American Journal of Preventive Medicine and Public Health
2020 VOL 7, NO. 1, PAGE 147-154

RESEARCH ARTICLE

Open Acess

The Effectiveness of a 6-Month Nutrition Intervention on Lowering Fasting Glucose and 8OHdG Levels in Prediabetic People Living with HIV (PLWH) in the MASH Cohort

Alicia Sneij*, Adriana Campa, Marianna Baum, Fatma Huffman, Florence George, Mary Jo Trepka, Sabrina Sales-Martinez, Leslie Seminario, Jacqueline Hernandez-Boyer
Center for Research on US Latino HIV/AIDS and Drug Abuse, Florida International University, Miami, USA

ABSTRACT

The rate of prediabetes in people living with HIV (PLWH) is 2-3 times higher than in the general population. Nutrition interventions have been effective in lowering diabetes risk in people with prediabetes in the general population, but this has not yet been shown in PLWH. The objective of this study was to assess the effectiveness of a 6-month randomized, controlled nutrition intervention for prediabetic PLWH. Participants (N=38) were randomized into the intervention group (n=20) or the control group (n=18). Inclusion criteria were being HIV+, prediabetic defined by the American Diabetic Association standards, 18 years of age and older, controlled HIV viral load, and not using glucose altering medications. Participants randomized into the intervention group met once a month for 1 hour to receive individualized medical nutrition therapy, nutrition counseling and nutrition education; participants in the control group received educational material at baseline. Outcome variables were collected for all participants at baseline and end of the study between 2017-2018 and analyzed 2018-2019.

We found significant improvements in fasting blood glucose (p=0.03), body mass index (p=0.03) and oxidative stress (p=0.04) in the intervention group when comparing their 6-month values to those at baseline; while differences between baseline and end of the intervention were not observed in the control group, with significance set at p<0.05. The results from this intervention support the notion that a nutrition intervention is effective in lowering diabetes risk by significantly lowering fasting blood glucose, body mass index and oxidative stress in PLWH who are prediabetics, who are at greater risk for diabetes and cardiovascular disease than the general population.

ARTICLE HISTORY
Received: November 28, 2020
Accepted: December 12, 2020
Published: December 19, 2020

KEYWORDS
Prediabetic; Nutrition; HIV; diabetes; intervention

Introduction

People living with HIV (PLWH) are known to have higher risk for co-morbidities with earlier onset ages compared with their non-infected counterparts, such as prediabetes/diabetes and cardiovascular disease [1,2]. Their increased risk may be due to a myriad of factors including, but not limited, to HIV infection and the chronic use of antiretroviral therapy (ART) [3-6]. The prevalence rate of prediabetes in PLWH is reported in the literature to be 2-3 times higher than the general non-HIV infected population and is expected to rise if effective interventions are not implemented [7-9].

Prediabetes is a transient state of hyperglycemia which is known to increase the risk of developing diabetes, with an annual conversion rate of 5-10%, if left unaddressed [10-11]. The American Diabetes Association (ADA) and the World Health Organization (WHO) have similar but slightly different diagnostic criteria for prediabetes. According to the ADA's guidelines, prediabetes is diagnosed with fasting blood glucose levels between 100 mg/dl to 125 mg/dl (fasting for ≥ 8 hours), hemoglobin A1C (HbA1C) values 5.7-6.4% and/or 2-hour plasma glucose of 140-199 mg/dl after a 75 gram of oral glucose tolerance test. The WHO have a stricter fasting blood glucose range of 110-125 mg/dl, similar 2-hr oral glucose tolerance test range to ADA guidelines, but no diagnostic range for HbA1C [10].

Prediabetes is an intermediate state between normal blood glucose levels and diabetes; people with prediabetes are a target population for the implementation of effective interventions to halt

Coressponding Author: Alicia Sneij, E-mail: asnei001@fiu.edu; Center for Research on US Latino HIV/AIDS and Drug Abuse, Florida International University, Miami, USA

and/or reverse back to normal glucose levels [11-15]. In a study conducted by Eriksson and Lindgarde, they found that glucose tolerance was normalized in >50% of the participants with impaired glucose tolerance (IGT) with effective lifestyle modifications. Prior research has shown the effectiveness of implementing lifestyle changes in reducing overall diabetes risk/incidence by 58% in people with prediabetes, thus supporting the importance of implementing interventions in this particular population [13,14,16,17].

Nutrition interventions for prediabetes

The Diabetes Prevention Program (DPP) was a large scale 27-center intervention randomized clinical study (n=1079) conducted to determine the effectiveness of a lifestyle intervention to lower diabetes risk and/or prevent diabetes incidence in people with prediabetes [13]. The intervention was multifaceted, consisting of a variety of ways to reduce diabetes risk including weight loss, physical activity and behavior change techniques. They utilized individual case managers or "lifestyle coaches" to implement the 16-session core curriculum that taught participants certain beneficial lifestyle changes. They found that certain lifestyle changes aimed at weight loss and increasing physical activity decreased the incidence of type 2 diabetes by 58% [13].

Another study conducted by Tuomilhto et al. [16] assessed the effectiveness of lifestyle modifications in reducing diabetes risk among overweight people with prediabetes (n=522). The participants that were randomized into the treatment group received nutrition counseling to increase physical activity, promote weight loss in overweight participants, increase fiber intake and reduce dietary fat intake. Similarly, to the Diabetes Prevention Program, they reported that the incidence rate was reduced by 58% ($p<0.001$) in the intervention group [16]. Moreover, a large-scale study by Pan et al. [18] aimed to determine if lifestyle changes in diet and exercise could delay and/or reduce diabetes incidence in people with impaired glucose tolerance. They conducted a randomized controlled clinical trial (n=110,660) and found that changes in diet and/or increasing exercise frequency reduced diabetes incidence by 31-46%.

Oxidative stress

Hyperglycemia, or elevated blood glucose levels, which is characteristic of prediabetes is known to increase the production of reactive oxygen species, i.e. oxidative stress [19]. Therefore, prediabetes has been associated with elevated levels of oxidative stress [19-24], with studies suggesting that hyperglycemia-induced oxidative stress may be responsible for the damage of pancreatic Islet beta cells, thus increasing diabetes risk [20]. It is reported that although beta cell death can be mediated by various etiological factors such as glucotoxicity, lipotoxicity, and pro-inflammatory mediators, hyperglycemia was the biggest contributor to beta cell destruction [20]. Chronic exposure to hyperglycemia has been shown to initiate beta cell death in cell cultures and animal models, as well as in human autopsies [20].

In an effort to minimize beta cell destruction and delay or prevent diabetes incidence in people with prediabetes, glycemic monitoring and control is highly encouraged, especially in PLWH, who already are exposed to elevated levels of oxidative stress associated with HIV infection and/or the chronic use of ART [25,26]. Kwak et al. demonstrated the effectiveness of a 4-week dietary intervention in significantly reducing blood glucose and oxidative stress in people with prediabetes or newly diagnosed type 2 diabetes; however, this is the first study that shows the success of this type of intervention in PLWH who were prediabetic [27].

Inflammation

In PLWH elevated levels of inflammation are frequent, despite sustained ART mediated viral suppression [28-31]. Although inflammation and immune activation normally decline during consistent ART treatment, they tend to remain elevated in many PLWH and predict mortality and/or co-morbidities, including diabetes and cardiovascular disease [28]. An Analysis of the FRAM Study Cohort revealed that PLWH have elevated inflammatory marker such as C-reactive protein (CRP). In FRAM, levels of CRP >3 mg/L had 2.7 folds higher adjusted odds of mortality than those with CRP levels of <1 mg/L [29].

Prediabetes and hyperglycemia have also been associated with elevated inflammation levels [30], independent of HIV status. The increased levels of inflammation in PLWH may increase risk for diabetes, as systemic inflammation has been associated with incident diabetes [32]. Therefore, in prediabetic PLWH, who have higher levels of inflammation and oxidative stress, it is not surprising to find elevated risk for developing diabetes, including inflammation related to HIV infection along with inflammation related to hyperglycemia.

Significance

Numerous studies have shown the effectiveness of lifestyle modifications in lowering diabetes risk in people with prediabetes [13,16-18]; however, research

on the effectiveness of lifestyle modifications in lowering diabetes risk in prediabetic PLWH has been scarce. Therefore, we conducted a randomized controlled clinical trial of a 6-month nutrition intervention in prediabetic PLWH to assess the effectiveness of lifestyle modifications in lowering blood glucose, oxidative stress and inflammation.

Materials and Methods

Approval from the Florida International University (FIU) Institutional Review Board (IRB) was obtained prior to the start of the study. A 6-month randomized, controlled nutrition intervention was conducted in prediabetic people living with HIV (PLWH). The study participants were recruited from the Miami Adult Studies of HIV (MASH) cohort. MASH cohort participants provided consent to review their medical documentation for eligibility. Inclusion/exclusion criteria were used to identify participants who were eligible, and telephone calls to these participants were made to attend a screening study visit. Upon their consent, the participants were randomized into the treatment group (intervention) or the control group. All participants visited the FIU Research Clinic at Borinquen Health Care Center at baseline for assessment and at the 6-month follow-up as part of the MASH cohort.

Participants were determined to be "prediabetic" based on the American Diabetes Association (ADA) diagnostic criteria of fasting blood glucose of 100 mg/dl to 125 mg/dl (fasting for ≥ 8 hours) or hemoglobin A1C (HbA1C) values 5.7-6.4% [10]. Inclusion criteria included to be HIV seropositive, prediabetic, 18-65 years of age, receiving stable ART for at least 6 months, undetectable HIV viral load (<50 copies/ml) and English speaking. Exclusion criteria included any previous history of type 2 diabetes, concomitant use of glucose altering medication (corticosteroids, etc.), use of weight loss drugs, pregnancy or breastfeeding and/or refusal or inability to give informed consent to participate in the study.

Participants (n=38) were randomized into either the intervention group (n=20) or the control group (n=18) in 2017-2018. Participants randomized in the intervention group received individualized sessions composed of Medical Nutrition Therapy (MNT), nutrition education and nutrition counseling, which are all based on the American Diabetes Association (ADA) Standards of Medical Care in Diabetes [33]. The first session lasted approximately 1 hour, and each subsequent visit lasted approximately 45 minutes, for a total of 6 visits. The intervention utilized a developed curriculum that was specifically tailored to PLWH, which provided structure to the intervention; however, each session was individualized and catered to each participant's nutritional needs at the time of the session. At baseline, the participants randomized into the control group received educational material on prediabetes/diabetes, also based on the ADA Standards of Medical Care in Diabetes [33].

The educational portion of the intervention included the following topics:

1) HIV, ART and prediabetes-how are they all interrelated?

2) Understanding BMI and the importance of maintaining normal body weight

3) Dietary Intake and the importance of fruits and vegetables

4) Energy Expenditure and the importance of physical activity

5) Dietary Fat and ways to avoid excessive eating

6) Alcohol and its effect on the body.

The overall goal of the intervention was to encourage fruits and vegetables intake and promote physical activity, both of which tends to be lacking in this low-income population. Fasting blood was drawn at baseline and at the 6-month follow up visit by a trained phlebotomist/registered nurse to measure the levels of biomarkers of interest. As whole blood was collected, it was separated and processed into plasma and aliquoted to be stored at -80oC freezers and was batch analyzed between 2018-2019. Samples were sent to LabCorp to obtain levels of FBG and CRP and Enzyme Linked ImmunoSorbent Assay (ELISA) kit from G-Biosciences was used to measure changes in 8OHdG.

Results

The study population (n=38) baseline characteristics are shown in Table 1. The mean age was ~57 years old, 58% were male with a mean annual income of ~$13,325.03/year, indicating that this is a low-income population. The average years of HIV infection was ~20 years, demonstrating that people are living longer with HIV. The average BMI was 30 kg/m^2, which is considered to be Obese Class I. Average waist circumference, was 40± 4.7 inches, hip circumference was 42 ± 4.7 inches and waist-to-hip ratio (WHR) was 0.95 ± 0.06. The mean fasting blood glucose (FBG) was 108± 7.3 mg/dl, which falls within the American Diabetes Association (ADA)

prediabetic guidelines of 100-125 mg/dl. The mean inflammatory marker, high sensitivity C-reactive protein (hs-CRP), was 7.73 ± 21.19 mg/dl, which is considered high, with normal ranges <3 mg/dl.

Table 1. Study Population Baseline Characteristics

Baseline Characteristic	Intervention Group Mean ± SD	Control Group Mean ±SD	Mean	Mann Whitney U-Test P value
Sex	Female: n=7 Male: n=13	Female: n=8 Male: n=9 Transgender Female: n=1	Males: n=22 (58%)	--
Age	55.55 ± 6.07	58.00 ± 8.72	56.7 ± 7.4 years	0.4
Income	13072.21 ± 8577.63	13605.94 ± 14323.91	$13,325.03 ± $11,495 / year	0.51
Years of HIV Infection	16.25 ± 6.78	24.83 ± 8.12	20.3 ± 8.5 years	0.002*
Body Mass Index	29.44 ± 5.55	30.74 ± 5.50	30.1 ± 5.5 (obese)	0.4
Waist Circumference (inches)	Female: 40.46 ± 6.3 Male: 39.60 ± 3.86 Total: 39.90 ± 4.72	Female: 40.59 ± 5.17 Male: 39.28 ± 4.85 Total: 40.07 ± 4.80	40 ± 4.7 inches	Female: 0.73 Male: 0.80 Total: 0.97
Hip Circumference (inches)	Female: 44.53 ± 6.00 Male: 41.14 ± 3.76 Total: 42.32 ± 4.80	Female:43.81 ± 5.20 Male: 41.09 ± 4.46 Total: 42.41 ± 4.73	42 ± 4.7 inches	Female:0.56 Male:0.89 Total: 0.84
Waist-to-hip ratio (WHR)	Female: 0.91 ± 0.05 Male: 0.96 ± 0.06 Total: 0.94 ± 0.06	Female:0.93 ± 0.06 Male:0.96 ± 0.05 Total: 0.95 ± 0.06	0.95 ± 0.06	Female: 0.27 Male: 0.80 Total: 0.84
Fasting Blood Glucose (FBG) (mg/dl)	107.80 ± 6.26	108.33 ± 8.56	108.1 ± 7.3 mg/dL	0.79
High-sensitivity C-Reactive Protein (hs-CRP) (mg/dl)	9.02 ± 28.08	6.30 ± 5.30	7.73 ± 21.19 mg/L	0.03*
8-hydroxydeoxyguanosine (8OHdG) (mg/dl)	127.23 ± 65.40	90.04 ± 58.66	82.05 ± 46.22 mg/dl	0.21

Note: *Denotes significant difference between study arms with significance determined at p≤ 0.05.

There were no significant differences between the two study arms at baseline for age, income, BMI, waist circumference, hip circumference, waist-hip circumference (WHR), fasting blood glucose or 8OHdG. Significant differences were found in the number of years of HIV infection between the intervention group (mean=16 years) and the control group (mean=24 years) (p=0.002) and levels of CRP within the intervention group (mean 9.02 mg/dl) and the control group (6.30 mg/dl, p=0.03).

Analyses using paired t-test, shown in Table 2, revealed significant differences within the intervention group for BMI (p=0.03), fasting blood glucose (p=0.03) and 8OHdG (p=0.04) after the 6-month nutrition intervention; however, these significant differences were not observed within the control group. No significant differences were

observed for waist circumference, hip circumference, waist-to-hip circumference or CRP levels in either the intervention group or the control group. Moreover, no significant difference was observed between the two study arms at the 6-month follow-up for any of these parameters (Mann Whitney U-test). However, a significant difference was observed for BMI change for the participants in the intervention group compared to the BMI change of the participants in the control group (p=0.05). No significant differences were observed for the remaining parameter changes (Table 3). All statistical analyses were conducted on Statistical Package for the Social Sciences (SPSS) Version 22.0 and p≤0.05 was considered significant difference.

Table 2. Results and Analyses

Parameters	Intervention Group (mean±SD)		Paired T-test (p-Value)	Control Group (mean±SD)		Paired T-test (p-value)	Mann Whitney U-Test (p-value)
	Baseline	6-Month		Baseline	6-Month		
BMI	29.44 ± 5.6	28.82 ± 5.5	*0.03	30.74 ± 5.6	31.56 ± 5.7	0.1	0.85
Waist (in)	39.9 ± 4.7	39.15 ± 5.2	0.16	40.07 ± 4.8	41.41 ± 4.9	0.13	0.93
Hip (in)	42.32 ± 4.8	42.32 ± 4.2	0.74	42.41 ± 4.7	43.29 ± 4.9	0.11	0.86
WHR	0.94 ± 0.1	0.93 ± 0.1	0.56	0.95 ± 0.1	0.96 ± 0.1	0.11	0.75
FBG	107.8 ± 6.3	96.2 ± 18.3	*0.03	108.33 ± 8.6	99.23 ± 34.7	0.07	0.86
CRP	9.02 ± 29.0	4.12 ± 4.2	0.4	6.3 ± 5.3	4.34 ± 4.1	0.12	0.43
8OHdG	111.18 ± 63.3	82.65 ± 8.7	*0.04	62.10 ± 24.8	76.80 ± 50.7	0.37	0.72

Note: *Denotes significant difference within study arm (paired t-test) with significance determined at p ≤ 0.05.

Table 3. Comparisons of Parameter Changes between Study Groups

Parameter	Intervention Group Change Mean ± SD	Control Group Change Mean ± SD	Mann Whitney U-test P-Value
BMI	-0.97 ± 1.75	0.122 ± 1.51	0.05*
Waist (in)	-0.89 ± 2.61	1.00 ± 2.11	0.08
Hip (in)	-0.02 ± 2.45	0.43 ± 2.73	0.52
WHR	-0.03 ± 0.07	0.01 ± 0.04	0.22
FBG	-12.20 ± 19.72	-10.69 ± 22.19	0.86
CRP	-7.48 ± 33.65	-2.68 ± 5.98	0.56
8OHdG	-22.55 ± 50.19	13.36 ± 60.78	0.17

Note: *Denotes significant difference within study arm (paired t-test) with significance determined at p ≤ 0.05.

Conclusion

After the 6-month nutrition intervention, there was a significant reduction (p=0.03) in the fasting blood glucose (FBG) levels within the intervention group at the 6-month follow-up when compared to their baseline values (paired t-test); however, this was not observed in the control group (p=0.07). As can be seen, although not significant, there was still an improvement in the fasting blood glucose levels in the control group after the 6-months, and this may be due to the unblinded nature of the study. When the participants were made aware of their prediabetic state at baseline, they were more likely to make changes at that point. They were also given educational material at baseline, which provided additional information, promoting lifestyle changes. It is also important to note that the FBG of the participants in the control group still bordered the prediabetes FBG range of 100-125 mg/dl, whereas the participants in the intervention group were well below that range and were

now in the normal FBG of <100 mg/dl. No significant difference (p=0.861) was observed when comparing the FBG values between the study groups at the 6-month follow-up (Mann Whitney U-test).

We also observed a significant reduction (p=0.03) in the body mass index (BMI) within the intervention group after the 6-month intervention, which was favorable for the control of hyperglycemia, with an average drop in 1 unit of mean BMI; however, the control group gained weight and increased BMI during the same period (p=0.10), resulting in a 1-unit increase in mean BMI. Therefore, there were significant differences for BMI changes between the groups (p=0.05). With the mean BMI change in the intervention group being negative and the mean BMI change in the control group being positive, it is evident that the participants in the intervention group were consistently losing weight, while the participants in the control group were gaining weight.

Although there was no significant difference within the groups after the 6-month intervention in regard to waist and hip circumferences, it is notable to mention that the waist and hip circumference in the control group actually increased by 1 inch (each anthropometric parameter), while the waist and hip circumference in the intervention group remained the same after the 6-month intervention. Moreover, although not significant, the waist-to-hip ratio (WHR) also improved in the intervention group by 1 unit, while the WHR in the control group increased by one unit, and thus further increasing risk for other metabolic conditions such as diabetes and cardiovascular disease. These findings suggest that nutrition interventions may be effective in halting the adverse effects of bodily dysmorphia associated with HIV infection and chronic use of ART treatment.

In relation to inflammation, no significant differences were observed within or between the study groups in C-reactive protein (CRP) levels. Lastly, a significant reduction (p=0.04) was observed in levels of 8-hydroxy deoxyguanosine (8OHdG), a biomarker of oxidative stress, within the intervention group; while the control group did not show significant difference (p=0.37). This finding suggests that nutrition interventions are effective in lowering oxidative stress in prediabetic PLWH by promoting lifestyle changes, thus lowering risk for metabolic complications such as incident diabetes and cardiovascular disease. No significant difference was observed between the study arms at the 6-month follow-up (p=0.72), which may be due to the small sample size (n=38).

Discussion

The increased risk for prediabetes/diabetes in PLWH is well documented in the literature [7-9] and while numerous studies have previously shown the effectiveness of nutrition/lifestyle interventions in lowering diabetes risk among people with prediabetes [13,16,17], this research has been lacking in PLWH. However, studies such as this one, are now emerging, demonstrating the effectiveness of interventions in promoting positive outcomes and lowering diabetes risk in prediabetic PLWH. A recent mixed-methods study by Duncan et al. [34] conducted a 6-month diet and physical activity intervention for prediabetic PLWH. They provided individualized advice monthly (n=28) and assessed diabetes risk based on pre-post glucose and insulin responses to 3-hour meal tolerance test. They found that glucose, insulin, waist circumference, systolic blood pressure and triglycerides were significantly reduced after the 6-month intervention [34]. They concluded that their 6-month intervention was effective in mitigating the increased risk of type 2 diabetes associated with HIV infection; however, they did not have a control group.

The results of the study conducted by Duncan et al. supports the results of this current intervention study, demonstrating the effectiveness of lifestyle changes in lowering diabetes risk in prediabetic PLWH. Along with significant reduction of fasting blood glucose in the intervention group (p=0.03) in our study, there were significant reductions in BMI (p=0.03) and 8OHdG levels (p=0.04) within the intervention group after the 6-month intervention. Moreover, while participants in the control group were gaining weight after the 6-month duration with a unit increase in BMI, waist and hip circumferences and WHR, these same anthropometric parameters (BMI, waist/hip circumference, WHR) of the participants in the intervention group either remained relatively the same (waist/hip circumferences) or improved (BMI, WHR); this suggests that the intervention was effective in halting and/or reversing the progressive adverse effects associated with prediabetes in PLWH.

The positive outcomes from this intervention study and the study by Duncan et al. demonstrated the effectiveness of lifestyle modifications in lowering diabetes risk by significantly lowering blood glucose levels, BMI, oxidative stress, insulin, waist/hip circumference, systolic blood pressure and triglyceride levels in prediabetic PLWH. There are no other known intervention studies that were conducted in this particularly unique population. Larger scale studies with longer duration of follow-up visits are

needed in this high-risk population to determine if they are effective in subsequently lowering diabetes incidence and overall prevalence in prediabetic PLWH.

Acknowledgements

This work was partially funded by NIH/NIGMS R25 GM061347 which provided funding for biomarker testing and NIDA grants # 1 U01 DA 040381-01, #1R01DA042712-01 and 1R01DA042712-0, which provided funding for the Clinic and access to the MASH Cohort for recruitment.

References

[1] Maciel RA, Kluck HM, Durand M, Sprinz E. Comorbidity is more common and occurs earlier in persons living with HIV than in HIV-uninfected matched controls, aged 50 years and older: A cross-sectional study. Int J Inf Dis. 2018; 70: 30-35.

[2] Levin J, Ni Gusti Ayu N, St-Jean M, Tafessu H, Lu M, Salters K, et al. Earlier age of onset and higher prevalence of comorbidities in people living with HIV: A population-based cohort study in british Columbia, Canada. Conference on retroviruses and opportunistic infections (CROI) 2019 March 4-7; Seattle, WA.

[3] Brown TT, Cole SR, Li X. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. Archives of Internal Medicine. 2005; 165 (10): 1179-84.

[4] Hadigan C, Meigs JB, Corcoran C. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. 2001; 32(1): 130-9.

[5] Position Paper of the American Dietetic Association. Nutrition Intervention and Human Immunodeficiency Virus Infection. Journal of the American Dietetics Association. 2010; 110:1105-19.

[6] Stanley TL, Grinspoon SK. Body Composition and Metabolic Changes in HIV-infected patients. J Infect Dis. 2012; 205(3):383-90.

[7] Arafath S, Campbell T, Yusuff J, Sharma R. Prevalence of and risk factors for prediabetes in patients infected with HIV. Diabetes Spectrum. 2018 May; 31(2): 139-43.

[8] 2011-2014 National Health and Nutrition Examination Survey (NHANES), National Center for Health Statistics, Centers for Disease Control and Prevention.

[9] Colaguiri S. Epidemiology of Prediabetes. Medical Clinics of North America. 2011; 95(2): 299-307

[10] Bansal N. Prediabetes diagnosis and treatment: A review. World J Diabetes. 2015 Mar 15; 6(2): 296-303.

[11] Tabak AG, Herder C, Wolfgang R, Brunner E, Kiyimaki M. Prediabetes: A high-risk state for developing diabetes. Lancet. 2012 Jun 16; 379(9833): 2279-90.

[12] Shrot RJ, Sahebzamani FM, Brownlee J. Case Study: Screening and treatment of pre-diabetes in primary care. Clinical Diabetes. 2004; (22):98-100.

[13] The Diabetes Prevention Reseach Program (DPP) Research Group. The Diabetes Prevention Program (DPP): Description of Lifestyle Intervention. Diabetes Care. 2002;25(12):2165-71

[14] Jali M. Prediabetes- Early Detection and Interventions. Medicine Update. 2008 (18):633-44.

[15] Hsueh WA, Orloski L, Wyne K. Prediabetes: the importance of early detection and intervention. Postgraduate Medicine. 2010; 122(4):129-43.

[16] Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Pirjo IP. Prevention of Type 2 diabetes mellitus by changes in lfestyle among subjects with impaired glucose tolerance. The New England Journal of Medicine. 2001; 344(18):1343-50.

[17] Eriksson K, Lindgarde F. Prevention of Type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. Diabetologia. 1991;34: 891-98.

[18] Pan XR, Li GW, Hu YH, Wang JX, Yang WY. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. Diabetes Care. 1997;20(4):537-44.

[19] Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circulation Research. 2010; 107(9):1058-70.

[20] Marrif HI, Al-Sunousi SI. Pancreatic beta cell mass death. Frontiers in Pharmacology. 2016; 7(83)

[21] Su Y, Liu X, Sun Y, Jin H, Fu R, Wang Y, et al. The relationship between endothelial dysfunction and oxidative stress in diabetes and prediabetes. Int J Clinical Practice. 2008; 62(6):877-82.

[22] Fiorentino T, Prioletta A, Zuo P, Folli F. Hyperglycemia induced oxidative stress and its role in diabetes mellitus related cardiovascular disease. Current Pharmaceutical Design. 2013; 19(32):5695-703.

[23] Ullah A, Khan A, Khan I. Diabetes Mellitus and Oxidative Stress-A Concise Review. Saudi Pharmaceutical J. 2016; 24(5): 547-53.

[24] Volpe CMO, Villar-Delfino PH, Ferreira dos Anjos PM, Nogueira-Machado JA. Celleular Death, ractive oxygen species (ROS) and diabetic complications. Cell Death and Disease. 2018;9(119)

[25] Ivanov AV, Valuev-Elliston VT, Ivanova ON. Oxidative Stress during HIV Infection: Mechanisms and Consequences. Oxidative Medicine and Cellular Longevity. 2016; (8910396):1-18

[26] Masia M, Padilla S, Fernandez M, Rodriguez, Moreno A, Oteo JA, et al. Oxidative Stress Predicts All-Cause Mortality in HIV-Infected Patients. PLOS ONE. 2016;11(4).

[27] Kwak JH, Paik JK, Kim HI, Shin DY, Kim HJ, Lee HJ, et al. Dietary treatment with rice containing resistant starch improves markers of endothelial function with reduction of postprandial blood glucose and oxidative stress in patients with prediabetes and or newly diagnoses type 2 diabetes. Atherosclerosis. 2012;224(2):457-64.

[28] Hunt P. HIV and Inflammation: Mechanisms and consequences. Current HIV/AIDS Reports. 2012;9(2):139-47.

[29] Tien PC, Choi A, Zolopa A, Benson C. Inflammation and Mortality in HIV-Infected Adults: Analysis of the FRAM Study Cohort. J Acquired Immunodeficiency Syndrome. 2010; 55(3):316-22.

[30] Chang SC, Yang WCV. Hyperglycemia tumorigenesis and chronic inflammation. Critical Reviews in Oncology/Hematology. 2016; 108:146-53.

[31] Neuhaus J, Jacobs D, Baker A, Calmy A. Markers of Inflammation, Coagulation and Renal Function are Elevated in Adults with HIV Infection. The J Inf Dis. 2010; 201(12):1788-95

[32] Brown TT, Tassiopoulos K, Bosch RJ. Association between systemic inflammation and incident diabetes in HIV-infected patients after initiation of antiretroviral therapy. Diabetes Care. 2010; 33(10):2244-49.

[33] American Diabetes Association (ADA) Standards of Medical Care in Diabetes. The J Clin and App Res and Edu. 2018; 41(1).

[34] Duncan AD, Goff LM, Peters BS, Rivas C, Goff. Reducing Risk of Type 2 Diabetes in HIV: A Mixed-Methods Investigation of the STOP-Diabetes Diet and Physical Activity Intervention. Diabetic Medicine. 2019: 00 (1-10).