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The role of adiposity, adipokines and polymorphisms of leptin and adiponectin in myelodysplastic syndromes

Ana Patrícia Nogueira Aguiar[1,2]*, Priscila da Silva Mendonça[1,2,3], Roberto Cesar Pereira Lima Junior[2,4], Anacelia Gomes de Matos Mota[1,2], Deysi Viviana Tenazoa Wong[2,5], Roberta Tatiane Germano de Oliveira[1,2], Howard Lopes Ribeiro-Júnior[1,2], Ronald Feitosa Pinheiro[1,2,6,7,8] and Silvia Maria Meira Magalhães[1,2,7,8]

[1]*Cancer Cytogenomic Laboratory, Federal University of Ceará, Fortaleza, CE 60430-275, Brazil*
[2]*Center for Research and Drug Development (NPDM), Federal University of Ceará, Fortaleza, CE, Brazil*
[3]*University Hospital Walter Cantidio, Brazilian Company of Hospital Services (EBSERH), Fortaleza, CE, Brazil*
[4]*Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza, CE, Brazil*
[5]*Department of Pathology and Forensic Medicine, Federal University of Ceará, Fortaleza, CE, Brazil*
[6]*Post-Graduate Program of Pathology, Federal University of Ceará, Fortaleza, CE, Brazil*
[7]*Department of Clinical Medicine, Federal University of Ceará, Fortaleza, CE, Brazil*
[8]*Post-graduate Program in Medical Science, Federal University of Ceará, Fortaleza, CE, Brazil*

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Abstract

The aim of the present study was to investigate the relationship between leptin and adiponectin gene polymorphisms, circulating levels of leptin and adiponectin, adiposity and clinical markers in patients with myelodysplastic syndrome (MDS). This cross-sectional study was conducted with 102 adults and elderly MDS patients and 102 age- and sex-matched controls. Clinical characteristics, co-morbidities, anthropometric data, laboratory evaluation and genetic analysis (polymorphisms −2548G > A/rs7799039 of the LEP gene and +276G > T/rs1501299 of the ADIPOQ gene) were investigated. Serum leptin was higher and adiponectin lower in MDS when compared with controls. There was a significant positive correlation between serum leptin levels and BMI ($r = 0{\cdot}264$, $P = 0{\cdot}025$), waist circumference ($r = 0{\cdot}235$, $P = 0{\cdot}047$), body fat percentage (BF %) ($r = 0{\cdot}373$, $P = 0{\cdot}001$) and the fat mass index (FMI) ($r = 0{\cdot}371$, $P < 0{\cdot}001$). A lower mean adiponectin was found among patients with high BF %, higher visceral adiposity index and metabolic syndrome. A significant association was found between the AA genotype (mutant) of the LEP polymorphism rs7799039 and male sex and blast excess (≥ 5 %). In addition, a significant association was observed between the TT genotype (mutant) of the ADIPOQ rs1501299 polymorphism and Fe overload. These results demonstrate the importance of a comprehensive and systematic evaluation in patients with MDS in order to identify and control negative factors not related to the disease at an early stage.

Keywords: **Myelodysplastic syndrome: Adipokines: Obesity: Polymorphism single nucleotide: Nutritional status**

Obesity rates have increased rapidly worldwide and represent a public health challenge. In Brazil, a large study showed that 55·7 % of the adult and elderly Brazilian population were overweight and that 19·8 % present obesity[(1)]. Obesity has been related to decrease in general health, metabolic co-morbidities, susceptibility to infectious diseases, and predisposition to carcinogenesis and is also a factor of poor prognosis in cancer patients. An umbrella review analysed 204 meta-analyses to investigate the association between clinical and biochemical markers of adiposity and the development of thirty-six primary cancer types. A relationship between body overweight and the risk of at least eleven types of cancer, including haematological neoplasm, was found[(2)]. Obesity over life course was a modifiable risk for myelodysplastic syndrome (MDS), the most prevalent haematological neoplasm among older people, characterised by cytopenias, ineffective haematopoiesis and increased risk of progression to acute myeloid leukaemia[(3)].

There is evidence that obesity disturbs haematopoiesis and the bone marrow niche, with a negative impact on the differentiation and function of haematopoietic cell populations,

Abbreviations: FMI, fat mass index; MDS, myelodysplastic syndrome; MetS, metabolic syndrome; SNP, single-nucleotide polymorphism; VAI, visceral adiposity index; WC, waist circumference.

* **Corresponding author:** Dr A. P. N. Aguiar, email patricianogueiraaguiar@yahoo.com.br

and unbalances the production of pro-inflammatory cytokines and adipokines[4]. Among abundant human adipokines, leptin and adiponectin have an opposing function and play a significant role in metabolic system and weight control.

Leptin is an adipocyte-derived hormone, with an important function not only in regulating appetite, energy consumption, and insulin sensitivity but also in inflammation and immunity system. Higher levels of this adipokine are associated with obesity[5]. On the other hand, adiponectin is a biologically active adipokine, which plays a role in the metabolism of nutrients, insulin resistance and inflammatory system. Adiponectin inversely correlates with BMI and visceral fat[6]. Several studies have shown the association between higher leptin and lower adiponectin and carcinogenesis and cancer progression[7–10]. Previous few studies among MDS individuals found increased leptin and decreased adiponectin concentration when compared with healthy control[11–14].

Common polymorphisms of the human leptin (*LEP*) and adiponectin (*ADIPOQ*) genes are known to influence the circulating levels of these adipokines. The single-nucleotide polymorphism (SNP) −2548G > A (rs7799039) has been extensively investigated for its influence in leptin expression and association with some chronic diseases (i.e. obesity, diabetes, metabolic syndrome (MetS) and cancer risk)[15]. The SNP + 276G > T (rs1501299) has been associated with circulating adiponectin concentration and chronic diseases, including obesity, coronary artery disease, MetS and different types of cancer[16–18]. To the best of our knowledge, there are no studies evaluating adipokines gene in patients with MDS.

It is, therefore, very important to assess the relationship between adiposity and MDS not only because of the effect of obesity on haematopoiesis but also because cardiovascular events are the most frequent cause of death unrelated to the disease. In this context, we investigated the association between *LEP* −2548G > A and *ADIPOQ* + 276G > T polymorphisms and circulating levels of leptin and adiponectin, adiposity and clinical markers in patients with MDS.

Subjects and methods

Study population

In this cross-sectional study, 102 sequential MDS patients and 102 age- and sex-matched control individuals were evaluated at a single tertiary university hospital.

Patients in the MDS group were included according to the following criteria: aged over 18 years and confirmed diagnosis of MDS. Exclusion criteria were undergoing disease-modifying therapy (i.e. hypomethylating agents and allogeneic stem cell transplantation), HIV infection, and current use of drugs affecting inflammatory system like corticosteroids and other medications. Only healthy adults were included in the control group.

Diagnosis and classification of MDS were established according to the 2016 WHO classification of myeloid neoplasms and acute leukaemia[19] and the Revised International Prognosis Scoring System (IPSS-R)[20]. Clinical and laboratory data (i.e. presence of co-morbidities, blood count, serum ferritin, and HDL and TAG levels) were evaluated by clinical assessment and medical records review. Ferritin level ≥ 1·000 ng/ml was considered Fe overload, and transfusion dependency was defined as transfusion of at least 4 unit/8 weeks.

This study was conducted in accordance with the guidelines set out in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the local ethics committee (ethics number: 1.513.488). Written informed consent was obtained from all subjects/patients.

Anthropometric measurements

Weight, height, circumferences and body skinfolds were measured by the trained researchers in a standardised way. BMI was calculated as body weight in kilograms divided by the square of height in metres. Individuals were classified according to BMI into three categories (underweight: BMI < 18·5 kg/m^2, eutrophic: BMI of 18·5 to 24·9 kg/m^2, excess body weight: BMI ≥ 25·0 kg/m^2 and obesity: BMI ≥ 30·0 kg/m^2)[21].

Circumferences were measured using a tape (CESCORF®, length 0–200 cm, accuracy ± 1 mm). Waist circumference (WC) was obtained using a measuring midway between the iliac crest and the lower costal margin, and the hip circumference was measured at the maximum protrusion of the gluteal region[21]. WC > 94 cm (male) or > 80 cm (female) were categorised as high abdominal fat accumulation[22].

Skinfold thickness measurements (i.e. biceps, triceps, subscapular and suprailiac) were obtained on the right side of the body by using Premier Cescorf Scientific Adipometer (opening 70 mm and precision of ± 0·2 mm, constant pressure of 10 g/mm^2; CESCORF®) in accordance with the procedures previously recommended[23,24]. Body fat percentage (BF %) was estimated using skinfold measurement equations. Durnin and Womersley equation[23] was used to estimate BF % in the equation where body density was calculated from a skinfold equation. BF % > 25 % (male) and > 30 % (female) was considered increased[25].

The fat mass index (FMI), a sex-specific measure of fat not confused by lean tissue, was determined using the following equation: FMI = fat mass (kg)/height (m^2)[26]. FMI > 6 (male) or > 9 (female) was categorised as excess of fat[27].

The visceral adiposity index (VAI) was obtained by the formulas proposed by Amato et al (2010). For males, VAI = (WC/36·58 + (1896 BMI)) × (TG/0·81) × (1·52/HDL) and for females, VAI = (WC/39·68+ (1886 BMI)) × (TG/1·03) × (1·31/HDL). The cutoff points for VAI in the detection of visceral adiposity in adults and the elderly followed as determined by Amato *et al.*[28,29]

Metabolic syndrome diagnoses

MetS criteria were used according to NCEP-ATPIII (2001): abdominal obesity ≥102 cm (male) ≥88 cm (female), HDL-cholesterol <40 mg/dl (male) <50 mg/dl (female), systolic blood pressure ≥130 mmHg or diastolic ≥85 mmHg, TAG ≥150 mg/dl and fasting blood glucose ≥ 110 mg/dl[30].

Adipokines analysis

Serum samples were obtained from MDS patients and controls after 12-h fast. Serum total adiponectin and serum total leptin

concentrations were measured using a commercial ELISA kit according to the manufacturer's protocol (Invitrogen).

DNA isolation and genotyping

DNA extraction. Genomic DNA was extracted from peripheral blood samples of MDS patients and sex- and age-matched healthy volunteers, using Trizol Reagent™ (Invitrogen), according to the manufacturer's protocol.

Allelic discrimination by real-time-PCR. Genotypes were identified in DNA samples by real-time PCR, using TaqMan SNP Genotyping Assay (ThermoFisher Scientific). SNP were selected based on a known or expected association with obesity, the resulting metabolic complications and cancer. We performed an allelic discrimination assay for rs7799039 and rs1501299 polymorphisms using the TaqMan Genotyping Master Mix kit® (ThermoFisher Scientific), according to the manufacturer's protocol.

Each 10 µl of PCR reaction contained 50 ng of genomic DNA in the final volume of 4·5 µl, 5·0 µl of 2X TaqMan Genotyping Master Mix and 0·5 µl of 20X TaqMan Genotyping Assay Mix. The following thermal cycling conditions were an initial activation at 95°C for 10 min, followed by 40 cycles of 95°C for 15 s of denaturation step at 95°C and annealing/enzyme extension at 60°C for 1 min. PCR was performed using 7500 Fast System® (Applied Biosystems).

Statistical analysis

Normality was verified by the Shapiro–Wilk test. Student's *t* test, Levene's test, Pearson's χ^2 test or Fisher's exact test, Pearson's correlation and the multinominal logistic regression analysis were performed using SPSS® (SPSS Inc.) software version 20.0. $P < 0{\cdot}05$ was considered significant.

The Pearson χ^2 was used to determine the Hardy–Weinberg (H–W) equilibrium and the differences in genotype distribution. All genotypes were divided and analysed in genotype distribution model (wild type *v.* heterozygous *v.* mutated), according to the study of Clarke *et al.*[31] Differences in allele and genotype frequencies and comparisons of variables between the control and MDS groups were evaluated using the Pearson's χ^2 test or Fisher's exact test. Multinomial logistic regression analysis was used to measure the association between an exposure and an outcome (odds ratio) with 95 % CI.

Results

Characteristics of myelodysplastic syndrome patients

One hundred and two sequential patients with MDS were included (22·5 % aged <65 years and 77·5 % aged ≥65 years). The mean age of all MDS patients was 72·0 years ± 11·6 (38–96). Most patients were women 64·7 % ($n = 66$). According to WHO classification of myeloid neoplasms and acute leukaemia[19], 71·6 % of patients were classified as lower risk (9·8 % MDS-SLD, 41·2 % MDS-MLD, 4·9 % MDS-RS-SLD, 11·8 % MDS-RS-MLD and 3·9 % MDS with isolated del5q-) and 28·4 % as higher risk (15·7 % MDS-EB-I, 7·8 % MDS-EB-II and 4·9 % t-MDS). According to the prognostic stratification proposed by the IPSS-R (2012), a higher percentage of patients, 28·4 % ($n = 29$), had a low-risk disease, with 18·6 % ($n = 19$) with risk intermediate, 8·8 % ($n = 9$) very high risk, 7·8 % ($n = 8$) high risk and 6·9 % ($n = 7$) very low risk (data not presented in the table).

Transfusion dependency was reported in 36·3 % ($n = 37$), and Fe overload was observed in 13·7 % ($n = 14$). The most prevalent cytopenia was anaemia (89·2 %/$n = 91$). Neutropenia and thrombocytopenia were present in 52·0 % ($n = 53$) and 58·8 % ($n = 60$), respectively. As for the percentage of blasts in the bone marrow, 23·5 % of the patients had 5 % or more blasts (data not presented in the table).

According to values proposed by IPSS-R, 63·7 % of patients presented Hb levels below 10 g/dl, 17·6 % of patients presented a number of neutrophils less than $0{\cdot}8 \times 10^9$ l and 43·1 % had platelet counts below 100×10^9/l (data not presented in the table).

Anthropometric assessment

According to the BMI classification, 47·1 % of patients ($n = 48$) were overweight. There was no significant difference between the BMI classifications between the groups ($P = 0{\cdot}096$). There was no significant difference between the mean values of BMI, WC, FMI, VAI and percentage of fat mass (FM%) between both groups ($P > 0{\cdot}05$) (Table 1).

Serum adipokines

The mean serum leptin among patients with MDS was 298·3 ± 153·07 ng/ml and among the control group was 184·68 ± 83·61 ng/ml ($P = 0{\cdot}03$) (Fig. 1).

Female MDS patients had significantly higher serum leptin concentration than male patients ($P = 0{\cdot}036$). Higher mean serum leptin was also found among patients with high WC ($P < 0{\cdot}001$) and FMI ($P = 0{\cdot}017$) (Table 2). There was no difference in serum leptin values between MDS who subtypes and controls ($P > 0{\cdot}05$) (data not presented in the table).

In the MDS group, there was a significant positive correlation between serum leptin levels and values: BMI ($r = 0{\cdot}264$, $P = 0{\cdot}025$), WC ($r = 0{\cdot}235$, $P = 0{\cdot}047$), BF % ($r = 0{\cdot}373$, $P < 0{\cdot}001$) and FMI ($r = 0{\cdot}371$, $P < 0{\cdot}001$) (Fig. 2). There was

Table 1. Mean value of anthropometric parameters of patients with MDS ($n = 102$) and controls ($n = 102$)

	Group				
	MDS		Control		
Anthropometric variables	Mean	SD	Mean	SD	*P*
BMI (kg/m²)	26·79	3·81	25·85	3·91	0·088*
Waist circumference (cm)	96·18	10·70	93·90	12·62	0·621*
Fat mass (kg)	21·43	7·15	20·88	6·83	0·577*
Fat mass (%)	32·64	6·76	31·64	8·48	0·224*
Fat mass index (kg/m²)	8·87	0·32	8·07	0·31	0·181†
Visceral adiposity index	1·93	0·28	2·84	0·24	0·093†

The data in bold were significant (*P* value ≤ with the
* Student's *t* test and
† Mann–Whitney test.
Data are represented as mean or median and SD.
P values were considered significant less than or equal to 5 %.

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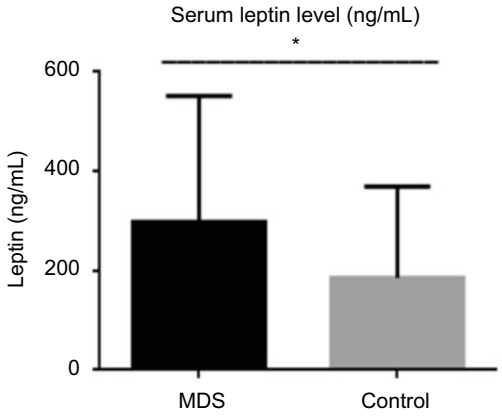

Fig. 1. Serum leptin level in MDS and control group. Bars represent means ± SD. Serum leptin level in patients with MDS was significantly different (*$P = 0{\cdot}03$) compared with the control group. MDS, myelodysplastic syndrome. Student's *t* test. *P* value was considered significant less than or equal to 5 %.

no significant correlation between leptin levels and the variables: age ($r = 0{\cdot}112$, $P = 0{\cdot}322$), Hb ($r = 0{\cdot}042$, $P = 0{\cdot}727$), neutrophils ($r = -0{\cdot}199$; $P = 0{\cdot}094$), platelets ($r = -0{\cdot}165$; $P = 0{\cdot}166$), percentage of blasts ($r = 0{\cdot}70$; $P = 0{\cdot}557$) and ferritin ($r = -0{\cdot}017$; $P = 0{\cdot}924$) (data not presented in the figure).

Serum adiponectin was significantly lower in MDS patients than the control group ($P = 0{\cdot}033$). The mean serum adiponectin among the MDS group was 7·10 ± 4·87 μg/ml and among control individuals was 9·00 ± 5·38 μg/ml (Fig. 3).

There was a significant negative correlation between the serum adiponectin levels of MDS patients and BMI values ($r = -0{\cdot}287$, $P = 0{\cdot}005$), WC ($r = -0{\cdot}226$, $P = 0{\cdot}028$), FMI ($r = -0{\cdot}266$, $P = 0{\cdot}010$) and VAI ($r = -0{\cdot}381$, $P < 0{\cdot}001$) (Fig. 4).

There was no significant correlation between adiponectin levels and the variables: age ($r = 0{\cdot}174$, $P = 0{\cdot}094$), Hb ($r = -0{\cdot}020$, $P = 0{\cdot}846$), neutrophils ($r = -0{\cdot}055$, $P = 0{\cdot}600$), platelets ($r = 0{\cdot}078$, $P = 0{\cdot}455$), percentage of blasts ($r = -0{\cdot}177$, $P = 0{\cdot}088$), ferritin ($r = -0{\cdot}024$, $P = 0{\cdot}878$) and fat mass percentage ($r = -0{\cdot}146$, $P = 0{\cdot}160$) (data not presented in the figure).

According to BMI, overweight MDS patients had significantly lower serum adiponectin than eutrophic patients ($P = 0{\cdot}016$). Likewise, a significant difference was observed in adiponectin concentration according to individuals with adequate and higher FMI ($P = 0{\cdot}013$). The lower mean of serum adiponectin was also found among patients with high fat mass percentage ($P = 0{\cdot}019$) and higher VAI ($P = 0{\cdot}004$) (Table 2).

When assessing the presence of co-morbidities and the serum level of adiponectin in patients with MDS, a lower concentration of this adipokine was observed in patients with MetS ($P = 0{\cdot}016$). Regarding clinical, haematological and prognostic parameters, MDS patients with excess blasts in bone marrow (≥ 5 %) had a significantly lower median of adiponectin concentration ($P = 0{\cdot}041$). There were no significant comparisons with the other variables (Table 2).

Genotype frequencies distributions of LEP and ADIPOQ polymorphisms

LEP rs7799039 and *ADIPOQ* rs1501299 polymorphisms are in Hardy–Weinberg equilibrium ($P > 0{\cdot}05$). The distributions of allele and genotype frequencies of MDS patients and controls are presented in Table 3.

Significant associations were found between the *LEP* gene rs7799039 polymorphism genotypes and the sex variable in the genotypic distribution model (GG × AG × AA) ($P = 0{\cdot}018$) and classification of blast percentage ($P = 0{\cdot}031$). Patients with AA genotype of the *LEP* gene rs7799039 polymorphism had a higher chance of being male (OR = 3·77, 95 % CI (1·08, 13·10)) when compared with patients with AG or GG genotype. In addition, patients with AA genotype had a higher chance ratio (OR: 4·42, 95 % CI (1·23, 15·89)) of having a blast percentage ≥ 5 %. The other variables did not show any significant association (Table 4).

Through the analysis of the polymorphism rs1501299 of the *ADIPOQ* gene, a significant association was observed in patients with MDS between genotypes and Fe overload (ferritin ≥ 1000 ng/ml) in the genotypic distribution model (GG × GT × TT) ($P = 0{\cdot}033$). Patients with TT genotype from SNP rs1501299 had an eight-fold significant chance of having ferritin greater than 1000 ng/ml (OR = 8000 (95 % CI (1·367, 46·812)) when compared with patients with GG or GT genotype. The other variables did not show any significant association (Table 5).

Discussion

This study investigated whether MDS patients have different anthropometric and adipokines status than healthy age- and sex-matched control group. Additionally, we verified whether the leptin gene polymorphism (rs7799039) and the adiponectin gene polymorphism (rs1501299) were associated with clinical and anthropometric status.

First, we found that MDS patients have significantly higher serum leptin concentration and significantly lower mean serum adiponectin than the control group. Considering that anthropometric parameters did not differ significantly, this finding suggests a possible relationship between the dysregulated adipokine production and MDS etiopathogenesis.

Dalamaga *et al.*[12], in their case–control study with 101 cases with MDS and 101 controls paired by sex and age, observed that higher serum levels of adiponectin were associated with a lower risk of MDS and individuals with lower levels of leptin had a lower risk of MDS than controls. Likewise, low leptin concentrations were observed in low-risk MDS patients with normal or good prognostic karyotypes after adjustment for age, sex and BMI.

Over the past few years, the relationship between leptin and cancer has drawn attention. Higher levels of leptin were also found in breast, gastric, colon, endometrial cancer and acute lymphoid leukaemia when compared with healthy population[32–36]. Dalamaga *et al.*[12] and Tsiotra *et al.*[11] found higher concentrations of leptin among MDS patients when compared with healthy controls.

Elevated leptin level is harmful to cancer patients. This cytokine can stimulate migration and metastasis stages. Association between increased leptin expression and metastasis was observed in some cancers, such as breast, colon,

Table 2. Comparison of leptin and adiponectin values according to clinical and anthropometric variables of patients with MDS ($n = 102$)

Variable		Leptin (ng/ml)			Adiponectin (μg/ml)		
		Mean	SD	*P*	Mean	SD	*P*
Age	<65 years	260·54	57·67	0·485*	6·31	4·94	0·397*
	≥65 years	310·01	58·59		7·33	4·87	
Sex	Female	324·58	68·65	**0·036***	7·16	4·40	0·841*
	Male	206·44	64·12		6·95	5·69	
BMI	<30 kg/m²	381·10	40·66	0·241*	7·61	4·95	**0·016***
	≥30 kg/m²	283·40	54·27		4·32	3·42	
Metabolic syndrome	Yes	276·69	47·56	0·654*	4·85	0·73	**0·016†**
	No	306·94	47·45		8·14	0·72	
Waist circumference	Adequate	97·46	12·33	**<0·001***	6·42	0·82	0·326†
	Higher	149·36	44·18		6·99	0·64	
Fat mass (%)	Adequate	242·82	43·86	0·151†	8·48	5·77	**0·019***
	Higher	331·63	55·61		6·10	3·89	
Fat mass index	Adequate	200·09	47·12	**0·017***	8·84	5·41	**0·013***
	Higher	347·44	36·31		4·45	3·33	
Visceral adiposity index	Adequate	271·19	48·13	0·581*	8·61	4·84	**0·004***
	Higher	308·21	46·18		5·61	4·60	
Bone marrow blasts (%)	<5 %	248·9	62·9	0·441†	7·50	0·55	**0·041†**
	≥5 %	309·21	68·7		4·34	1·14	
Hb (g/dl)	<10	225·81	40·69	0·293†	6·77	4·41	0·421*
	≥10	291·59	43·73		7·61	5·61	
Absolute neutrophil count (/l)	<800	295·45	84·04	0·480†	7·21	1·28	0·669†
	≥800	222·19	31·81		6·98	0·55	
Platelet count (/l)	<100	255·47	47·03	0·277†	6·14	0·76	0·238†
	≥100	214·35	38·25		7·98	0·68	
IPSS-R	Lower risk	311·70	43·52	0·348*	6·97	4·58	0·788*
	Intermediate	323·39	87·28		6·07	4·23	
	Higher risk	231·19	54·4		6·01	4·58	
Ferritin	<1000 ng/dl	184·11	33·43	0·251*	7·22	5·24	0·791*
	≥1000 ng/dl	261·78	54·18		7·67	4·15	
Transfusion dependency	Yes	263·82	52·0	0·360*	6·26	4·04	0·220*
	No	320·28	35·97		7·55	5·27	

MDS, myelodysplastic syndrome; IPSS-R, International Prognostic Scoring System Revised.
The data in bold were significant with the
* Student's *t* test or ANOVA and
† Mann–Whitney test.
Data are represented as mean or median and SD.
P values were considered significant less than or equal to 0·05.

oesophagus, lung, ovary, pancreas, stomach and thyroid[9,10]. In haematological cancers, leptin can act in the genesis and progression of the disease. This cytokine was shown to have proliferative and apoptosis-inhibitory action in leukaemic cells[11,37].

In addition, adiponectin levels are reduced in various types of cancers, such as breast cancer[38], colorectal cancer[39], endometrial cancer[40], gastric[41], liver[42] and pancreatic[43], including haematological cancer[13,36].

Although the mechanisms that associate adiponectin and carcinogenesis have not yet been elucidated, some studies report proliferative and anti-apoptotic actions of adiponectin in cancer cell lines[44,45]. Low levels of adiponectin were associated with increased synthesis of fatty acids and proteins, thus enabling cell proliferation and growth, as well as DNA mutagenesis[46]. Furthermore, hypoadiponectinemia supports tumour proliferation by increasing anabolic hormones, such as insulin and IGF-1, which can act by inhibiting apoptosis and increasing cell proliferation[8].

Regarding the concentration of adiponectin and the prognostic parameters for MDS, we found in our study that patients with excess bone marrow blasts (≥5 %) had a significantly lower median of adiponectin when compared with patients with a lower amount at 5 % blasts in the BM ($P = 0·041$). Aref *et al.*[36] found a significant negative correlation between serum adiponectin levels and the percentage of blast cells in the bone marrow in patients with acute leukaemia, an important adverse prognostic factor.

A possible explanation for this finding is the fact that the large percentage of blast cells in the bone marrow may lead to a reduction of adipose tissue in the marrow and, thus, to lower levels of adiponectin, since it is produced almost exclusively by adipose tissue. This hypothesis is due to the fact that the number of adipocytes encroaching into the bone marrow space correlates inversely with the number of other cells[4,47].

It is noteworthy that adipose tissue, responsible for the production of adiponectin and leptin, makes up most of the structure of bone marrow, especially among older people. In addition, since it was discovered in 1994, leptin has been associated with obesity. Many studies have found higher levels of leptin in fat individuals when compared with lean population[48,49].

In our study, there was a clear relationship between serum leptin levels and body fat markers. Higher serum leptin concentration was found in patients with higher WC and FMI (Table 2). A weak, but significant, positive correlation was found

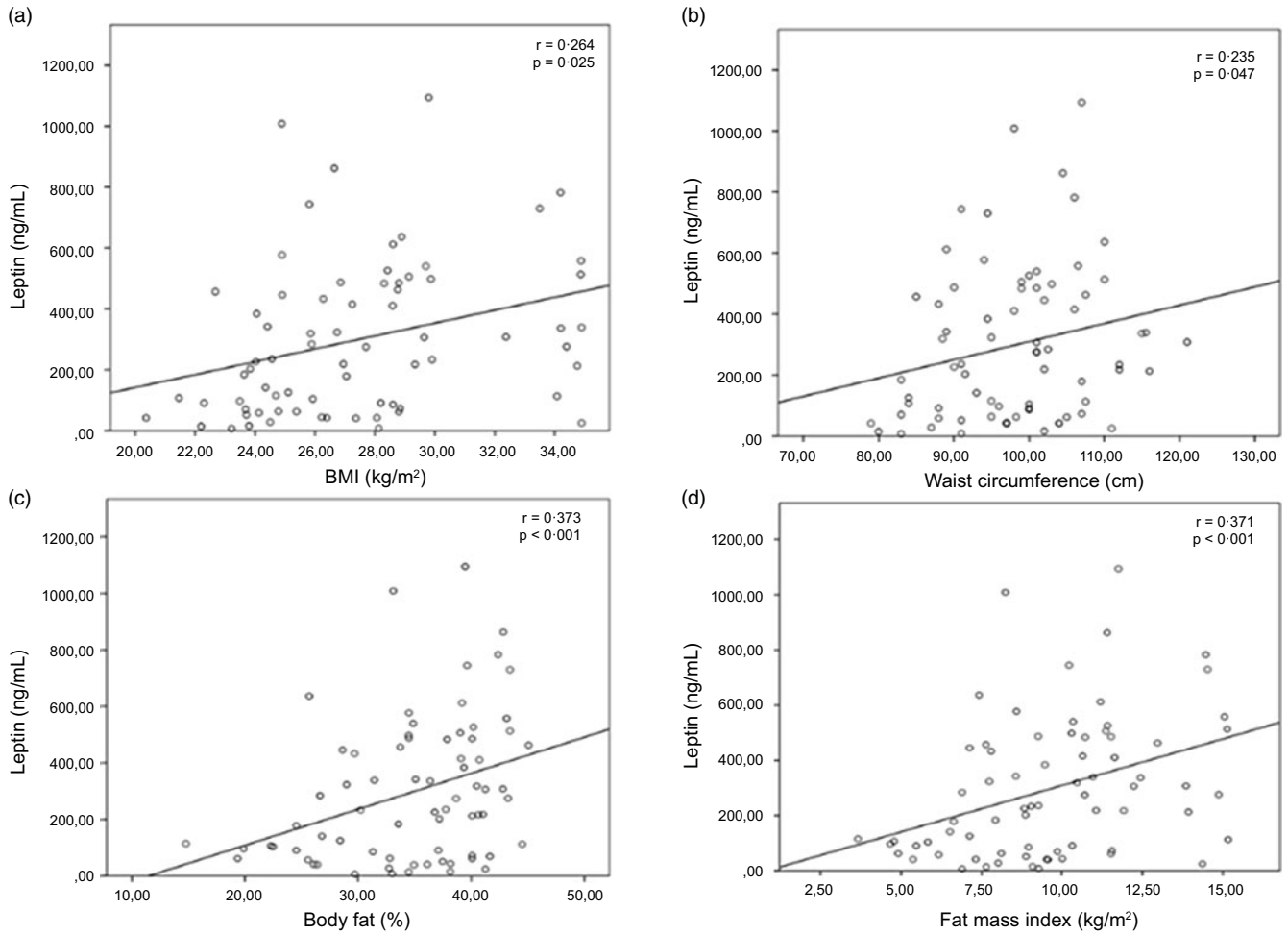

Fig. 2. (a) Correlation between leptin and BMI. (b) Correlation between leptin and waist circumference. (c) Correlation between leptin and body fat percentage. (d) Correlation between leptin and fat mass index *Pearson's correlation test (r) $P < 0{\cdot}05$.

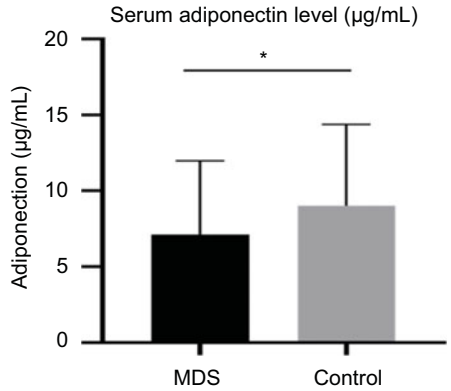

Fig. 3. Serum adiponectin level in MDS and control group. Bars represent means ± SD. Serum adiponectin level in patients with MDS was significantly different (*$P = 0{\cdot}033$) compared with the control group. MDS, myelodysplastic syndrome. Student's *t* test. *P* value was considered significant less than or equal to 5 %.

between serum leptin and BMI, WC and BF % (Fig. 2). Several other studies support our findings. A positive relationship between leptin levels and body adipose tissue volume is well established[50].

Positive correlation between BMI and leptin was observed in patients with colon, prostate, breast and haematological cancer[14,51–53]. Tsiotra *et al.*[11] found a significant positive correlation between leptin and BMI, but not with other haematological and clinical parameters of the disease in patients with MDS.

Furthermore, female MDS patients had higher leptin mean when compared with male patients. Similar findings were observed in healthy population and MDS individuals Awede *et al.*[54], Ayina *et al.*[55] and Tsiotra *et al.*[11]. Oestrogen has been linked to a possible role in stimulating leptin production[56,57].

In our study, we also observed significantly lower concentrations of adiponectin in higher body adiposity patients, according to BMI, FM %, FMI and VAI compared with lean individuals (Table 2). Srivastava *et al.*[58], studying obesity markers in 159 patients with acute leukaemia, including BMI, observed a significantly lower mean level of serum adiponectin in individuals with obesity compared with patients with adequate BMI, a result similar to what was demonstrated in our study.

A weak, but significant, negative correlations between serum adiponectin levels of MDS patients and BMI values were also observed in our study, as well as among other anthropometric markers such as WC, FMI and VAI (Fig. 4).

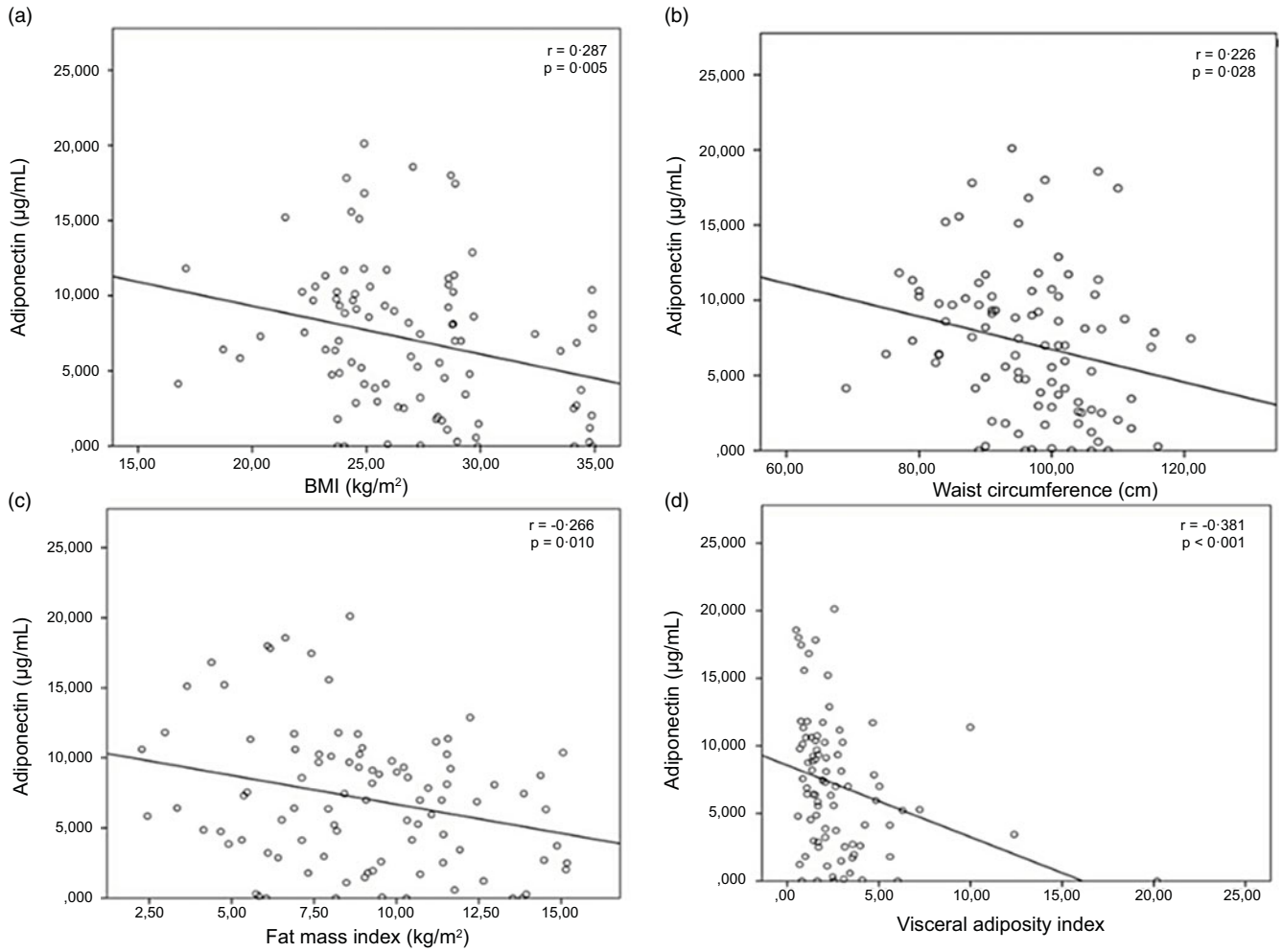

Fig. 4. (a) Correlation between adiponectin and BMI. (b) Correlation between adiponectin and waist circumference. (c) Correlation between adiponectin and fat mass index. (d) Correlation between adiponectin and visceral adiposity index. *Pearson's correlation test (r) $P < 0{\cdot}05$.

Table 3. Distributions of genotype frequencies of MDS patients and controls ($n = 92$)

	Groups				χ^2		Groups				χ^2
Polymorphism/genotype	MDS *n*	%	Controls *n*	%	*P	Polymorphism/allele	MDS *n*	%	Controls *n*	%	*P
LEP rs7799039						*LEP rs7799039*					
GG	39	42·4	40	41·2		G	116	63·0	127	65·5	0·62
AG	38	41·3	47	48·4	0·300	A	68	37·0	67	34·5	
AA	15	16·3	10	10·3							
ADIPOQ rs1501299						*ADIPOQ rs1501299*					
GG	39	42·4	36	37·1		G	114	61·9	118	60·8	0·82
GT	36	39·1	46	47·4	0·51	T	70	38·1	76	39·2	
TT	17	18·5	15	15·5							

MDS, myelodysplastic syndrome.
* Pearson or Fisher's χ^2.

Adiponectin is secreted by adipose tissue in an amount inversely proportional to BMI, thus being in reduced concentrations in individuals with obesity[59]. In addition, serum levels of this adipokine are more associated with the amount of visceral fat than total body fat[6]. Excess visceral fat, which results in visceral adipose tissue dysfunction, leads to unregulated production of adipokines, such as underproduction of adiponectin. Hypoadiponectinemia and the deposition of excess visceral fat may play important roles in the mechanism associated with the onset of chronic diseases[60].

Mihu *et al.*[61], when evaluating the amount of abdominal fat and plasma levels of adiponectin in patients with endometrial cancer, found a significantly lower level of adiponectin compared with the control group, as well as abdominal fat showed a negative correlation with the level of adiponectin, a finding that corroborates our study. Serretta *et al.*[62] found no

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Table 4. Comparison of *LEP* gene polymorphism rs7799039 with clinical and anthropometric data in patients with MDS ($n = 92$)

		LEP rs7799039								
		Genotypes								
		AA		GG		AG				
Variable		*n*	%	*n*	%	*n*	%	*P**	OR	95 % CI
Sex	Male	11	68·8	10	27·0	14	36·8	**0·018**	AAxGG	1·08, 13·10
	Female	5	31·3	27	73·0	24	63·2		3·77	
Age	<65	4	22·2	5	27·8	9	50·0	0·500		
	≥65	12	16·4	32	43·8	29	39·7			
IPSS-R	Lower risk	4	12·1	18	54·5	11	33·3	0·171		
	Intermadiate	6	37·5	4	25·0	6	37·5			
	Higher risk	4	30·8	4	30·8	5	38·4			
Hb (g/dl)	<10	12	21·1	22	38·6	23	40·4	0·570		
Absolute neutrophil count (/l)	<800	3	20·0	5	33·3	7	46·7	0·803		
Platelet count (/l)	<100	7	17·1	19	46·3	15	36·6	0·592		
Bone marrow blasts percentage	<5 %	8	50·0	30	81·1	31	81·5	**0·031**	AAxGG	1·23, 15·89
	≥5 %	8	50·0	7	18·5	7	18·5		4·42	
Ferritin	≥1000 ng/dl	0	0	6	50·0	6	50·0	0·134		
Transfusion dependency	Yes	6	18·8	11	34·4	15	46·9	0·648		
Metabolic syndrome	Presence	6	17·6	10	29·4	18	53·0	0·131		
BMI	≥30 kg/m²	3	23·0	5	38·5	5	38·5	0·834		
Waist circumference	Higher	9	17·0	25	47·2	19	35·8	0·288		
Body fat percentage	Higher	8	16·0	23	46·0	19	38·0	0·522		
Fat mass index	Higher	10	18·2	24	43·6	21	38·2	0·618		
Visceral adiposity index	Higher	5	13·2	14	36·8	19	50·0	0·269		

IPSS-R, International Prognostic Scoring System Revised.
* Pearson or Fisher's χ^2.
Comparisons between groups: (1) the genotype distribution model was modelled in three categories.
The data in bold were significant at $P \leq 0{\cdot}05$.
Statistically significant value for $P \leq 0{\cdot}05$.

Table 5. Comparison of the polymorphism of the ADIPOQ rs1501299 gene with clinical and anthropometric data in patients with MDS ($n = 92$)

		ADIPOQ rs1501299								
		Genotypes								
		GG		GT		TT				
Variable		*n*	%	*n*	%	*n*	%	*P* value*	OR	95 % CI
Sex	Male	14	40·0	13	37·1	8	22·9	0·698		
	Female	25	43·9	23	40·4	9	15·8			
Age	<65	8	42·1	7	36·8	4	21·1	0·943		
	≥65	31	42·5	29	39·7	13	17·8			
IPSS-R	Lower risk	13	41·9	13	41·9	5	16·1	0·978		
	Intermediate	6	35·3	5	29·4	6	35·6			
	Higher risk	7	46·7	7	46·7	1	6·7			
Hb (g/dl)	<10	26	45·6	20	35·1	11	19·3	0·592		
Absolute neutrophil count (/l)	<800	6	40·0	5	33·3	4	26·7	0·661		
Platelet count (/l)	<100	26	45·6	20	35·1	11	19·3	0·310		
Bone marrow blasts percentage	<5 %	29	40·8	28	39·4	14	19·7	0·802		
	≥5 %	10	47·6	8	38·1	3	14·3			
Ferritin	≥1000 ng/dl	3	25·0	3	25·0	6	50·0	**0·033**	GGxTT	1·36, 46·81
									8·00	
Transfusion dependency	Yes	13	41·9	10	32·3	8	25·8	0·294		
Metabolic syndrome	presence	13	37·1	14	40·0	8	22·9	0·871		
BMI	≥30 kg/m²	6	42·9	4	28·6	4	28·6	0·501		
Waist circumference	Higher	22	40·7	22	40·7	10	18·5	0·918		
Fat mass (%)	Higher	20	40·0	18	36·0	12	24·0	0·347		
Fat mass index	Higher	22	39·3	22	39·2	12	21·4	0·669		
Visceral adiposity index	Higher	16	41·0	14	35·9	9	23·1	0·697		

MDS, myelodysplastic syndrome; IPSS-R, International Prognostic Scoring System Revised.
* Pearson or Fisher's χ^2.
Comparisons between groups: (1) the genotype distribution model was modelled in three categories.
The data in bold were significant at $P \leq 0{\cdot}05$.
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significant correlation between BMI, VAI and plasma levels of adiponectin in patients with prostate cancer.

In our study, we also observed a significantly lower amount of adiponectin in MDS patients with MetS. Our group was the first to describe the MetS prevalence in MDS patients. A significantly higher prevalence of MetS was observed in elderly patients when compared with younger patients. In addition, MetS was associated with transfusion dependence, a poor prognostic factor in MDS. Thus, it was concluded that the presence of MetS is an additional factor not related to the disease that potentially increases its morbidity[63].

Furthermore, as already noted, visceral fat is inversely correlated with adiponectin levels, thus suggesting a close relationship between visceral obesity, hypoadiponectinemia and metabolic diseases. Cho *et al.*[64] observed a higher incidence of MetS in the group that had a greater area of visceral adipose tissue and a lower serum level of adiponectin, data that corroborate our study.

In our study, there was no difference in genotypes and alleles of *LEP* rs7799039 G > A polymorphism between MDS and control group. The adipocyte-derived peptide hormone LEP has a well-known role on inflammation, tumour growth and metastasis of cancer. In a recent meta-analysis, the *LEP* rs7799039 G > A polymorphism indicated a risk of the development of cancer, including haematological cancer[65].

We found a significant association between AA genotype and bone marrow blasts percentage ≥ 5 % (Table 4). The concentration of blasts in the bone marrow is an important clinical marker and one of the factors with the greatest negative impact on the prognosis of patients with MDS[20].

In this study, there was no significant difference between leptin levels and rs7799039 polymorphisms. Similar results were found in South Africans, Japanese and Malays individuals[66–68]. In contrast, studies have shown that the presence of the −2548G/A (rs7799039) polymorphism influences leptin expression, probably by transcription[69–71]. It is noteworthy that the ethnic influence on the distribution of LEP gene polymorphisms has been recognised[68].

As was observed in the LEP rs7799039 G > A polymorphism, in our study, we also found no difference in genotypes and alleles for ADIPOQ rs1501299 T > G between MDS and the control group. However, it is important to note that the rs1501299 T > G SNP was associated with a lower risk of some solid cancers, such as breast[72], oesophageal and hepatocellular[73]. Besides, this SNP was also associated with decreased serum concentrations of adiponectin[74,75] and increased risk of obesity in some populations[18,76]. In our study, we did not observe a significant association between adiponectin levels and anthropometric parameters with the gene frequencies of this SNP.

On the other hand, we found a significant association between genotypes and Fe overload (ferritin ≥1000 ng/ml). Patients with the polymorphic TT genotype had a significantly higher chance of having Fw overload when compared with patients with the GT and GG genotype.

Ferritin is considered a marker of inflammation, an acute phase reactant. Furthermore, Fe overload in transfusion-dependent patients results in tissue damage caused by oxidative stress and inflammation. In patients with haematological malignancies, including MDS, it has been observed that Fe overload can lead to liver dysfunction, hepatic sinusoidal obstruction syndrome and type 2 diabetes, which substantially influence the long-term survival of patients[77,78].

Strengths of this study included that it was the first group to assess patients with different anthropometric markers and not just BMI. It is known that BMI is a relatively rough measure of body adiposity, as it does not differentiate between lean mass and fat mass and does not inform about the distribution of body fat[79]. Furthermore, adipose tissue dysfunction and its consequences do not occur exclusively in patients with obesity by BMI. Insulin resistance and inflammation have been reported in individuals with normal BMI, as well as individuals with high BMI who were considered metabolically healthy[80]. Our study showed the importance of assessing body adiposity through the use of other markers of nutritional status, avoiding the use of BMI as an isolated measure of nutritional diagnosis. Furthermore, this was the first study that evaluated adipokine polymorphisms in patients with MDS.

However, there are limitations to consider. As this is a cross-sectional study, the association between exposure to the disease is not the same as that detected at the same point in the population. Perhaps the evaluation of more polymorphisms could find an association with the disease.

Conclusion

It is concluded that body adiposity excess was present in an important percentage of patients with MDS, although not significantly different from control. Higher leptin and hypoadiponectinemia were found in MDS patients compared with controls, with even higher leptin and lower adiponectin values in patients with higher body adiposity. Patients with a less favourable prognosis, according to blast percentage and ferritin levels, showed associations with the LEP −2548G > A and the ADIPOQ + 276G > T SNP, respectively.

These results demonstrate the importance of a comprehensive and systematic evaluation in MDS patients in order to identify and early control negative non-disease-related factors. Nutritional status, circulating adipokines, and leptin and adiponectin polymorphisms may play a potential role in disease pathogenesis. The association between these factors, not only with anthropometric parameters but also with some characteristics of the MDS, deserves further in-depth studies.

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References

1. Ministry of Health (2019) *Vigitel Brazil 2018. Surveillance of Risk and Protective Factors for Chronic Diseases by Telephone Survey*. Brasília: Ministry of Health.
2. Kyrgiou M, Kalliala I, Markozannes G, *et al.* (2017) Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ* **356**, j477.
3. Poynter JN, Richardson M, Blair CK, *et al.* (2016) Obesity over the life course and risk of acute myeloid leukemia and myelodysplastic syndromes. *Cancer Epidemiol* **40**, 134–140.
4. Adler BJ, Kaushansky K & Rubin CT (2014) Obesity-driven disruption of haematopoiesis and the bone marrow niche. *Nat Rev Endocrinol* **10**, 737–748.
5. Dalamaga M, Chou SH, Shields K, *et al.* (2013) Leptin at the intersection of neuroendocrinology and metabolism: current evidence and therapeutic perspectives. *Cell Metab* **18**, 29–42.
6. Marinou K, Tousoulis D, Antonopoulos AS, *et al.* (2010) Obesity and cardiovascular disease: from pathophysiology to risk stratification. *Int J Cardiol* **138**, 3–8.
7. Esfahani M, Movahedian A, Baranchi M, *et al.* (2015) Adiponectin: an adipokine with protective features against metabolic syndrome. *Iran J Basic Med Sci* **18**, 430–442.
8. Spyrou N, Avgerinos KI, Mantzoros CS, *et al.* (2018) Classic and novel adipocytokines at the intersection of obesity and cancer: diagnostic and therapeutic strategies. *Curr Obes Rep* **7**, 260–275.
9. Ray A & Cleary MP (2017) The potential role of leptin in tumor invasion and metastasis. *Cytokine Growth Factor Rev* **38**, 80–97.
10. Ghasemi A, Saeidi J, Azimi-Nejad M, *et al.* (2019) Leptin-induced signaling pathways in cancer cell migration and invasion. *Cell Oncol* **42**, 243–260.
11. Tsiotra PC, Pappa V, Koukourava A, *et al.* (2005) Expression of leptin receptors in mononuclear cells from myelodysplastic syndromes and acute myeloid leukemias. *Acta Haematol* **114**, 71–77.
12. Dalamaga M, Nikolaidou A, Karmaniolas K, *et al.* (2007) Circulating adiponectin and leptin in relation to myelodysplastic syndrome: a case-control study. *Oncology* **73**, 26–32.
13. Dalamaga M, Karmaniolas K, Nikolaidou A, *et al.* (2008) Adiponectin and resistin are associated with risk for myelodysplastic syndrome, independently from the insulin-like growth factor-I (IGF-I) system. *Eur J Cancer* **44**, 1744–1753.
14. Han TJ & Wang X (2015) Leptin and its receptor in hematologic malignancies. *Int J Clin Exp Med* **8**, 19840–19849.
15. He J, Xi B, Ruiter R, *et al.* (2013) Association of LEP G2548A and LEPR Q223R polymorphisms with cancer susceptibility: evidence from a meta-analysis. *PLoS ONE* **8**, 1–12.
16. Lee JY, Cho JK, Hong HR, *et al.* (2012) Genetic effects of adiponectin single nucleotide polymorphisms on the clustering of metabolic risk factors in young Korean adults. *Eur J Appl Physiol* **112**, 623–629.
17. Oliveira SC, Saddi-Rosa P, Crispim F, *et al.* (2012) Association of ADIPOQ variants, total and high molecular weight adiponectin levels with coronary artery disease in diabetic and non-diabetic Brazilian subjects. *J Diabetes Complications* **26**, 94–98.
18. Zayani N, Omezzine A, Boumaiza I, *et al.* (2017) Association of ADIPOQ, leptin, LEPR, and resistin polymorphisms with obesity parameters in Hammam Sousse Sahloul Heart Study. *J Clin Lab Anal* **31**, 1–10.
19. Arber DA, Orazi A, Hasserjian R, *et al.* (2016) The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. *Blood* **127**, 2391–2405.
20. Greenberg PL, Tuechler H, Schanz J, *et al.* (2012) Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* **120**, 2454–2465.
21. World Health Organization Expert Committee (1995) Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee. *World Health Organ Tech Rep Ser* **854**, 1–452.
22. World Health Organization (2000) Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* **894**, 1–253.
23. Durnin JV & Womersley J (1974) Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr* **32**, 77–97.
24. Harrison GG, Buskirk ER, Carter LJE, *et al.* (1988) Skinfold thicknesses and measurement technique. In *Anthropometric Standardization Reference Manual*, pp. 55–70 [TG Lohman, AF Roche and R Martorell, editors]. Champaign: Human Kinetics Books.
25. Lohman TG (1992) *Advances in Body Composition Assessment. Current Issues in Exercise Science Series (Monograph 3)*. Champaign, IL: Human Kinetics.
26. Van Itallie TB, Yang MU, Heymsfield SB, *et al.* (1990) Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. *Am J Clin Nutr* **52**, 953–959.
27. Kelly TL, Wilson KE & Heymsfield SB (2009) Dual energy X-Ray absorptiometry body composition reference values from NHANES. *PLoS ONE* **4**, e7038.
28. Amato MC, Giordano C & Galia M (2010) Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care* **33**, 920–922.
29. Amato MC, Giordano C, Pitrone M, *et al.* (2011) Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. *Lipids Health Dis* **10**, 183.
30. National Cholesterol Education Program (2001) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Anon expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *JAMA* **285**, 2486–2497.
31. Clarke GM, Anderson CA & Pettersson FH (2011) Basic statistical analysis in genetic case-control studies. *Nat Protoc* **6**, 121–133.
32. Hosney M, Sabet S, El-Shinawi M, *et al.* (2017) Leptin is overexpressed in the tumor microenvironment of obese patients with estrogen receptor positive breast cancer. *Exp Ther Med* **13**, 2235–2246.
33. Geng Y, Wang J, Wang R, *et al.* (2012) Leptin and HER-2 are associated with gastric cancer progression and prognosis of patients. *Biomed Pharmacother* **66**, 419–424.

34. Wang D, Gao L, Gong K, *et al.* (2017) Increased serum leptin level in overweight patients with colon carcinoma: a cross-sectional and prospective study. *Mol Clin Oncol* **6**, 75–78.
35. Wang PP, He XY, Wang R, *et al.* (2014) High leptin level is an independent risk factor of endometrial cancer: a meta-analysis. *Cellular Physiol Biochem* **34**, 1477–1484.
36. Aref S, Ibrahim L, Azmy E, *et al.* (2013) Impact of serum adiponectin and leptin levels in acute leukemia. *Hematology* **18**, 198–203.
37. Konopleva M, Mikhail A, Estrov Z, *et al.* (1999) Expression and function of leptin receptor isoforms in myeloid leucemia and myelodysplastic syndromes: proliferative and anti-apoptotic activities. *Blood* **93**, 1668–1676.
38. Mantzoros C, Petridou E, Dessypris N, *et al.* (2004) Adiponectin and breast cancer risk. *J Clin Endocrinol Metab* **89**, 1102–1107.
39. Wei EK, Giovannucci E, Fuchs CS, *et al.* (2005) Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. *J Natl Cancer Inst* **97**, 1688–1694.
40. Petridou E, Mantzoros C, Dessypris N, *et al.* (2003) Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece. *J Clin Endocrinol Metab* **88**, 993–997.
41. Ishikawa M, Kitayama J, Kazama S, *et al.* (2005) Plasma adiponectin and gastric cancer. *Clin Cancer Res* **11**, 466–472.
42. Arano T, Nakagawa H, Tateishi R, *et al.* (2011) Serum level of adiponectin and the risk of liver cancer development in chronic hepatitis C patients. *Int J Cancer* **129**, 2226–2235.
43. Stolzenberg-Solomon RZ, Weinstein S, Pollak M, *et al.* (2008) Prediagnostic adiponectin concentrations and pancreatic cancer risk in male smokers. *Am J Epidemiol* **168**, 1047–1055.
44. Barb D, Williams CJ, Neuwirth AK, *et al.* (2007) Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. *Am J Clin Nutr* **86**, S858–S866.
45. Lang K & Ratke J (2009) Leptin and adiponectin: new players in the field of tumor cell and leukocyte migration. *Cell Commun and Signal* **7**, 27.
46. Wang Y, Lam KSL & Xu A (2007) Adiponectin as a negative regulator in obesity-related mammary carcinogenesis. *Cell Res* **17**, 280–282.
47. Azadniv M, Myers JR, McMurray HR, *et al.* (2020) Bone marrow mesenchymal stromal cells from acute myelogenous leukemia patients demonstrate adipogenic differentiation propensity with implications for leukemia cell support. *Leukemia* **34**, 391–403.
48. Halaas JL, Gajiwala KS, Maffei M, *et al.* (1995) A plasma protein encoded by the obese gene. *Science* **269**, 543–546.
49. Friedman J (2016) The long road to leptin. *J Clin Invest* **126**, 4727–4734.
50. Izquierdo AG, Crujeiras AB, Casanueva FF, *et al.* (2019) Leptin, obesity, and leptin resistance: where are we 25 years later? *Nutrients* **11**, e2704.
51. Stachowicz M, Mazurek U, Nowakowska-Zajdel E, *et al.* (2010) Leptin and its receptors in obese patients with colorectal cancer. *J Biol Regul Homeost Agents* **24**, 287–295.
52. Singh SK, Grifson JJ, Mavuduru RS, *et al.* (2010) Serum leptin: a marker of prostate cancer irrespective of obesity. *Cancer Biomark* **7**, 11–15.
53. Pan H, Deng LL, Cui JQ, *et al.* (2018) Association between serum leptin levels and breast cancer risk: an updated systematic review and meta-analysis. *Medicine* **97**, e11345.
54. Awede B, Adovoekpe D, Adehan G, *et al.* (2018) Adiponectin, in contrast to leptin, is not associated with body mass index, waist circumference and HOMA-IR in subjects of a west-African population. *Physiol Rep* **6**, e13718.
55. Ayina CN, Noubiap JJ, Etoundingoa LS, *et al.* (2016) Association of serum leptin and adiponectin with anthropomorphic indices of obesity, blood lipids and insulin resistance in a Sub-Saharan African population. *Lipids Health Dis* **15**, 96.
56. Moon HS, Dalamaga M, Kim SY, *et al.* (2013) Leptin's role in lipodystrophic and nonlipodystrophic insulin-resistant and diabetic individuals. *Endocr Rev* **34**, 377–412.
57. Hu S, Gan C, Wen R, *et al.* (2014) Role of leptin in the regulation of sterol/steroid biosynthesis in goose granulosa cells. *Theriogenology* **82**, 677–685.
58. Srivastava R, Batra A, Tyagi A, *et al.* (2015) Adiponectin correlates with obesity: a study of 159 childhood acute leukemia survivors from India. *Indian J Cancer* **52**, 195–197.
59. Obeid S & Hebbard L (2012) Role of adiponectin and its receptors in cancer. *Cancer Biol Med* **9**, 213–220.
60. Roberts DL, Dive C & Renehan AG (2010) Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med* **61**, 301–316.
61. Mihu D, Ciortea R & Mihu CM (2013) Abdominal adiposity through adipocyte secretion products, a risk factor for endometrial cancer. *Gynecol Endocrinol* **29**, 448–451.
62. Serretta V, Abrate A, Siracusano S, *et al.* (2018) Clinical and biochemical markers of visceral adipose tissue activity: body mass index, visceral adiposity index, leptin, adiponectin, and matrix metalloproteinase-3. Correlation with Gleason patterns 4 and 5 at prostate biopsy. *Urol Ann* **10**, 280–286.
63. Aguiar APN, Mendonça PDS, Ribeiro-Júnior HL, *et al.* (2020) Myelodysplastic syndromes: an analysis of non-hematological prognostic factors and its relationship to age. *J Geriatr Oncol* **11**, 125–127.
64. Cho SA, Joo HJ, Cho JY, *et al.* (2017) Visceral fat area and serum adiponectin level predict the development of metabolic syndrome in a community-based asymptomatic population. *PLoS ONE* **12**, e0169289.
65. Tang W, Kang M, Liu C, *et al.* (2019) Leptin rs7799039 (G2548A) polymorphism is associated with cancer risk: a meta-analysis involving 25,799 subjects. *Onco Targets Ther* **12**, 2879–2890.
66. Okpechi IG, Rayner BL, Van Der Merwe L, *et al.* (2010) Genetic variation at selected SNPs in the leptin gene and association of alleles with markers of kidney disease in a Xhosa population of South Africa. *PLoS ONE* **5**, 1–10.
67. Gaukrodger N, Mayosi BM, Imrie H, *et al.* (2005) A rare variant of the leptin gene has large effects on blood pressure and carotid intima-medial thickness: a study of 1428 individuals in 248 families. *J Med Genet* **42**, 474–478.
68. Fan SH & Say YH (2014) Leptin and leptin receptor gene polymorphisms and their association with plasma leptin levels and obesity in a multi-ethnic Malaysian suburban population. *J Physiol Anthropol* **33**, 1–10.
69. Hoffstedt J, Eriksson P, Mottagui-Tabar S, *et al.* (2002) Polymorphism in the leptin promoter region (−2548 G/A) influences gene expression and adipose tissue secretion of leptin. *Hormone Metab Res* **34**, 355–359.
70. Hinuy HM, Hirata MH, Forti N, *et al.* (2008) Leptin G-2548A promoter polymorphism is associated with increased plasma leptin and BMI in Brazilian women. *Arq Bras Endocrinol Metabol* **52**, 611–616.
71. Terrasi M, Fiorio E, Mercanti A, *et al.* (2009) Functional analysis of the -2548G/A leptin gene polymorphism in breast cancer cells. *Int J Cancer* **125**, 1038–1044.
72. Kaklamani VG, Sadim M, Hsi A, *et al.* (2008) Variants of the adiponectin and adiponectin receptor 1 genes and breast cancer risk. *Cancer Res* **68**, 3178–3184.
73. Pei Y, Xu Y & Niu W (2015) Causal relevance of circulating adiponectin with cancer: a meta-analysis implementing Mendelian randomization. *Tumour Biol* **36**, 585–594.
74. Kyriakou T, Collins LJ, Spencer-Jones NJ, *et al.* (2008) Adiponectin gene ADIPOQ SNP associations with serum

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adiponectin in two female populations and effects of SNPs on promoter activity. *J Hum Genet* **53**, 718–727.
75. Xu Y, He B, Pan Y, *et al.* (2013) The roles of ADIPOQ genetic variations in cancer risk: evidence from published studies. *Mol Biol Rep* **40**, 1135–1144.
76. Ramya K, Ayyappa KA, Ghosh S, *et al.* (2013) Genetic association of ADIPOQ gene variants with type 2 diabetes, obesity and serum adiponectin levels in south Indian population. *Gene* **532**, 253–262.
77. Alessandrino EP, Della Porta MG, Bacigalupo A, *et al.* (2010) Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a GITMO study. *Haematologica* **95**, 476–484.
78. Yang Y, Tang Z, An T, *et al.* (2019) The impact of iron chelation therapy on patients with lower/intermediate IPSS MDS and the prognostic role of elevated serum ferritin in patients with MDS and AML: a meta-analysis. *Medicine* **98**, e17406.
79. Singer P, Blaser AR, Berger MM, *et al.* (2019) ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* **38**, 48–79.
80. Chen S, Chen Y, Liu X, *et al.* (2014) Insulin resistance and metabolic syndrome in normal-weight individuals. *Endocrine* **46**, 496–504.