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BIOCHEMICAL PROFILE OF INDIVIDUALS WITH HIV/AIDS IN HAART: A PROPOSAL FOR NUTRITIONAL INTERVENTION USING A BIOACTIVE FOOD COMPOUND

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ABSTRACT

AIDS currently has chronic disease status because of the side effects of HAART. A study with 91 adult subjects undergoing HAART with or without hypolipidemic and/or hypoglycemic medication. Subjects were divided into groups A (GA) and B (GB) based on HAART and GB received 3.6 kg of Bioactive Food Compound (BFC) for three months. The variables were: immunological and virologic, biochemical parameters, HAART and BFC. Group A consisted of 2 NRTIs + 2 PIs (boosted with ritonavir) or 2 NTRIs + 1 NNRTI + 2 PIs, and this group was further divided into 2 subgroups: GA1 and GA2, consisting of atazanavir boosted with ritonavir and ritonavir boosted with lopinavir. Group B was formed by 2 NRTIs + 1 NNRTI. GB had a higher degree of immunodepression. The viral load was undetectable, and the exposure time to HAART was kept for more than two years. After 3 months of BFC consumption, GB presented better laboratory results for TG, TC, HDL-c, LDL-c and glucose levels. GA1 intra-group was a decrease in TG levels. In individuals without medication, it was possible to observe a decrease in TG levels, and a maintenance of the other parameters. The intra-group in GA2, using drugs to control lipids and glucose, it was decrease in TC and LDL-c in the same way as for individuals without medication, besides an increase in HDL-c. There is a need for multidisciplinary health interventions with people living with HIV / AIDS to control factors associated with chronic non-communicable diseases.

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INTRODUCTION

Worldwide, AIDS is considered one of the most important public health problems, a disease of great impact and magnitude since it has a high potential for dissemination. By 2015, it had approximately 36.7 million people carrying it, and less than half are undergoing antiretroviral therapy (US, 2016). The impact of this disease on the scientific, social, economic and cultural scenario has shown a possibility of decrease since the introduction of HAART (*highly active*

antiretroviral therapy). The disease assumed a chronicity status. If it is managed and treated properly, that is, if due importance and seriousness is given, it is possible to reduce considerably the probability of illness and death. This has been expressively addressed by several studies. Such studies report that treatment is effective in the control process and consequently improves the quality of life of individuals with HIV/Aids. It also reduces the transmissibility potential of the virus (Myron, 2011 and Montaner, 2013). In this sense, HAART therapy in Brazil immediately after diagnosis is recommended since 2013. The main HAART regimens are nucleoside or nucleotide reverse transcriptase inhibitors (NRTI), whose mechanism of action is to act on the reverse transcriptase (RT) enzyme, integrating the double helix of the DNA developed by the virus, making it unable to multiply and preventing it from reproducing. Non-nucleoside reverse transcriptase inhibitors (NNRTI) act by directly blocking RT activity, preventing the multiplication of the virus. Protease inhibitors (PI), which act on the protease enzyme by blocking it, prevent the synthesis of new cellular units infected with the virus (Brasil, 2017). However, adherence and the risk of adverse effects, such as changes in lipid and glucose profile, should be taken into account and may evolve with the development of chronic noncommunicable diseases (CNCD) (http://www.aids.gov.br/sites/default/files/anexos/publicacao/2013/55559/_p_boletim_2013_internet_pdf_p__51315.pdf.). It should be noted that healthy foods should respect the cultural identity of populations or communities, favoring a change in consumption of unhealthy foods to healthier foods. Nutritionally complete and functional foods should be valued, and dietary advice should be offered in an individualized way. Food should be physically and financially accessible, tasty, varied, colorful, harmonious and safe (http://www.aids.gov.br/sites/default/files/manual_alimentacao_nutricao.pdf).However, as a nutritional strategy, the consumption of foods with functional characteristics is recommended, since they offer benefits to the gastrointestinal and cardiovascular system besides acting on the metabolism of substrates, growth, cell development and differentiation, behavior of physiological functions and antioxidative processes (Souza, 2003).

In view of the benefits of functional nutrition, a BFC was developed. It has a high nutritional potential because it is rich in PUFA, especially α-linolenic acid. It shows low atherogenicity and thrombogenicity indexes, and a potential contribution to the control of atherosclerotic diseases. The BFC also showed a high protein and fiber content, reinforcing its nutritional value. This product was shown to be suitable for inclusion in the diets of HIV-positive patients. The BFC may also be used as a nutritional accompaniment for health maintenance, or to treat patients with other disorders such as hypercholesterolemia, hypertriglyceridemia, intolerance to glucose and diabetes (Ferreira, 2014). Therefore, this study aims to assess the impact on lipid profile and glucose in people with AIDS in HAART with or without protease inhibitors (PI) atazanavir or lopinavir boosted with ritonavir with nutritional intervention of the CAB.

METHODOLOGY

Research design

This is a prospective study of non-randomized controlled intervention based on the evaluation (before and after) of individuals with HIV/AIDS undergoing HAART therapy monitored in the outpatient clinics in the state of Mato Grosso do Sul (MS), Brazil. The protocol follows the ethical guidelines of the 1075 Declaration of Helsinki. This Project was approved by the local Ethical Committee, Federal University of Mato Grosso do Sul, under no. 1630, as well as Trial Url Register number RBR-6m2fch.

Population studied

Outpatient clinical follow-up comprised 91 adult individuals with HIV/AIDS who underwent HAART with PI therapy with or without hypolipidemic and/or hypoglycemic medication aiming to control cholesterol, triglyceridemia and glycaemia according to medical evaluation and prescription. The individuals were given a recommendation on lifestyle change (LSC) and nutritional guidance on healthy eating (Organização Mundial de Saúde, 2017; http://saudepublica.bvs.br/ pesquisa/ resource/pt/lil-448353; Brasil, 2015), hypocholesterolemia (American Heart Association Nutrition Committee, 2006; NAM Nutrition, 2006), hypotriglyceridemia and hypoglycemia (Sartorelli, 2006; Villela, 2017), besides an incentive to practice physical exercises (Organização Mundial de Saúde, 2017). They also received 3.6 kg of Bioactive Food Compound (BFC) for (40 g/ day) consumption for three months in preparations based on milk, soups, yogurts, beans and sauces. This was delivered at the monthly nutrition consultation. Subjects were divided into groups A (GA) and B (GB) based on drug classes according to antiretroviral regimens.

Immunological and virologic variables

The variables were established by T CD4+/CD8+ lymphocyte counts and quantification of HIV-1 viral load (VL) using the Abbot Real Time HIV1 method and flow cytometry (FACScalibur multi test).

Biochemical parameters

For the determination of total cholesterol, HDL-c, LDL-C, triglycerides and fasting glucose, the enzyme-colorimetric methodologies (Flegg, 1973). Examinations were performed after three months of BFC consumption at the Clinical Analysis Laboratory of reference centers of infectious diseases care in MS.

Classes of drugs according to antiretroviral regimens

Drug classes that comprise the antiretroviral regimens were identified as NRTI (nucleoside analogue reverse transcriptase inhibitors), NNTRI (non-nucleoside reverse transcriptase inhibitors) and PI (protease inhibitors). The Group A (n = 58) consisted of 2 NRTIs + 2 PIs (boosted with ritonavir) or 2 NTRIs + 1 NNRTI + 2 PIs, and this group was further divided into 2 subgroups: GA1 and GA2, consisting of atazanavir boosted with ritonavir (A1 - atazanavir/r) and ritonavir boosted with lopinavir (A2 - lopinavir/r). Group B (n = 38) was formed by 2 NRTIs + 1 NNRTI.

Bioactive food compound (BFC)

The food formulation consisted of 20 g of oat bran, 10 g of texturized soya protein and 10 g of ground flax seed in a previously established ratio (2:1:1), totaling 40 g of final product called Bioactive Food Compound (BFC) for the treatment of changes in lipid and glucose metabolism.

The BFC was submitted to a patent application at the National Institute of Industrial Property (INPI). It was registered under case no. BR 10 2013 018002 5, on July 15, 2013, by the Federal University of Mato Grosso do Sul (UFMS). On August 8, 2015, it was published by the Ministry of Development and Foreign Trade, Brazil.

Data processing and analysis

Statistical analyses were performed at before and after consumption of BFC with groups A (A1 - atazanavir/ritonavir and A2 - lopinavir/ritonavir) and, finally, the group B. Student t (parametric data) or Wicoxon (non-parametric data) tests were applied to total cholesterol, LDL-c, HDL-c, triglycerides and glycaemia. Student's t-tests (parametric data) or Mann-Whitney (non-parametric data) were used between groups A and B. For anthropometric, immunological and virologic data of groups A and B, the Chi-square test was performed. The statistical analysis was performed using the software BioEstat 5.0, Origin 8.0 and EpiInfo 3.5, considering differences as significant with a $p<0.05$.

RESULTS

Of the patients studied there was no difficulty in acceptance or side effects associated with the BFC consumption. With regard to immunological, virologic and HAART exposure times, we noticed by the analysis of the groups that the population of group B had a higher degree of immunodepression. As for the virologic aspect, a good response to the therapeutic regimen was observed. The viral load was undetectable, and the exposure time to HAART was kept for more than two years (Table 1).

LDL-c, while GB had higher levels of TC and glucose. In relation to the post-treatment period of 3 months of BFC consumption, higher levels of TG, TC, LDL-c and glucose (p= 0.05) were identified in GA. GB presented better laboratory results for TG, TC, HDL-c, LDL-c and glucose levels (p= 0.05).

Table 1. Values and percentages of individuals undergoing HAART according to immunological, virologic and antiretroviral therapy periods

Variable	Groups		*p*
	A	B	
CD4			
< 500	24.0 (45.3)	20.0 (52.6)	(1)0.63
≥ 500	29.0 (54.7)	18.0 (47.4)	
Viral load			
Detectable	6.0 (11.3)	5.0 (13.2)	
Undetectable	47.0 (88.7)	33.0 (86.8)	(1)0.95
HAART time			
< 2 years	7.0 (13.2)	5.0 (13.2)	
≥ 2 years	46.0 (86.8)	33.0 (86.2)	(1)0.76

(1) Chi-square test.

The biochemical parameters of individuals exposed to BFC after 3 months showed that GA increased the levels of TG, TC and glucose and decreased the levels of LDL-c, unlike GB, which increased the levels of TG, TC, HDL-c, LDL-c and glucose. At the beginning of the study (without BFC), comparing GA with no drug use, it was shown that GA showed higher levels of TG (p= 0.001) and TC. On the other hand, GB showed laboratory results within normal limits. After the BFC treatment period, GA showed higher levels of TG (p= 0.02), TC and LDL-c, and GB remained within normal limits.

Table 2. Biochemical parameters (mg/dL) of group A (n = 53) and group B (n = 38) with or without exposure to lipid-lowering and/or hypoglycemic drugs

Laboratory levels	GA *vs* GB					
	Using medication*			Without medication*		
	GA	GB	*p*	GA	GB	*p*
Triglycerides	(n= 18)	(n= 11)		(n= 35)	(n= 27)	
Before	177.17	173.91	(1)0.92	187.54	126.37	(1)0.001
After	189.94	140.91	(1)0.11	177.00	136.52	(1)0.02
p	(1)0.39	(1)0.45		(1)0.44	(1)0.29	
Total cholesterol	(n= 13)	(n= 22)	*p*	(n= 40)	(n= 30)	*P*
Before	196.85	216.37	(1)0.34	206.51	198.00	(1)0.35
After	198.54	195.37	(1)0.88	199.80	196.40	(1)0.71
p	(1)0.87	(1)0.37		(1)0.28	(1)0.81	
HDL-c	(n= 12)	(n= 07)	*p*	(n= 41)	(n= 31)	*P*
Before	47.50	49.28	(1)0.80	42.83	45.71	(2)0.39
After	45.92	52.00	(1)0.43	43.46	45.68	(2)0.48
p	(1)0.48	(1)0.75		(1)0.74	(1)0.99	
LDL-c	(n= 11)	(n= 08)	*p*	(n= 42)	(n= 30)	*P*
Before	135.90	131.75	(1)0.89	124.09	125.40	(1)0.86
After	120.45	120.37	(1)0.56	120.63	120.03	(1)0.94
p	(2)0.39	(1)0.58		(1)0.04	(1)0.32	
Glucose	(n= 02)	(n= 09)	*p*	(n= 51)	(n= 29)	*P*
Before	70.50	100.11	(1)0.08	82.21	86.17	(1)0.15
After	132.50	96.00	(1)0.05	83.23	87.72	(1)0.06
p	(1)0.44	(1)0.49		(1)0.42	(1)0.46	

(1)T test for paired samples, (2)Wilcoxon test; *Average

By analyzing the biochemical parameters of groups A and B, exposed or not to drugs to control the lipid and glycemic profile (Table 2), we observed that, by comparing group A, characterized by a HAART regimen with 2 NRTIs + 2 PIs (boosted ritonavir) or 2 NTRIs + 1 NNTRI + 2 boosted PIs, with group B, which presents an antiretroviral regimen represented by 2 NRTIs + 1 NNRTI, prior to the consumption of BFC, we observed that GA showed higher levels of TG and

When analyzing "before" and "after" times intra-group without medication, there was a decrease in TG, TC and LDL-C levels in GA. Regarding GB, it was possible to notice a decrease in TC and LDL-c levels. Upon analyzing GA1 intra-group as for biochemical parameters in individuals exposed to lipid-lowering and/or hypoglycemic drugs, at baseline and after 3 months of BFC consumption, we observed that there was a decrease in TG levels.

Table 3. Biochemical parameters (mg/dL) of group A1 using atazanavir boosted with ritonavir (n = 9) and group A2 using lopinavir (n = 37) with or without hypolipidemic and/or hypoglycemic drugs

GA1 with Atazanavir boosted with Ritonavir				
Laboratory Levels	Using medication*		Without medication*	
Triglycerides	(n= 02)		(n= 07)	
Before	132.50 ± 10.61	(1)0.93**	205.14 ± 59.05	(1)0.48**
After	127.00 ± 62.22		190.42 ± 56.03	
Total cholesterol	(n= 01)		(n= 08)	
Before	177	-	187.87 ± 33.74	(1)0.98**
After	206		188.12 ± 34.17	
HDL-c	(n= 01)		(n= 08)	
Before	50	-	38.25 ± 11.39	(1)0.73**
After	37		38.75 ± 12.27	
LDL-c	(n= 00)		(n= 09)	
Before	-	-	114.33 ± 27.17	(1)0.84**
After	-		115.78 ± 24.99	
Glucose	(n= 01)		(n= 08)	
Before	92	-	95.00 ± 16.71	(1)0.99**
After	102		95.00 ± 9.16	
GA2 with Lopinavir				
Laboratory levels	Using medication*		Without medication*	
Triglycerides	(n= 11)		(n= 26)	
Before	192.36 ± 97.86	(1)0.26**	185.54 ± 62.08	(1)0.31**
After	218.00 ± 137.10		168.35 ± 70.60	
Total cholesterol	(n= 08)		(n= 29)	
Before	216.00 ± 32.19	(1)0.44**	211.48 ± 43.72	(1)0.06**
After	204.00 ± 29.13		200.76 ± 35.12	
HDL-c	(n= 07)		(n= 30)	
Before	47.43 ± 14.15	(1)0.33**	44.93 ± 15.59	(1)0.66**
After	44.43 ± 10.74		46.07 ± 12.46	
LDL-c	(n= 07)		(n= 30)	
Before	162.57 ± 50.13	(1)0.16**	125.67 ± 35.37	(1)0.33**
After	127.14 ± 15.92		119.75 ± 32.40	
Glucose	(n= 00)		(n= 37)	
Before	-	-	79.92 ± 9.10	(1)0.29**
After	-		81.38 ± 8.71	

(1)T test for paired samples. * Mean ± SD. ***p*

In individuals without medication, it was possible to observe a decrease in TG levels, and a maintenance of the other parameters (Table 3). In relation to the intra-group biochemical parameters in GA2, using drugs to control lipids and glucose, it was possible to observe a decrease in TC and LDL-c in the same way as for individuals without medication, besides an increase in HDL-c (Table 3).

DISCUSSION

Among the 91 individuals undergoing HAART treated at Reference Day Hospitals in MS, the immunological, virologic and HAART periods of half of them were well controlled, since GA and GB presented CD4 ≥500 cells/mm^3, an undetectable viral load and most were subjected to HAART for more than 2 years. As for virologic status, the results of this study express the Brazilian reality, Program Joint United Nations on HIV/AIDS (2016) predicts that, by 2020, 90% of people living with HIV will be diagnosed. Among them, 90% are in treatment and 90% of those under treatment have an undetectable viral load. In groups A and B, we found that there was an improvement in the lipid profile of individuals who used or not control medication, a fact that evidences a response to the active principles of BFC. The results of the meta-analysis conducted by Pan *et al*., (2009) suggest that the consumption of flaxseed markedly affects the reduction of the blood concentration of TC and the LDL-c fraction in daily doses of 20 g to 50 g. Data from the study conducted by Henriques *et al*., (2008), using fiber mix, are consistent with the findings of this study. Throughout the study, we noted in Groups A and B that BFC may have actually had an influence on the improvement of the lipid profile, with a little numeric expression for blood glucose levels. These results corroborate with Henriques *et al*., (2008), as they obtained a decrease of 21.5% of total TC levels in a biological assay with oat fiber and flax seed. As for glycaemia, there was also a stabilization, keeping it within normality limits. Regarding the laboratory variables in groups A and B, it was evidenced that there was a positive impact of the use of BFC for all studied variables, except for glucose, where the mean increased even in the face of exposure to control drugs. This did not occur in groups A and B without medication. It seems that unmedicated individuals are metabolically more competent or may have changed the modifiable factors recommended when they were included in the study. Stein (2005), Carosi (2007) and Mutimura (2008) report that serum levels of TC, LDL-c, HDL-c, TG and glucose have been recommended to these individuals by dietary intervention and regular physical activity. Regarding GA, as for the use of medication for metabolic control, we observed an increase in glycaemia after consumption of BFC. However, the lipid and glucose metabolism of those who did not use medication resulted in a better response, closer to normal. This finding corresponds to that of Marques *et al*., (2011) upon evidencing in an experiment that fasting glucose was numerically lower after exposure to raw, roasted or oil flaxseed. Regarding the GB group, all biochemical parameters resulted in decreased levels or within normal limits after 3 months of BFC consumption, nutritional orientation and stimulation of physical activity, with adherence to lifestyle change recommendations, similar to what happened in the studies conducted by Wohl (2005) and Valmorbida (2013). This can be justified by the active principles of BFC, which positively impact GB, improving the lipid and blood glucose profile and responding in a similar way to the general population with chronic noncommunicable

diseases (CNCD). In addition, Tsiodras *et al*., (2000) reported that changes in the lipid profile, specifically the increase in TG levels, are also observed in individuals using NRTIs regardless of the use of PIs. Therefore, it is suggested that other factors interfere with such dyslipidemic outcome (Valente *et al*., 2005). In this study, we observed evidences of cardiovascular risk strongly associated with protease inhibitors (PIs), especially in GA2 undergoing its HAART regimen. PIs present a strong association with early atherosclerosis and cardiovascular events (DAD, 2007), a fact widely reported in the literature and by prospective and cohort studies with HIV-infected individuals (Mary-Krause, 2003; Glass, 2006). We observed that in GA1 - atazanavir and GA2 - lopinavir there was a decrease or a maintenance of normal limits for all biochemical parameters evaluated in individuals not using control medication. This can be justified in the same way as for the previous group. The results of the study conducted by Caramelli *et al*., (2001) are similar. The authors report that one group treated with atazanavir had the lowest levels of TC and LDL-c, although no benefit was observed in terms of TG levels. Unexpectedly, higher levels of HDL-c were observed, and hypercholesterolemia was present in 43% and hypertriglyceridemia in 53% of patients treated with PIs.

In vitro studies demonstrate that PIs reduce insulin-mediated glucose uptake into the skeletal muscle and into adipocytes, selectively and potentially decreasing the activity of GLUT4 glucose transmembrane transporter without affecting the signaling events of insulin or GLUT4 translocation. Since glucose transport is one of the limiting steps for glucose elimination, the inhibitory effect of PIs on GLUT4 causes insulin resistance in HIV-positive individuals using this class of drugs. This effect is greatly minimized when the PI is atazanavir and maximal when the PI is ritonavir (Murata, 2000; Koster, 2003). Another mechanism of induction of PI insulin resistance is its effect on SREBP-1 transcription factor (steroid regulatory element binding protein-1c), affecting glucose metabolism by producing imperfect expressions of proliferator-activated gamma receptor of peroxisome (PPAR-y), which plays an important role in the metabolism of glucose, lipids and agonists of PPAR-y, such as thiazolidinediones (rosiglitazone and pioglitazone), which improve insulin sensitivity (Satoshi, 2013).

Finally, the findings of this study corroborate important research (Cahn *et al*., 2010)34 on neglected infectious diseases such as HIV/AIDS. Therefore, it should be noted that the data found in Campo Grande/MS resemble the Brazilian reality of people living with HIV/AIDS (http://www.brasil.gov.br/saude/2016/01/brasil-bate-recorde-de-pessoas-em-tratamento-contra-o-hiv-e-aids) and the world scenario (https://www.hhs.gov/about/index.html). The results of this study also reveal that individuals who did not use medication to control biochemical parameters did not fully benefit from the BFC. This is possibly because they did not follow the indications of the best and most adequate forms of feeding, which help to control losses of fat mass and form muscular mass, in addition to physical inactivity. This does not meet the guidelines established by the Clinical Manual on Food and Nutrition in Assistance to HIV Infected Adults (http://saudepublica.bvs.br/pesquisa/resource/pt/lil-448353). recommended to individuals participant in this research. It is known that lifestyle is a modifiable risk factor that encompasses all actions, reactions and behaviors adopted by people producing a more or less adequate health profile. It is also known that adherence to treatment has been observed in the presence of nutritional guidance and individualized diets[36].

Conclusion

This study infers that the immunological and virologic status of the participants remained in good control. It also demonstrated that groups A and B had a positive impact by BFC on the biochemical profile, which showed that there was possibly some implementation of modifiable lifestyle factors. Groups A and B responded metabolically by decreasing or maintaining biochemical parameters within normal ranges after consuming BFC. This study points to a need for targeting multidisciplinary health interventions with people living with HIV/AIDS to control factors associated with chronic noncommunicable diseases (CNCD).

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