ORIGINAL

One-hundred days monitoring patients submitted to hematopoietic stem cell transplantation: Events of metabolic syndrome[1]

Cem dias de monitoramento de pacientes submetidos ao transplante de células-tronco hematopoéticas: *eventos da síndrome metabólica*

Maria Cláudia Bernardes SPEXOTO[2]
Maria Rita Marques de OLIVEIRA[3]

ABSTRACT

Objective

This study assessed early manifestations of metabolic syndrome determinants in patients submitted to hematopoietic stem cell transplantation.

Methods

Twenty-seven individuals participated in the study (20 with autologous and 7 with allogeneic hematopoietic stem cell transplantation). Anthropometric variables and biochemical indicators of lipid and glucose metabolism were determined before and 100 days after hematopoietic stem cell transplantation.

[1] Article based on the master thesis of SMB SPEXOTO intitled "Consumo alimentar, estado nutricional e resposta precoce dos fatores de risco relacionados a síndrome metabólica de pacientes submetidos ao transplante de células-tronco hematopoéticas". Universidade Estadual Paulista Júlio de Mesquita Filho, 2010.

[2] Universidade Estadual Paulista Júlio de Mesquita Filho, Faculdade de Ciências Farmacêuticas, Programa de Pós-Garduação em Alimentos e Nutrição. Araraquara, SP, Brasil.

[3] Universidade Estadual Paulista Júlio de Mesquita Filho, Instituto de Biociências, Departamento de Educação. Caixa-Postal 510, Distrito de Rubião Jr., 18618-000, Botucatu, SP, Brasil. *Correspondência para*/Correspondence to: MRM OLIVEIRA. E-mail: <mrmolive@ibb.unesp.br>.

Results

The mean total cholesterol (p=0.086), very low density lipoprotein-cholesterol (p=0.069) and triglycerides (p=0.086) of all patients did not change significantly between the two study periods, but when the patients were separated by type of hematopoietic stem cell transplantation, triglycerides and very low density lipoprotein-cholesterol were close to the critical level of significance for individuals with allogeneic hematopoietic stem cell transplantation (p=0.060) and total cholesterol was significant in individuals with autologous hematopoietic stem cell transplantation (p=0.027). Anthropometric variables did not change significantly between before and 100 days after hematopoietic stem cell transplantation.

Conclusion

Metabolic syndrome risk factors may be associated with lipid metabolism in the early phase of allogeneic and autologous hematopoietic stem cell transplantation.

Indexing terms: Body composition. Hematopoietic stem cell transplantation. Lipids. Metabolic syndrome.

RESUMO

Objetivo

Este estudo avaliou as manifestações precoces de fatores determinantes da síndrome metabólica em pacientes com transplante de células-tronco hematopoéticas.

Métodos

Vinte e sete indivíduos participaram do estudo (20 autólogos e 7 alogênicos). Variáveis antropométricas e indicadores bioquímicos do metabolismo glicídico e lipídico foram determinados antes e após 100 dias do transplante.

Resultados

A média de colesterol total (p=0,086), lipoproteínas de muito baixa densidade-colesterol (p=0.069) e triglicerides (p=0.086) de todos os pacientes não sofreu alteração significativa entre os dois perídos, porém, quando os pacientes foram separados pelo tipo de transplante de células-tronco hematopoéticas, os triglicerídeos e o lipoproteínas de muito baixa densidade-colesterol apresentaram-se próximos do nível crítico de significância para os indivíduos com transplante alogênico (p=0,06) e o colesterol total aumentou significativamente entre os indivíduos autólogos (p=0,027). As variáveis antropométricas não alteraram significativamente na comparação antes e após transplante de células-tronco hematopoéticas.

Conclusão

Os fatores de risco para síndrome metabólica podem ser associados com o metabolismo de lipídios na fase inicial do transplante alogênico e autólogo.

Termos de indexação: *Composição corporal. Transplante de células-tronco hematopoéticas. Lipídeos. Síndrome metabólica.*

INTRODUCTION

Hematopoietic Stem Cell Transplantation (HSCT), regardless of the origin of the Hematopoietic Stem Cells (HSC), results in a series of early or late metabolic complications. One of these complications, the Metabolic Syndrome (MS), has been a somewhat common finding in individuals with HSCT, especially allogeneic HSCT[1-3].

Metabolic syndrome is characterized by high blood pressure, changes in glucose and lipid metabolism, and abdominal obesity[4-12]. The causes include factors that change glucose and lipid metabolism, such as diet and medication. These

metabolic changes can be directly or indirectly influenced by diet. It is known that the nutritional requirements of these patients are higher than normal because of the intense catabolism that occurs before HSCT[13]. The cholesterol and triglyceride levels of HSCT patients usually increase in the long run[14]. Current data indicate that there is a high prevalence of MS risk factors in patients with HSCT[3,14], but little is known about the changes in body composition and manifestations of these factors after HSCT. Hence, the objective of the present study was to assess early manifestations of MS risk factors and body composition in the first 100 days following HSCT.

METHODS

This longitudinal study used a nonprobabilistic sampling design. We used a convenience sample, where all patients evaluated in the study period were enrolled.

Twenty-seven patients aged 44±14 years were studied from June 2009 to March 2010, 20 with autologous HSCT and seven with allogeneic HSCT. Most (60%) autologous HSCT patients had multiple myeloma. The most common diagnosis (43%) in allogeneic HSCT patients was acute myeloid leukemia. Other diagnoses included non-Hodgkin's lymphoma, severe aplastic anemia, Hodgkin's lymphoma and myelodysplastic syndrome. Patients with hypothyroidism, Cushing's syndrome, chronic kidney failure, Human Immunodeficiency Virus (HIV) infection, alcoholism (>40g of alcohol/day), and genetic syndromes associated with obesity were excluded. The patients were recruited at the Cancer Hospital of *Barretos, São Paulo*, Brazil. The Hospital's Research Ethics Committee approved the study (Protocol number 288/10).

Anthropometric indicators of nutritional status (waist, calf and hip circumferences, and biceps, triceps, subscapular and suprailiac skinfold thicknesses) and biochemical markers of lipid and glucose metabolism were determined before and 100 days after HSCT.

The biochemical tests included C-reactive protein, Triglycerides (TG), Total Cholesterol (TC), High Density Lipoprotein-cholesterol, low Density Lipoprotein-cholesterol and Very Low Density Lipoproteins-cholesterol (HDL-C, LDL-C and VLDL-C, respectively), and glucose and insulin after a 12-hour fast (HITACHI-902, Roche®). Insulin Resistance (IR) was assessed according to the Homeostasis Model Assessment (HOMA) index. The metabolic syndrome was assessed according to the International Diabetes Federation's (IDF) diagnostic criteria[4].

Female patients were asked if they were on hormone replacement therapy, and the use of drugs to control blood glucose, pressure and lipids, and immunosuppressive drugs was monitored during the study.

The biochemical variables before and 100 days after HSCT were compared by the Student's *t* test for paired samples. The determinants of MS in the study cases were investigated by the Fisher's exact test for the variables of interest. The significance level was set at 5% ($p \leqslant 0.05$) for all tests. All the analyses were made by the BioEstat software for *Windows*, version 3.0.

RESULTS

Before hematopoietic stem cell transplantation, 85% of the women and 42% of the men were overweight or obese, while only one allogeneic HSCT patient was malnourished.

The most common risk factors associated with MS before HSCT were high blood pressure, found in 4 men and 2 women, and dyslipidemia, found in 1 man and 3 women. Table 1 shows the changes in MS determinants in autologous and allogeneic HSCT patients. Only high blood pressure was found to be significantly lower in autologous HSCT patients 100 days after the transplantation (p=0.047).

The mean TC (p=0.086), VLDL-C (p=0.069), and TG (p=0.086) of all patients did not change significantly between the two study periods. But when the patients were separated by type of HSCT, TC differed significantly in autologous patients (n=20, p=0.027) (Table 2). Anthropometric variables did not vary significantly between before and 100 days after HSCT.

Table 1. Metabolic syndrome determinants factors of the in patients before and 100 days after allogeneic or autologous hematopoietic stem cell transplantation. *Barretos* (SP), Brazil, 2010.

Diagnostic criteria for the metabolic syndrome	Allogeneic (n=7)					Autologous (n=20)					Allogeneic and Autologous (n=27)				
	Before HSCT		D+100		*p*	Before HSCT		D+100		*p*	Before HSCT		D+100		*p*
	Y	N	Y	N		Y	N	Y	N		Y	N	Y	N	
Abdominal obesity															
Men: ⩾94 cm	1	3	1	3	1.000	4	6	5	5	0.685	5	9	6	8	1.000
Women: ⩾80 cm	2	1	3	0	1.000	10	0	10	0	1.000	12	1	13	0	1.000
Triglycerides ⩾150 mg/dL or treatment	2	5	6	1	0.103	13	7	12	8	0.757	15	12	18	9	0.421
HDL-C															
Men <40 mg/dL	3	1	4	0	1.000	7	3	3	7	0.101	10	4	7	7	0.440
Women <50 mg/dL	2	1	2	1	1.000	8	2	9	1	1.000	9	4	11	2	0.645
Blood pressure															
Systolic ⩾130 mmHg or treatment	1	6	2	5	1.000	5	15	0	20	0.047	6	21	2	25	0.250
Fasting glucose ⩾100 mg/dL or treatment	2	5	1	6	1.000	8	12	7	13	1.000	10	17	9	18	0.785

Note: D+100: 100 Days After Hematopoietic Stem Cell Transplantation (HSCT); HDL-C: High Density Lipoprotein-Cholesterol; Y: Yes; N: No.

Table 2. Biochemical tests in patients before and 100 days after hematopoietic stem cell stransplantation according to type of procedure. *Barretos* (SP), Brazil, 2010.

Variables	Allogeneic HSCT (n=7)				Autologous HSCT (n=20)			
	Before		100 days after		Before		Before	
	M	SD	M	SD	M	SD	M	SD
Total cholesterol	179.0	± 69.0	174.0	± 60.0	187.0	± 49.0	210.0	± 72.0
HDL-C (mg/dL)	42.0	± 16.0	*p*=0.788 32.0	± 12.0	39.0	± 17.0	*p*=0.027 44.0	± 12.0
LDL-C (mg/dL)	115.0	± 51.0	*p*=0.114 105.0	± 39.0	104.0	± 38.0	*p*=0.105 106.0	± 42.0
VLDL-C (mg/dL)	22.0	± 14.0	*p*=0.544 37.0	± 16.0	43.0	± 33.0	*p*=0.847 52.0	± 58.0
Triglycerides (mg/dL)	109.0	± 69.0	*p*=0.060 185.0	± 79.0	221.0	± 160.0	*p*=0.226 261.0	± 288.0
C-reactive protein (mg/dL)	2.2	± 3.8	*p*=0.060 3.0	± 5.2	1.3	± 1.7	*p*=0.275 1.0	± 1.6
Fasting glucose (mg/dL)	93.0	± 21.0	*p*=0.720 91.0	± 12.0	103.0	± 20.0	*p*=0.630 102.0	± 24.0
Fasting insulin (uU/mL)	9.0	± 4.2	*p*=0.842 10.0	± 6.8	11.0	± 9.0	*p*=0.895 10.0	± 7.1
HOMA index	2.1	± 1.3	*p*=0.731 2.2	± 1.5	3.0	± 2.7	*p*=0.782 2.5	± 1.6
			p=0.872				*p*=0.480	

Note: LDL-C: Low Density Lipoprotein-Cholesterol; HDL-C: High Density Lipoprotein-Cholesterol; VLDL-C: Very Low Density Lipoprotein-Cholesterol; HOMA: Homeostasis Model Assessment; M: Mean; SD: Standard Deviation.

Only one woman of the seven allogeneic HSCT patients developed Graft-Versus-Host Disease (GVHD), but she was successfully treated with corticosteroids. It manifested as acute GVHD of the intestine and lasted only a few days, allowing her to remain in the study. All allogeneic patients were taking the immunosuppressive drug ciclosporin during the study period.

DISCUSSION

Since there is a higher prevalence of MS risk factors in HSCT patients, the present study tried to detect early changes in these risk factors by measuring anthropometric indicators of nutritional status. Although the sample size does not allow generalization of the results and their inconclusiveness also prevents the confirmation of some associations, the data suggest that early MS manifestations do occur in both autologous and allogeneic HSCT patients.

Advances in hematopoietic stem cell transplantation techniques and the support and care provided to these patients increased survival significantly. Yet, exposure to chemotherapy before the procedure, the procedure itself, long periods of immunosuppression, and high risk of recurrence have many complications, MS being one of them[15,16].

Despite the small sample size, variation in TC, VLDL-C, and TG levels between the two study periods was very close to the significance level of 5%. This is a relevant finding that should be further investigated since changes in the lipoprotein profile occasionally occur early.

An interesting observation was that the TC of autologous patients varied significantly over time. These patients require milder post-HSCT treatment but they are still vulnerable to MS risk factors. Meanwhile, although the number of allogeneic patients (n=7) was small, the increase in their TG and VLDL-C levels over time was almost significant (p=0.060).

But metabolic syndrome manifestations did not occur within 100 days of follow-up and we do not know whether they would occur during a longer follow-up.

The cholesterol and triglyceride levels of HSCT patients usually increase in the long run. However, the present study found that changes in the lipid profile may be detectable as early as 100 days after the procedure in allogeneic HSCT patients.

The negative impact of corticosteroids on the lipid profile is well established; however, only one of the seven allogeneic HSCT patients took corticosteroids until day 100 after the procedure. Most allogeneic HSCT patients needed only ciclosporin for immune suppression.

Elevated total cholesterol may be due to other mechanisms, such as the effect of drugs on the synthesis or removal of LDL-C or the treatment given before autologous HSCT. It may also be due to higher consumption of cholesterol and fats after HSCT, as this study found that the diet of these patients after the procedure became more atherogenic with cholesterol intake exceeding 200 mg/day (314±168 mg 100 days after the procedure - dietary data were not shown in this study).

This study shows that autologous HSCT patients also need to be concerned with vulnerability to metabolic changes. And some of the changes may be attributed to dietary behavior changes, not only to metabolic changes.

Anthropometric variables and fasting glucose and insulin remained unchanged after 100 days. The results of the present study show that extra energy and macronutrient intakes are capable of preventing weight loss.

Hematopoietic stem cell transplantation patients need individualized nutritional care before and after the procedure. Before HSCT, patients undergo treatments that often debilitate their immune system. During this period, involuntary weight loss may be a reflection of an unwanted process of acute malnutrition. After the procedure, priority is given to the sanitation aspect of the diet, much more than its nutritional quality[13,17].

Metabolic syndrome pathogenesis is complex and its precise mechanisms are not well known. What

is known is that diet can either promote or prevent MS. The prevalence of lifestyle-associated diseases, such as obesity, hyperlipidemia, atherosclerosis, secondary diabetes mellitus, and high blood pressure in industrialized countries is increasing[18]. In the specific case of transplanted patients, anti-rejection drugs add to the insult.

CONCLUSION

In the 100 days that followed HSCT, the nutritional status of the study population remained stable. However, we conclude that in 100 days there are changes in factors associated with lipid metabolism, but they do not contribute to the onset of MS because MS does not depend only on lipid metabolism.

ACKNOWLEDGEMENTS

We thank the Cancer Hospital of *Barretos, São Paulo*, Brazil, especially the Department of Hematology and Bone Marrow Transplantation, for their direct collaboration with the study.

CONTRIBUTORS

All authors contributed substantially and equally to the manuscript.

REFERENCES

1. Annaloro C, Airaghi L, Saporiti G, Onida F, Cortelezzi A, Deliliers GL. Metabolic syndrome in patients with hematological diseases. Expert Rev Hematol. 2012; 5(4):439-58.
2. Annaloro C, Onida F, Saporiti G, Lambertenghi Deliliers G. Cancer stem cells in hematological disorders: Current and possible new therapeutic approaches. Curr Pharm Biotechnol. 2011; 12(2):217-25.
3. Annaloro C, Usardi P, Airaghi L, Giunta V, Forti S, Orsatti A, *et al.* Prevalence of metabolic syndrome in long-term survivors of hematopoietic stem cell transplantation. Bone Marrow Transplant. 2008; 41(9):797-804.
4. Federation ID. The IDF consensus worldwide definition of the metabolic syndrome. Belgium: International Diabetes Federation; 2006.
5. Hildrum B, Mykletun A, Hole T, Midthjell K, Dahl AA. Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: The Norwegian HUNT 2 study. BMC Public Health. 2007; 7:220.
6. Lorenzo C, Serrano-Rios M, Martinez-Larrad MT, Gonzalez-Sanchez JL, Seclen S, Villena A, *et al*. Geographic variations of the International Diabetes Federation and the National Cholesterol Education Program-Adult Treatment Panel III definitions of the metabolic syndrome in nondiabetic subjects. Diabetes Care. 2006; 29(3):685-91.
7. Mannucci E, Monami M, Cresci B, Pala L, Bardini G, Petracca MG, *et al.* National Cholesterol Education Program and International Diabetes Federation definitions of metabolic syndrome in the prediction of diabetes. Results from the FIrenze-Bagno a Ripoli study. Diabetes Obesity Metabol. 2008; 10(5):430-5.
8. Mertens I, Van Gaal LF. New International Diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment panel III (NCEP-ATPIII) criteria and the involvement of hemostasis and fibrinolysis in the metabolic syndrome. J Thrombosis Haemostasis. 2006; 4(5):1164-6.
9. Nawabzad R, Champin B. [Concordance between three definitions for metabolic syndrome (Hypertriglyceridemic waist, National Cholesterol Education Program, International Diabetes Federation), and prevalence of the syndrome in a French population]. Rev Prat. 2010; 60(10 Suppl):15-23.
10. Rezaianzadeh A, Namayandeh SM, Sadr SM. National Cholesterol Education Program Adult Treatment Panel III *Versus* International Diabetic Federation Definition of Metabolic Syndrome, Which One is Associated with Diabetes *Mellitus* and Coronary Artery Disease? Intern J Preventive Medicine. 2012; 3(8):552-8.
11. Rodriguez A, Delgado-Cohen H, Reviriego J, Serrano--Rios M. Risk factors associated with metabolic syndrome in type 2 diabetes *Mellitus* patients according to World Health Organization, Third Report National Cholesterol Education Program, and International Diabetes Federation definitions. Diabetes Metab Syndr Obes. 2011; 4:1-4.
12. Yoon YS, Lee ES, Park C, Lee S, Oh SW. The new definition of metabolic syndrome by the international

diabetes federation is less likely to identify metabolically abnormal but non-obese individuals than the definition by the revised national cholesterol education program: The Korea NHANES study. Inter J Obesity. 2007; 31(3):528-34.

13. Martin-Salces M, de Paz R, Canales MA, Mesejo A, Hernandez-Navarro F. Nutritional recommendations in hematopoietic stem cell transplantation. Nutrition. 2008; 24(7-8):769-75.
14. Majhail NS, Flowers ME, Ness KK, Jagasia M, Carpenter PA, Arora M, *et al.* High prevalence of metabolic syndrome after allogeneic hematopoietic cell transplantation. Bone Marrow Transplan. 2009; 43(1):49-54.
15. Baker KS, Armenian S, Bhatia S. Long-term consequences of hematopoietic stem cell transplantation: Current state of the science. Biol Blood Marrow Transplant. 2010; 16(1 Suppl):S90-6.
16. Baker KS, Chow E, Steinberger J. Metabolic syndrome and cardiovascular risk in survivors after hematopoietic cell transplantation. Bone Marrow Transplant. 2012; 47(5):619-25.
17. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, *et al.* Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: A global perspective. Biol Blood Marrow Transplant. 2009; 15(10):1143-238.
18. Nagao K, Yanagita T. Bioactive lipids in metabolic syndrome. Progress Lipid Res. 2008; 47(2):127-46.

Received on: 2/4/2013
Final version on: 8/6/2013
Approved on: 10/29/2013