls t = -1.258 $p> 0.05$. CD4 T cell count increased among all age groups on test 3-5years (+ 267.1),5-8 years(+200.3) 9-15 years (+71.2) cells/mm3 and while in matched controls there was a decrease in all age groups 3-5 years(-71),5-8 years (-125) and 9-13years(-10.1)cells/mm3 . No significant difference was observed in CD4 T cell count between boys and Girls {F (df 5, 81) = 1.379 p=0.241} between girls {F (df 2,32) = 1.531, p= 0.232} and between boys { F (df 2, 49) = 1.040, p= 0.361} on selenium and between boys and girls {F (df 5, 86) = 1.168, p= 0.332} on control at six months. Conclusion It can be concluded that there was significant increase in CD4 T cell count among the children on selenium, but no significant difference in the effect of selenium on CD4 T cell count between pre-menopausal females and male.

Contribution/Originality: This study contributes to understanding of the effects of selenium administration to HIV positive children. The yeast selenium provided is commonly available in chemists as nutritional supplements. From this study it is observed that selenium supplementation leads to increase in weight gain and equally increase in CD4 cell count ($p< 0.05$) between baseline and six month sampling, and delayed progression of the AIDS patients as seen by improvement in WHO clinical staging, and the WAZ-Score.

1. INTRODUCTION

Selenium is an essential component of a group of enzymes called seleno- proteins (WHO, 1998). Among the 20-30 seleno-proteins a distinction can be made between different families –containing enzymes.

Seleno-protein Glutathione peroxidase (GSH-px) is involved in control of tissue concentration of highly reactive oxygen containing species (ROS) and is therefore essential for maintaining cell mediated immunity against infections(GART). GSH-px is present in blood cells and blood platelets and is encoded by the genes GPX1 to GPX6. The activity of GSH-px enzymes decrease rapidly at early stage of selenium deficiency (Royman, 2002). HIV encodes the selenoprotein with homology to GSH-px hence depriving the host of selenium and other components needed for endogenous synthesis of the selenoprotein GSH-px.

Deficiency of selenium and other amino acids leads to susceptibility to cancers, diarrhea, myocardial infarction, muscle wasting, psychosis and dementia (Foster, 2004). Despite mutagenic rate of the virus the HIV-GSH-px sequence is well conserved in various strains of the virus suggesting important role of the selenoprotein to viral infection. It is suggested that it could be providing anti-apoptotic resistance to viral damage to virus which could enhance viral multiplication in early stages of infection.

Earlier studies shows that the level of CD4 T cell count is directly affected by the level and activity of seleno-protein GSH-px (Betz and Fox, 1991; Hiscott *et al*., 2001) while level of GSH-px is correlated well with the level of selenium in the body. The measure of CD4 T cells therefore is a surrogate measure of the level of selenium in the body which is as a result of selenium intake (Debski *et al*., 1989; Meltzer *et al*., 1993). Furthermore, selenium functions in oxidative defense, in GSH-px enzyme system.

Poor selenium levels in the body leads to lower GSH-px level which may lead to oxidative stress followed by apoptosis of CD4T-Lymphocytes (Roy and Robert, 1992) and increased viral multiplication rates (Staal *et al*., 2008). Further evidence, show that low selenium levels in plasma was found to be related to poor child survival among HIV infected children in an earlier study (Campa *et al*., 1999).

Some studies has shown selenium associated GSPx was decreased in the elderly women (menopausal) compared with the younger (Veronique et al.,). Other studies has shown increased activity of GSH-px activity in erythrocyte of pre-menopausal adult women compared to menopausal ones, and higher activity in women compared to age matched men (Massafra *et al*., 2002).

The objective of current study was to determine the effects of yeast selenium intake by pre-puberty female children compared to the age matched male children.

2. MATERIALS AND METHODS

2.1. Study Subjects

The study subjects were the orphan children, enrolled at, Nyamasaria in Kisumu County, who were tested and those found to be HIV positive were selected to join the study. Each child was given equal opportunity to join the study and were randomly assigned in selenium or control group as indicated below.

2.2. Inclusion and Exclusion Criteria

2.2.1. The Inclusion Criteria

Children above three years and below 16 years

Children who were HIV positive

Children whose guardians gave consent

On HIV stage three and below.

2.2.2. The Exclusion Criteria

The children who were HIV negative

The children who were HIV Stage 4

The Children who's Guardians did not give consent.

Less than three and above 15 years

2.2.3. Sampling Techniques

2.2.3.1. Sample Size Determination

CASCADE cohort shows that in HIV positive patients CD4 depletion rate is 114 cells/μL per year and 54% of patients losing >100 cells/μL per year. It is therefore expected that about 60% of children are at risk becoming symptomatic in first year with an average decline of 169 cells/μL. Since no evidence exist from previous studies on selenium intervention on children3-16 years, it is assumed that CD4 depletion will occur in about 60% of children at one year with no intervention. At power of 80% and α of 0.5% (CI of 95%) use Epi-Info version 6 to estimate sample size.

As shown in table 3.2 at confidence interval of 95% (1-α) or probability that if the two samples are different this reflect a true difference in the two populations, power of 80% (1-β) or probability that if the two populations differ the samples will show significant difference, and prevalence of HIV of 14.9%(KAIS., 2012). Relative risk of 4.4% the ratio of 1:1.The minimum number required is 17 for test and 17 for control (total 34).

Table-3.2. Sample size calculation for Cohort Studies (Epi Info.Version 6)

CI	POWER	PREVALENCE	RATIO EXP:UNEXP	RELATIVE RISK	SAMPLE SIZE(MINIMUM)		TOTAL
		HIV			Exp.	Unexp.	Both
95%	80%	15%	1:1	4.4	17	17	34

2.3. Randomization

Each of the children meeting the above indicated criteria was assigned a number. Using random table the first 34 children were chosen, these formed the test group on selenium, while the remaining 34 were on control group which was put on placebo.

2.4. Training of Research Assistants

Two enumerators one of them a nurse were selected. They were given orientation on purpose of the research and methods of data collection. The orientation was also done on handling of the electronic weighing machine, taking weight, and recording of measurements accurately. The orientation was also done on collecting and handling blood samples. Care was taken to select only those who understood local language but with at least secondary level of education.

2.5. Data Collection

(a) Interview of Guardians

At baseline, an interview of Childrens' guardians were done by trained research assistants who collected data of children's' socioeconomic status and those of their guardians using structured questionnaire. Foods eaten by the children in the community were determined and samples were also collected.

(b) Administering of Selenium to the Children

The children on test were given daily dose of yeast selenium capsules. The participants on test were assigned to, and received 50μg selenium (yeast) for up to 6 months. The dose was about a half of tolerable upper limit for children which are 100μg (yeast selenium) per day hence considered safe. Every week a evaluation of the intervention was done and replenishment of the selenium stock and monitor the compliance with the treatment. At 3 months intervals, the research assistants collected data on Weight and Blood samples to measure change in CD4-T cell count and weight for age- Z score.

2.6. Blood Sample Collection and CD4 T Cell Estimation

(i) Blood Samples Collection

The details of each child was recorded, this included names, gender and age.

The blood samples (2ml) were collected from study subjects by venipuncture, in vacuutainers with anticoagulant (EDTA) and transported to the laboratory. A total of 68 blood samples were collected. Special numbers were generated which linked the source population to the sample for case of archiving.

(ii) CD4 T Cell Estimation

A complete CD4 T cell count was quantified among children at baseline, and subsequent three months by ELISA according to the methods suggested by Millipore (2009).The blood samples were put on a roller. Into a vial, 10µL of Guava®CD4/CD4% auto-cocktail was added, this was followed by 10µL blood from a patient, and the mixture was incubated for about 30 minutes in darkness. To the mixture was added 380µL of Guava lyse solution, this mixture was further incubated for 15 minutes in darkness. The fluorescent labeled sample was aspirated through a proportioned micro-capillary flow cell. A green laser excited the cells and each of the cells emitted a signal which was individually detected by photomultipliers and photo iodide. The system allowed for absolute cell count without reference beads.

3. RESULTS

3.1. Demographics and Clinical Characteristics of the Study Populations

3.1.1. Age and Gender Distribution of Study Subjects

As shown in table **4.1**, the mean age for the group on selenium was 7.7±3.4 years, while for the matched controls it was 8.8±3.2 years. In the matched controls 54.05% were boys and 44.95% were Girls.

Table-4.1. Gender distribution of study subjects

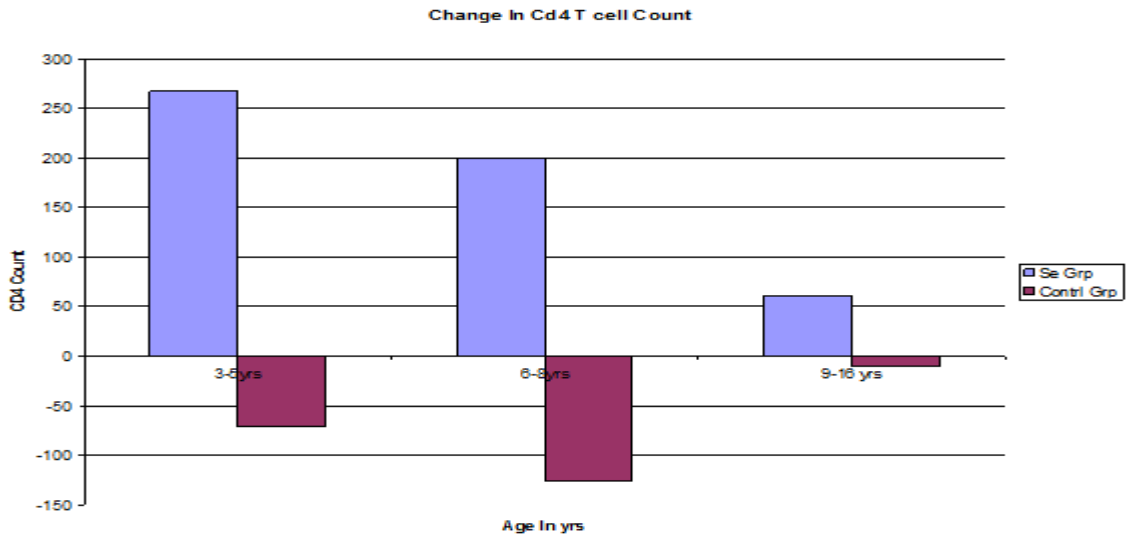
	Selenium Group	Controls	P-Value
Mean Age(yrs)	7.7± 3.4	8.8±3.2	0.185
Gender			
Girls	22 (64.7%)	20 (54.05%)	
Boys	12 (35.3%)	15 (44.9%)	0.853
Median Weight (kg)	18±10.9	19±9.5	

3.2. The Mean CD4 T cell Count at Baseline

The Results of the mean CD4 Cell count at baseline for both control and test children are presented in the table 4.2 below, for both the children on control and on selenium. The children were divided in to age categories 3-5 years (1670cells/µL) , 6-8 years (1340 cells/µL) and 9-15 years (1071 cells/µL) in controls and 3-5year (1031cells/µL),6- 8 years (1300 cells/µL) 9-15 years (928cells/ µL). CD4 Cell count (cells/µL) of children on test and control at three months.

Table-4.2. CD4 T cell count of both test and control at Three Months

CHILDREN IN CONTROL			
	Minimum (cells/µL)	Maximum (cells/µL)	Mean (cells/µL)
3 -5 years	833	2248	1554
6-8 years	1004	1431	1215
9-15 years	815	2215	1237
CHILDREN ON TEST			
3-5 years	350	2237	1244
6-8 years	830	1853	1372
9-15 years	360	1889	989



3.3. Changes in CD4 T Cell Count by Gender (Sex of Respondents)

Analysis of Variance in table **4.3,** show that among the group on selenium there was no significant differences in CD4 T cell between girls at six months{F (df 2,32) =1.531, p = 0.232}.Similarly no significant differences in CD4 T count was observed between boys{ F (df 2,49) =1.040, p=0.361} and between boys and girls {F(5,81) =1.379 p=0.241) at six months among the children on selenium. In the matched controls there was no significant difference in CD4T cell count between different gender {F (df 5, 86) = 1.168 p= 0.332} at six months.

Table-4.3. ANOVA CD4 T cell count at six months by sex of children

GIRLS ON SELENIUM				
	Df	**Mean SS**	**F**	**P**
Between groups	2	129.060	1.531	0.232
Within Groups	32	84.294		
Total	34			
Boys On Selenium				
	Df	**Mean SS**	**F**	**P**
Between groups	2	104.097	1.040	0.361
Within groups	49	100.120		
Total	51			
Boys And Girls On selenium				
	Df	**Mean SS**	**F**	**P**
Between groups	5	130.180	1.379	0.241
Within groups	81	94.413		
Total	86			

Further analysis table **4.4**, of CD4 T cell count change between boys and girls on control show that there was no significant difference between the two gender at six months { F (5,86) =1.168 p=0.352}.

Table-4.4. ANOVA of CD4 count between Girls and Boys on Control.

	DF	**F**	**SIGNF.**
Between Groups	5	1.168	0.332
Within Groups	86		
Total	91		

3.4. Correlation of CD4 T cell count on Z-Score for Weight and gender

As shown in table **4.5**, the model above multivariate analysis was done of the correlation between dependent variable absolute CD4T cell count, and independent variables sex and weight for age (WAZ score).It was established that WAZ-score was positively correlated to change in CD4 cell count for the children on test {t (2, N=27) = 2.94,p=0.007} with R = 0.2523 and adjusted R^2 being 0.2016. In the matched controls there was no significant correlation between WAZ, and CD4 cell count observed {t (2, N = 23) =0.08 p=0.934} with R being 0.0337 while adjusted R^2 being -0.0503. The gradients of correlation of the two variables gender (sex), weight for age (WAZ) and CD4 T Cell count varied. In the selenium group WAZ score interaction with change in CD4 T cell count the coefficient (β_2) was +252.23.The interaction of gender (sex) with change in CD4 T cell count, the analysis among the selenium group shows no significant correlation {t (2 , N= 27) = -0.69 p= 0.495}, the coefficient (β_1) -138.23. In the matched controls group the WAZ interaction with change in the CD4T cell count the coefficient (β_2) was, +3.366 while the gender(sex) interaction with change in CD4 T cell count was not significant {t (2,N= 26) = - 0. 90, p= 0.380} and the coefficient (β_2) was -135.50.

Table-4.5. Correlations between CD4 T Cell Count, Sex (gender) and WAZ Scores

	B	S.E	T	P-VALUE	95% C.I.	
Selenium Group						
WAZ	+252.23	85.890	2.94	0.007	75.99	428.46
Sex(gender)	-138.23	199.710	-0.69	0.495	-548.02	271.56
Control Group						
WAZ	+3.366	40.426	0.08	0.934	-80.26	86.99
Sex(gender)	-135.49	151.29	-0.90	0.380	-448.47	177.47

Source: Data from the study

3.5. The selenium effects on Mean CD4 T Cell Count Change

Change in the mean of CD4T Cell count between baseline and six months sampling was found to be significant among the test group at 95% confidence interval {F (2, 27) = 4.65 p= 0.0183}, while in the matched controls no significant difference was observed at six months {F (2, 23) =0.40 p=0.6742}.There was significant difference in CD4 cell count between test group and the matched controls {F_t /F_c (df 30,25) = 11.625 p< 0.05}.

4. DISCUSSION

4.1. Selenium Effects on CD4 T Cell Count

Significant change in mean CD4 count (Table 4.10) was noted among the group on selenium, compared to the controls in which there was no significant difference noted after six months. Mean CD4 cell counts all age groups rose significantly in the selenium group between the baseline and 6 months, indicative of an improved immunity (p< 0.05) as opposed to the matched controls where no significance was observed at six months (p> 0.05).The typical CD4 count for a healthy child (1-12 years old) is between 500-2500 cells/µL, in HIV-positive patients not receiving ARVs, the CD4 count decreases on average between 50 to 100 cells/µL per year (Foster, 2003). In this study an increase of mean CD4 count of up to 267 cells/µL was observed (in 3 to 5years age group) on test while a decrease of 125 cells/µL was observed (in children 6-8 years old) amongst the controls. These findings is consistent with another study in which elevation of serum selenium concentrations in adult HIV positive patients which was related to selenium supplementation were associated with decrease in HIV-Viral load, which in turn were related to increased CD4 T cell count compared to control cohort (Hurwitz *et al.*, 2007). This tends to imply that the observed increase in CD4 T cell count could be due to reduced viral load in the study subjects.

The mean CD4 T cell count at various stages show significance (p<0.05) between second and third sampling representing second sampling (90 days) and 180 days of supplementation and between baseline and 180 days

compared to the control groups where there was no significance between all groups. Similar evidence has been reported (Véronique *et al*., 2005) that optimum GSH-px activity is observed from 90 days after begining of selenium suplimentation.

Evidence from earlier studies show that the level of CD4 T cell count is directly affected by the level and activity of seleno-protein GSH-px (Betz and Fox, 1991; Hiscott *et al*., 2001) while level of GSH-px correlates well with the level of selenium in the blood (Debski *et al*., 1989; Meltzer *et al*., 1993).The measure of CD4 T cells therefore is a surrogate measure of the level of selenium in the body which is as a result of selenium intake. Further more, selenium functions in oxidative defense, in GSH-px enzyme system. Poor selenium levels in the body leads to lower GSH-px level which may lead to oxidative stress followed by apoptosis of CD4T-Lymphocytes (Roy and Robert, 1992) and increased viral multiplication rates (Staal *et al*., 2008).The increase of CD4T cell count in this study therefore suggests that selenium intake improves the immunity of the HIV positive children in the study site and hence a factor in determining the progression of HIV positive children to AIDS. Similar to this evidence, low selenium levels in plasma was found to be related to poor child survival among HIV infected children in an earlier study (Campa *et al*., 1999; Kupka *et al*., 2004).

4.2. Correlation of CD4 T Cells on Gender and WAZ Score

To establish predictors of increase of CD4 T cell count, a multiple regression analysis was used to assess the relationship between the CD4 counts as dependent variable and the gender, Weight-for-Age Z-scores as independent variables. In the regression model was; $CD4count=\beta_0+\beta_1 age+\beta_2 WAZ+\varepsilon$, the R square is the proportion of variation in the dependent variable explained by the regression model while adjusted R^2 attempts to correct R^2 to more closely reflect the goodness of fit of the model in the population. The dependent variable CD4 T cell count indicate whether a childs improved immunity is correlated to improved WAZ or Gender. In the model we expected β_1 which reflects the average effect on the children's health as a result of selenium administration to be >0 as increase in weight is always associated with improved immunity. In the model ε represent other damy variables like psychosocial factors, individual differences, effect of stigma and other biological factors.

The average adjusted R^2 for the model was 0.2016, which implies that the (WAZ) variable explains only 20.16% of the CD4 counts in the test group at six months (Table 4.13). This implies that 79.84% of the variation remains unexplained by change in WAZ. This could be due several reasons one of them is that there might be some other influencing variables that have not been included in the present model most likely increased GSH-px (which follows selenium intake). This underlines the likelihood of faster recovery of HIV positive children given selenium .These findings underscore the importance of selenium suplimentation to improve immunity in children infected with HIV. Given that the demographic profiles were comparable at enrolment ($p> 0.05$), selenium level in the body as reflected by GSH-px activity which could be responsible for the biggest change in CD4 cell count. The gender factor has been reported to affect efficacy of selenium (Veronique *et al*., 2005). However from the analysis, model shows that the change in parameter (WAZ) is statistically associated with CD4 cells since the p-value is 0.007 at 95% significance level with the change of CD4 counts, among the children given the selenium. It further shows that the coefficient β_1 is +252.23 which confirms earlier expectation. As shown in the data there was no significant correlation between CD4 T cell count increase and gender amongst the controls further confirming the observation with β_2 being negative -138.23 and p of 0.495.

Several studies have suggested evidence of beneficial effects of selenium to HIV positive patients (Hurwitz *et al*., 2007). Selenium in the body influences both cell mediated and humoral immunity (Baum *et al*., 2000) and expression of receptors of interleukin-2(IL-2) which influences cytotoxic T-Lymphocyte activity (Kirimedjian-Schumacher *et al*., 2009) and increases interferon yield and T-Cell count. Absence of selenium leads to CD4 T Cells apoptosis and increased HIV replication through activation of Nuclear Factor kappa by unchecked increase of H_2 O_2 activity. Several other studies have shown relationship between patient survival and selenium levels in blood (Baum

et al., 1997; Campa *et al*., 1999). A study in Miami in 2002 did examine the effects of selenium administration to adult men and women over a 9 month period, showed that increased selenium in the body is associated with decreased HIV load in the body and improvement of CD4 cell count (Hurwitz, 2007). How ever in these earlier studies it is not clear weather confounding factors which include concurrent intake of antiretroviral drugs could have influenced the outcome.

Earlier studies have shown association between low selenium levels in childrens' blood and survival (Campa *et al*., 1999; Kupka *et al*., 2004). A previous study has also shown correlations between age, gender and GSH-px activity among adults taking selenium (Véronique *et al*., 2005). This has been attributed to activity of estrogen level in the blood especially in young women. In this study no correlation has been observed ($p > 0.05$) between gender and CD4 cell count, perhaps due to the age of the study population as the level of hormonal activity may not be playing a major factor. This observation suggests that in children GSH-px activity which is reflected as level of CD4 T Cell counts and percent is not influenced by either of the two factors.

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