Low Levels of High-density Lipoprotein in Patients with Pediatric Cancer at Diagnosis

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Baixos Níveis de Lipoproteínas de Alta Densidade em Pacientes com Câncer Infantojuvenil ao Diagnóstico

Bajos Niveles de Lipoproteínas de Alta Densidade en Pacientes con Cáncer Juvenil en el Momento del Diagnóstico

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Abstract

Introduction: Cancer patients have metabolic imbalances due to the disease, treatment and their complications. Increases in triglycerides and glucose profile and catabolism of protein have been described and are associated with inflammatory response as result of the tumor activity or necrosis. **Objective:** To evaluate the blood lipid, lipoproteins, glucose and albumin levels in pediatric cancer patients at diagnosis. **Method:** Observational cross-sectional study. The inclusion criteria were children and adolescents with newly diagnosed malignancies and blood analysis results. The exclusion criteria were: previous anticancer therapy or surgical treatment, blood sample not collected and patients who refused to participate in the study. **Results:** It were evaluated 81 children and adolescents with newly diagnosed malignancies. There was decrease of 56% and 41% of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), 14% and 10% of albumin and glucose, and 10% and 7.6% of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), respectively, for the patients. HDL-C showed statistical differences between solid and hematological cancer patients ($p < 0.05$). The means and medians of albumin, glucose, HDL-C and TG demonstrated that hematological patients are more prone to metabolic disturbances. HDL-C in this group was 24 ± 12 *versus* 40 ± 15mg/dl in other cancers. **Conclusion:** The primary result found in the present study was in HDL-C, mainly in patients with hematological and metastatic cancer. These disturbances could be associated with cancer-related acute inflammatory response.

Key words: Triglycerides/blood; Cholesterol, HDL/blood; Blood Glucose; Serum Albumin; Neoplasms.

Resumo

Introdução: Pacientes com câncer apresentam desequilíbrios metabólicos em virtude da doença, do tratamento e de suas complicações. Alterações nos triglicerídeos, perfil de glicose e catabolismo de proteínas foram descritas e estão associadas à resposta inflamatória por conta da atividade tumoral ou necrose. **Objetivo:** Avaliar os níveis de lipídios no sangue, lipoproteínas, glicose e albumina em pacientes com câncer infantojuvenil no momento do diagnóstico. **Método:** Estudo observacional transversal. Os critérios de inclusão foram crianças e adolescentes com neoplasias recém-diagnosticadas e resultados de exame de sangue; e os critérios de exclusão, terapia anticâncer ou tratamento cirúrgico prévio, amostra de sangue não coletada e pacientes que se recusaram a participar do estudo. **Resultados:** Foram avaliadas 81 crianças e adolescentes com neoplasias recém-diagnosticadas. Houve decréscimo de 56% e 41% para lipoproteína de alta densidade-colesterol (HDL-C) e triglicerídeos (TG), 14% e 10% para albumina e glicose e 10% e 7,6% para colesterol total (CT) e colesterol de lipoproteína de baixa densidade (LDL-C), respectivamente. O HDL-C mostrou diferenças estatísticas entre pacientes com câncer sólido e hematológico ($p < 0,05$). As médias e medianas de albumina, glicose, HDL-C e TG demonstraram que pacientes com tumores hematológicos são mais propensos a distúrbios metabólicos. O HDL-C neste grupo foi de 24 ± 12 *versus* 40 ± 15 mg / dl em outros cânceres. **Conclusão:** A principal alteração encontrada no presente estudo foi no HDL-C, principalmente em pacientes com câncer hematológico e metastático. Essas alterações podem estar associadas à resposta inflamatória aguda relacionada ao câncer.

Palavras-chave: Triglicerídeos/sangue; HDL-Colesterol/sangue; Glicemia; Albumina Sérica; Neoplasias.

Resumen

Introducciòn: Los pacientes con cáncer tienen desequilibrios metabólicos debido a la enfermedad, el tratamiento y sus complicaciones. Los cambios en los triglicéridos y el perfil de glucosa y el catabolismo de las proteínas se han descrito y están asociados con la respuesta inflamatoria debido a la actividad tumoral o la necrosis. **Objetivo:** Evaluar los niveles de lípidos, lipoproteínas, glucosa y albúmina en sangre en pacientes con cáncer juvenil en el diagnóstico. **Método:** Estudio transversal observacional. El criterio de inclusión fue niños y adolescentes con neoplasias recién diagnosticadas con análisis de sangre realizado. Criterios de exclusión: terapia anticancerígena previa o tratamiento quirúrgico, muestra de sangre no realizada y pacientes que se negaron a participar en el estudio del protocolo. **Resultados:** Se evaluaron 81 niños y adolescentes con neoplasias recién diagnosticadas. Se observó un cambio en 56% y 41% para el colesterol de lipoproteínas de alta densidad (HDL-C) y triglicéridos (TG), 14% y 10% para albúmina y glucosa, y 10% y 7,6% para colesterol total (TC) y colesterol de lipoproteínas de baja densidad (LDL-C), respectivamente. HDL-C mostró diferencias entre pacientes con cáncer sólido y hematológico ($p < 0.05$). Las medias y medianas de albúmina, glucosa, HDL-C y TG demostraron que el grupo hematológico tienden a alteraciones metabólicas más importantes. El HDL-C en este grupo fue de 24 ± 12 *versus* 40 ± 15 mg / dl en otros tipos de cáncer. **Conclusión:** El cambio primario encontrado en el presente estudio fue en HDL-C, principalmente en pacientes con cáncer hematológico y metastásico. Estos cambios podrían estar asociados con la respuesta inflamatoria aguda relacionada con el cáncer.

Palabras clave: Triglicéridos/sangre; HDL-Colesterol/sangre; Glucemia; Albúmina Sérica; Neoplasias.

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INTRODUCTION

Cancer patients may present metabolic unbalances because of the disease, the treatment and their complications. Increases in lipid, lipoprotein and glucose profile and catabolism of protein have been described in these patients and are associated with inflammatory response due to the presence of the tumor, infectious or anticancer therapy complications. This condition has been described as anorexia-cachexia syndrome[1,2], which is generated by elevated pro-inflammatory cytokines levels[3-5]. It is believed that inflammatory response is an important factor in the inter individual variability of response and toxic effects of cancer chemotherapy[6].

Low HDL-C and high glucose and triglycerides levels were reported in children with leukemia and lymphoma and other forms of widespread malignant disease[7-10]. High triglycerides and glucose levels, for example, are deleterious to the immune system, increasing the risk of infection; low clearance of triglycerides leads to a partial blockage of both macrophage and granulocyte function, increasing the risk of infectious complications and morbidity[11-16]. Lipids and glucose intolerance impair oxidation and incorporation of the nutrients during inflammatory response[14-16].

All these alterations have been documented in the international literature, but have never been reported in Brazilian pediatric cancer patients. Therefore, the impact of these factors in Brazilian patients is still unknown, since genetic and dietary profiles may play a role in the aforementioned alterations.

The importance of this study is to identify those abnormalities in different groups of Brazilian patients with cancer, in order to propose studies about prognosis and immunomodulation in the future. To that end, the aim of the study was to evaluate the blood lipid, lipoproteins, glucose and albumin levels in pediatric cancer patients at diagnosis.

METHOD

This is an observational cross-sectional study conducted at the Pediatric Oncology Institute (IOP) of the Federal University of São Paulo (UNIFESP-EPM) with patients who presented newly diagnosed malignancies. All the patients with previous anticancer treatment or history of corticosteroid use were excluded from this analysis.

Blood samples were collected after an overnight fast (8 hours) at the enrollment day, in ethylenediaminetetraacetic acid (EDTA) or heparin anticoagulating tubes to be immediately centrifuged. Total plasma cholesterol (CH) was measured by calorimetric method (HDL cholesterol enzymatic, K015, Bioclin, Belgium). Total Cholesterol Assay Kit measures the total cholesterol within serum, plasma, lysate, or tissue samples. The assay is based on the enzyme driven reaction that quantifies both cholesterol esters and free cholesterol. Cholesterol esters are hydrolyzed via cholesterol esterase into cholesterol, which is then oxidized by cholesterol oxidase into the ketone cholest-4-en-3-one plus hydrogen peroxide. Then, the hydrogen peroxide is detected with a highly specific colorimetric probe. Horseradish peroxidase catalyzes the reaction between the probe and hydrogen peroxide, which bind in a 1:1 ratio. Samples are compared to a known concentration of cholesterol standard in a 96-well microtiter plate format. Samples and standards are incubated for 45 minutes and then read with a standard 96-well colorimetric plate reader.

HDL-C determination was performed by calorimetric-enzymatic method (HDL cholesterol enzymatic, K015, Bioclin, Belgium). It is measured in serum or plasma after selective precipitation of LDL and VLDL. In a centrifuge tube pipette 250 µL of the sample and 250 µL of the precipitate, shaken strongly for 30 seconds, centrifuged at 3500 rpm for 15 minutes to obtain a clear supernatant, pipette the clear supernatant immediately after centrifugation, taking care to not resuspend the precipitate to avoid falsely high results. Colorimetry: identify the test tubes and pipette, homogenize and incubate in a water bath at 37° C for 10 minutes. The water bath level should be above the level of the reagents in the tubes, make the photometric readings of the Standard (AP) and the Test (AT) at 500 nm, resetting the device to White. The color is stable for 60 minutes.

Plasma triglycerides (TG) were enzymatically measured. Serum was separated up to 2 hours after collection and stored under refrigeration at 2 to 8° C, to maintain stability for 72 hours. The temperature of the water bath or thermostat was adjusted to 37° C. The temperature remained constant during the test. Homogenization and immediately incubation for 5 minutes at 37° C. The absorbance was read within 60 minutes against the white reagent. For calculations: triglycerides (mg/dL) = Sample Absorbance X Standard Concentration / Standard Absorbance. Calibration Factor (Fc) = Standard Concentration (mg/dL) / Standard Absorbance. Triglycerides (mg/dL) = Sample Absorbance x Fc).

The Friedewald et al.[17] equation was applied to calculate low-density lipoprotein cholesterol (LDL-C) from CH, TG, and HDL-C Glucose Hexokinase II determined blood glucose. It is an enzymatic method that uses the enzymes hexokinase and glucose-6-phosphate dehydrogenase. Glucose is phosphorylated by ATP in the presence of hexokinase. The glucose-6-P is oxidized in the

presence of glucose-6 phosphate dehydrogenase, resulting in the reduction of NAD to NADH, whose absorbance is measured. GLUH applied to biochemical systems of Advia is a reagent containing two components, reagent 1 (R1) and reagent 2 (R2). The blood sample is added to the R1, which contains buffer, ATP and NAD. The absorbance readings of the sample in R1 are obtained and used to correct the interfering substances in the sample. Then, R2 is added, initiating the conversion of glucose and the development of absorbance at 340/410nm. The difference between the absorbance at R1 and R2 is proportional to the glucose concentration.

Turbidimetrical method was used to measure serum albumin. This method is based on the dispersion of suspended particles. When a collimated beam of light reaches a suspended particle, portions of the light are absorbed, reflected or dispersed by the solution. The amount of light transmitted in the front direction is detected. The amount of light absorbed by a suspension of particles depends on the concentration and size of the particles. Solutions that require quantification by turbidimetric methods are carried out by means of photometers or spectrophotometers of visible region.

Reference of lipids was based on the "Guidelines of the National Cholesterol Education Program"[18]. When albumin and glucose were below 3.5 mg/dl and above 110 mg/dl, respectively, they were considered abnormal. It were also assessed the family history of hypertriglyceridemia and hypercholesterolemia.

Patients over 18 years old and the parents or guardians of patients below that aged signed an informed consent approved by the Institutional Review Board of UNIFESP, which reviewed and approved the study (number 0840/06).

Statistical analysis

Descriptive data are expressed as means and standard deviation (SD) or median (minimum e maximum) in case of skewed distributions, and as frequencies and percentages or ranges.

The Chi-square test was adopted to compare the rate of abnormalities between hematological *versus* solid and metastatic *versus* non-metastatic cancers. T test or Mann' Whitney were used to compare means or medians for hematological *versus* solid and metastatic versus non-metastatic cancer, depending on the normality of the sample. A p-value below 5% was statistically significant.

RESULTS

Eighty-one patients were included: twenty-one with hematological and sixty-four with solid cancers. The median age was 8.7 years (range, 0.2 - 21.9 years). Serum TG, CH and HDL-C were evaluated in 81 patients, whereas serum albumin, glucose and LDL-C in 73, 77 and 79, respectively. Table 1 shows the demographic characteristics.

Table 1. Demographic characteristics of pediatric and adolescent cancer patients (n = 81)

Characteristic	Median (year)	Range
Age	8.7	(0.2 - 21.9)
Gender	**Number**	**Percentage**
Male	52	64
Female	29	36
Diagnostics		
ALLa	12	15
AMLb	4	5
Biphenotipic leukemia	1	1
NHLc	2	2.5
HLd	2	2.5
CNSe	18	22
Neuroblastoma	2	2.5
Wilms tumor	2	2.5
Bone tumors	14	17
Rabdomyosarcoma	2	2.5
Germ cells tumor	4	5
Carcinomas	4	5
Retinoblastoma	8	10
Others	6	7.5

[a]ALL: acute lymphoblastic leukemia; [b]AML: acute myeloid leukemia; [c]NHL: non-Hodgkin lymphoma; [d]HL: Hodgkin lymphoma; [e]CNS: central nervous system (craniofaringioma, astrocitoma, ependimoma, Medulloblastoma, pineal germ tumor).

Seventeen (21%) of the patients had a family history of hypertriglyceridemia and/or hypercholesterolemia; two of them had solid tumor.

Forty-five out of 81 (56%) and 10/73 (14%) presented low levels of HDL-C and albumin, and 33/81 (41%) and 8/77 (10%) showed high levels of TG and glucose, respectively. CH was elevated in 8/81 (10%) and LDL-C in 6/79 (7.6%).

The abnormalities of HDL-C rates were statistically higher (p = 0.001) in the hematologic tumor when compared to the solid tumor patients. The percentage of patients with albumin and TG abnormalities were higher in the hematologic tumor group, although not reaching statistical significance (Figure 1).

The mean of HDL-C levels of patients with hematological tumors demonstrated to be lower than the solid tumors (Table 2).

The analysis for metastatic (n = 27) versus non-metastatic (n = 54) cancer (Figure 2) demonstrated higher incidence of abnormalities in the HDL-C and lower mean of the values (Table 3).

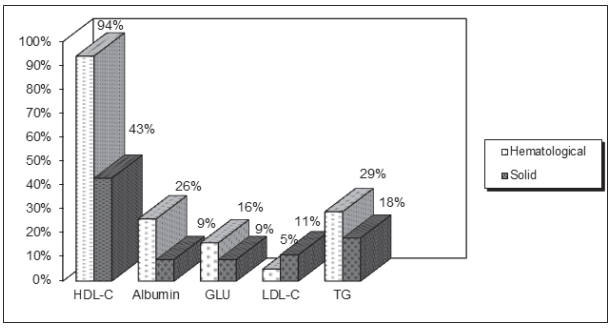

Figure 1. Percentage of patients with abnormalities in the biochemical data between hematological and solid cancers

[a] Significant difference between leukemia and other cancers with p = 0.001; X2 = 10.23 (OR = 12.43: 2.65 – 58.18; 95% CI).
HDL-C = high-density lipoprotein cholesterol; GLU = glucose; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

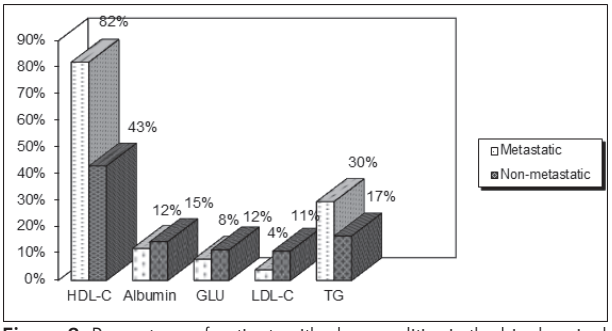

Figure 2. Percentage of patients with abnormalities in the biochemical data of metastatic (n = 27) and non-metastatic (n = 54) cancers

[a] Significant difference between metastatic and non-metastatic cancer; p = 0.001; X2 = 9.87 (OR = 5.93; 1.95 – 18).

DISCUSSION

This study confirmed in Brazilian patients similar abnormalities observed in other studies[5,7-9], mainly higher prevalence of HDL-C in hematological and metastatic cancer patients. Other studies also reported low HDL-C in patients with leukemia and lymphoma, corroborating our results. In one of these studies, abnormalities with other forms of widespread malignant disease were observed in children at diagnosis, but not in localized disease[7]. In our analysis with metastatic patients it was also demonstrated higher percentage of HDL abnormalities. Prevalence of metabolic alterations is, therefore, probably associated to the severity of the disease, when the body prioritizes protein synthesis due to the pro-inflammatory response caused by the most aggressive cancer disease. However, other mechanisms must be explored. On the other hand, glucose and albumin did not demonstrate an important decrease in the present study.

Iqbal et al.[5] showed lower mean CH, LDL-C, HDL-C and albumin in cancer in comparison to non-cancer patients; they were also significantly lower in those with metastatic solid tumors. They also found that TG was lower in non-metastatic disease and no association was observed between LDL-C, HDL-C and TG and the stage of disease[5]. In the current study, TG abnormalities were observed mainly in metastatic group, however without statistical differences in the prevalence rate. Possibly, the qualitative analysis (percentage of abnormalities) and the

Table 2. Blood lipid, glucose and albumin profile in patients with hematological (n= 21) *versus* solid cancers (n = 64)

Serum/plasma	Patients	Hematological	Solid	P value*
Albumin (g/dl)	73	3.8 ± 0.7	4.2 ± 0,6	*NS*
Glucose (mg/dl)	77	94 ± 21	89 ± 25	*NS*
Cholesterol (mg/dl)	81	135 ± 33	152 ± 41	*NS*
HDL-C (mg/dl)	81	24 ± 12	40 ± 15	*0.001*
LDL-C (mg/dl)	79	81 ± 29	92 ± 29	*NS*
Triglycerides (mg/dl)	81	147 ± 105	112 ± 75	*NS*
Triglycerides (mg/dl)	81	109 (59 – 493)	87 (17 – 429)	*NS*

Values are expressed as mean ± standard deviation, excepted for the values for triglycerides, which are also expressed as the range and the median. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. *T test or Mann' Whitney test.

Table 3. Blood lipid, carbohydrate and albumin profile in patients with metastatic (n = 27) *versus* non-metastatic (n = 54) cancers

Serum/plasma	Patients	Metastatic	Non-metastatic	P value*
Albumin (g/dl)	73	4.0 ± 0.6	4.2 ± 0,7	*NS*
Glucose (mg/dl)	77	87 ± 19	91 ± 26	*NS*
Cholesterol (mg/dl)	81	140 ± 33	151 ± 42	*NS*
HDL-C (mg/dl)	81	29 ± 12	40 ± 16	*0.002*
LDL-C (mg/dl)	79	82 ± 27	93 ± 30	*NS*
Triglycerides (mg/dl)	81	149 ± 111	108 ± 64	*NS*
Triglycerides (mg/dl)	81	108 (58 – 493)	88 (17 – 303)	*NS*

Values are expressed as mean ± standard deviation, excepted for the values of triglycerides, which are also expressed as the range (minimum and maximum) and the median. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. *T test or Mann' Whitney test.

heterogeneity of the diagnosis of the sample did not allow differences to be found.

Lower mean of HDL-C was found, comparing our patients with a study performed in healthy Brazilian children and adolescents[19-21]. Higher TG and lower LDL-C and CH, also were encountered in children with hematological cancer and metastatic patients when compared to the Brazilian study[21].

Malignant tumors are associated with synthesis of pro-inflammatory mediators – TNF-a, Interleukins 1 and 6 and others[22,23]. These cytokines stimulate acute inflammatory response, increasing positive and decreasing negative acute phase proteins synthesis. They cause metabolic disturbances such as higher fat utilization, glucose and lipid intolerance, leading to a catabolic status[2,24]. HDL-C could be reduced due to cytokines action, acting as a negative acute phase protein.

These abnormalities are present in several conditions such as inflammation, infection and trauma[25-28]. Herishanu et al.[29], demonstrated that elevated baseline C reactive protein levels are associated with shorter survival and development of second cancers in patients with chronic lymphoid leukemia[29].

Albumin has been studied and high TG levels were observed in patients with blood or bone marrow invasion, suggesting a correlation with the turnover of the malignant proliferation[30].

Malignancy also seems to influence CH levels. Hypocholesterolemia has been observed in various forms of cancer at diagnosis, particularly in hematological ones[5,31]. Low CH has been associated with increased mortality from cancer in several observational and clinical studies[32].

Naik et al.[33] found that low CH and HDL-C together with hypertriglyceridemia were the most prominent features in pediatric patients with leukemia and Hodgkin's disease[33].

Recently, two other studies about leukemia showed that these abnormalities are correlated with the disease activity, being reversed during remission[34,35].

It were not observed any important abnormalities in CH and LDL-C, but apparently, the means values were slightly reduced in hematological and metastatic cancer.

Previous studies have demonstrated that cancer patients often present aberrant blood lipid profiles. Moreover, blood lipid levels of cancer patients have shown to be associated with pathogenesis and progression of cancer. High-density lipoprotein cholesterol has anti-inflammatory properties.

This study has some limitations, for example, its cross-sectional design, which does not allow causal analysis, the greater number of solid than hematological cancer, the absence of control group with healthy population, and the loss of some blood analyses. Future studies need to investigate subtypes of lipoprotein, tracking changes in values and analyze how they correlate with clinical outcomes. It was not possible to affirm that the present results found were related to inflammatory response because it were not measured CRP or other inflammatory marker.

Limited published studies have focused on pediatric cancer inflammation and its metabolic consequences. However, inflammation could be associated with a pre-cachexia status in a high percentage of patients at diagnosis, mainly in those with widespread metastatic disease. This condition leads to anorexia, weight loss, insulin resistance and increased destruction of muscle proteins and reduced functional capacity and quality of life[36-38], increasing morbidity and mortality in cancer patients[39]. The presence of malignant tumor cells stimulates the host to produce cytokines and other pro-inflammatory mediators responsible for alterations in substrate metabolism. In some studies with cancer patients, albumin has been suggested as a prognostic factor and its alterations may be associated with other aspects, in addition to the inflammatory response[40,41]. This profile depends on the cancer diagnosis and stage/severity of the disease[36].

A recent study on the HDLs of young ALL survivors indicates an altered metabolism and a shift in their proteome affecting specifically their anti-thrombotic, anti-apoptotic and anti-inflammatory capacities. These HDLs have an abnormal composition with a lower content of free and esterified cholesterol compared to controls. They also expressed some proteins not detectable in the control samples; most of them are either pro-thrombotic or pro-apoptotic. These findings may be relevant to the field of cancer survivorship in providing potential diagnostic, prognostic or therapeutic biomarkers of HDL-C functionality and metabolism in ALL[42].

More studies are necessary to know the metabolic behavior of these components, comparing with healthy subjects, evaluating patients prospectively in different phases of treatment, and correlating with the disease, drugs, energy expenditure and nutritional condition. These abnormalities could be involved in the response to chemotherapy and in the mechanism of oncogenesis. Thus, it is important to elucidate that influence on the cancer prognostic[29,34,35].

CONCLUSION

The primary result found in the present study was low HDL-C levels at diagnosis of cancer. Albumin and TG also

presented abnormalities in cancer patients. Hematological and metastatic cancer demonstrated to influence these abnormalities more importantly. The prevalence of metabolic alterations is, therefore, probably associated to the spread and severity of the cancer, when the body prioritizes protein synthesis due to pro-inflammatory response caused by the most aggressive tumor.

CONTRIBUTIONS

Adriana Garófolo participated of the conception and design of the study, collection, analysis and interpretation of the study data, wording and critical review with intellectual contribution and approval of the final version for publication. Priscila dos Santos Maia-Lemos participated of the conception and design of the study, collection, analysis and interpretation of the study data and approval of the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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