

EVALUATION OF GROWTH IN LONG-TERM FOLLOW-UP IN INDIVIDUALS WITH PHENYLKETONURIA

FENİLKETONÜRİLİ BİREYLERDE UZUN SÜRELİ TAKİPTE BÜYÜMENİN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: The aim of our study was to evaluate the anthropometric parameters of patients with Phenylketonuria (PKU) receiving special nutritional therapy and how these parameters changed over time, and to evaluate anthropometric measurements in the early years of life in terms of predicting the development of overweight/obesity later in life.

Material and Methods: In this single-centre, long-term, observational, and descriptive study, 102 individuals with phenylketonuria who were diagnosed in the first two months of life and initiated nutritional treatment were included.

Results: The ratios of overweight and obesity were found to be lower in our patient group compared with the general population in both evaluations. The weight-for-age ($p=0.000$), height-for-age ($p=0.000$), weight-for-height ($p=0.000$), and body mass index ($p=0.052$) of the patients decreased compared with the evaluation at the baseline of the follow-up period. Forty-six patients had a change in their anthropometric evaluations.

Conclusion: Monitoring anthropometric measurements and body composition changes in all patient groups receiving specialised nutritional therapies is critical in determining and monitoring treatment efficacy. The reason for the low ratios of obesity and overweight in our patient group compared with the healthy population is thought to be the close monitoring of nutritional therapies and anthropometric parameters of the patients in the follow-up.

Keywords: Phenylketonuria, nutrition therapy, body mass index, obesity, overweight

ÖZET

Amaç: Çalışmamızın amacı özel beslenme tedavisi alan Fenilketonüri (PKU) hastalarının antropometrik indekslerini ve bu indekslerin zaman içerisinde nasıl değiştiğini incelemek, hayatın erken yıllarındaki antropometrik ölçümleri hayatın ilerleyen dönemlerinde aşırı tartıllık/obezite gelişimi öngörüsü açısından değerlendirmektir.

Gereç ve Yöntem: Tek merkezli, uzun dönemli, gözlemsel ve tanımlayıcı çalışmaya, yaşamın ilk iki ayında tanı alarak beslenme tedavisine başlanmış 102 fenilketonürlü birey dâhil edilmiştir.

Bulgular: Hasta grubumuzda yapılan her iki değerlendirmede de aşırı tartıllık ve obezite oranları genel topluma kıyasla düşük bulunmuştur. Hastaların boya göre tartı ($p=0.000$), yaşa göre tartı ($p=0.000$), yaşa göre boy ($p=0.000$) ve beden kitle indekslerinde ($p=0.052$) izlem sürecinin başındaki değerlendirmeye kıyasla azalma tespit edilmiştir. Kırk altı hastanın antropometrik değerlendirmelerinde değişiklik gözlenmiştir.

Sonuç: Özel beslenme tedavileri alan tüm hasta gruplarında antropometrik ölçümlerin ve vücut kompozisyonu değişikliklerinin izlemi tedavi etkinliğinin belirlenmesi ve izleminde kritik öneme sahiptir. Hasta grubumuzda obezite ve aşırı tartıllık oranlarının sağlıklı topluma kıyasla düşük olmasının nedeninin izleminde hastaların beslenme tedavilerinin ve antropometrik parametrelerinin yakından izlenmesi olduğu düşünülmüştür.

Anahtar Kelimeler: Fenilketonüri, beslenme tedavisi, vücut kütlesi indeksi, obezite, aşırı tartı

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INTRODUCTION

Phenylketonuria (PKU; OMIM 261600) is an inherited metabolic disorder characterised by a deficiency of the enzyme phenylalanine hydroxylase, which converts the amino acid phenylalanine (Phe) to tyrosine. The specialised nutritional therapy involved in the main treatment of the disease has three pillars; (a) regulation of natural protein intake according to individual Phe tolerance, (b) administration of a synthetic protein constructed from Phe-free amino acids and (c) use of low-protein specialised nutritional products (1). Phe-free amino acid mixtures comprise essential and non-essential amino acids other than Phe, carbohydrates and fats as energy sources, in addition to vitamins, minerals and trace elements. The protein content of low-protein foods is reduced, and the proportion of energy derived from carbohydrates and fat in these foods is increased compared to that derived from natural foods. Specialised nutritional therapies are used to achieve this, using diets in which the energy provided by carbohydrates and fats is higher than that in a healthy diet (1). There are concerns that these specialised nutritional therapies may lead to an increased prevalence of overweight and obesity in patients with PKU in the long term (2).

Since 1975, the global prevalence of overweight has almost tripled (3). Abdominal obesity is associated with dyslipidemia, hypertension, insulin resistance, and inflammation (4). In the long-term, it has been suggested that non-communicable diseases such as non-insulin-dependent diabetes mellitus, musculoskeletal disorders, lung diseases, and cancer may be linked to these changes in body composition (5, 6).

The aim of our study was to investigate the anthropometric indices of weight-for-age (WFA), height-for-age (HFA), weight-for-height (WFH) and body mass index (BMI) of PKU patients receiving special nutritional therapy and how these indices changed over time, and to evaluate anthropometric measurements in the early years of life in terms of predicting the development of overweight/obesity later in life.

MATERIAL AND METHODS

This single-centre, long-term, observational, and descriptive study was conducted between October 2023 and June 2024 in the Department of Paediatric Nutrition and Metabolism, Istanbul University, Istanbul Faculty of Medicine. The cohort consisted of PKU patients who were born at term, diagnosed in the first 2 months of life and receiving nutritional treatment. Patients with a history of small for gestational age (SGA) and other conditions that could affect normal physical development were excluded from the study. The Istanbul Faculty of Medicine Clinical Research Ethics Committee approved the study (Date: 22.09.2023, No: 19).

This study was conducted in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration. Informed consent was obtained from patients or their legal guardians after the procedure had been fully explained.

Patients with Phe levels >1200 $\mu\text{mol/L}$ at initial diagnosis or Phe tolerance <20 mg/dl at follow-up were classified as classic PKU (cPCU), whereas patients with Phe levels $600\text{--}1200$ $\mu\text{mol/L}$ at initial diagnosis or Phe tolerance >20 mg/dl at follow-up were classified as having mild PKU (mPKU). All patients received nutritional therapy consisting of a low-Phe diet and a Phe-free L-amino acid mixture since diagnosis.

Data obtained from the volunteers included age, sex, diagnostic classification, anthropometric indices of WFH, WFA, HFA, and BMI during the first 5 years of life and 9 years after the initial assessment. The first anthropometric measurements were obtained from the patients' medical records, and the second anthropometric measurements were taken using standardised techniques, without shoes and in light clothing. It was planned to measure body weight and height from the anthropometric measurements and to calculate the anthropometric indices of WFA, HFA, WFH and BMI from these data. BMI was calculated as $\text{weight (kg)}/\text{height}^2$ (m^2). For participants over 18 years of age, BMI <18.5 kg/m^2 was considered as underweight, $18.5\text{--}24.9$ kg/m^2 as normal, $25\text{--}29.9$ kg/m^2 as overweight, and >30 kg/m^2 as obese (7). Between the ages of 5 and 18 years, a BMI z-score below -2 was considered underweight, between -2 and 1 was considered normal, between 1 and 2 was considered overweight, and above 2 was considered obese (8). For the first 5 years of life, BMI was considered underweight if it was below the 5th percentile, normal if it was between the 5th and 85th percentiles, overweight if it was between the 85th and 95th percentiles and obese if it was above the 95th percentile (9).

The mean, standard deviation, median, minimum, maximum, frequency and ratio values were used in the descriptive statistics of the data. We evaluated the distribution by the Kolmogorov–Smirnov test. Paired samples t-test was used in the analysis of quantitative-dependent data. The Wilcoxon test was used to analyse qualitative-dependent data. The SPSS 28.0 (IBM SPSS Corp., Armonk, NY, USA) program was used in the analyses.

RESULTS

In the patient group, 54 of 102 participants were female (52.9%) and 48 were male (47.1%). The mean age of the patients was 15.3 ± 3.0 (median: 14.8; range: 10.2–22.3) years. Eighty patients (78.4%) were followed up with a diagnosis of classical PKU and 22 patients (21.6%) with mild PKU. The mean follow-up period of patients was 14.9 ± 3.9 (median: 14.5; range: 10.1–22.0) years.

The data related to WFH, WFA, HFA, and BMI of the overall patient group at the beginning and end of the follow-up period are presented in Table 1. At the end of the follow-up period, a statistically significant reduction was found in the mean values of WFH, HFA, and WFA z-score. In the first assessment, there were no underweight patients according to BMI, while the proportion of normal, overweight, and obese patients were 65%, 18.6%, and 17.6%, respectively. In the second assessment, the proportions of underweight, normal, overweight, and obese patients according to BMI were 2.9%, 59.8%, 28.4%, and 8.8%, respectively. The difference between the rates of underweight, normal weight, overweight and obese patients was not statistically significant ($p=0.140$). The anthropometric data of 10 patients initially classified as normal weight exhibited characteristics compatible with overweight at the subsequent evaluation. The anthropometric data of the two patients initially classified as normal weight were found to be compatible with obesity at the subsequent evaluation. The anthropometric data of two patients who were initially classified as overweight at the first evaluation were found to be compatible with the criteria for obesity at the second evaluation. Twenty-three patients had decreased BMI z-scores during the second evaluation; Nine patients initially classified as obese exhibited an overweight status at the subsequent evaluation. Four patients initially classified as obese were subsequently determined to have a normal weight at the second evaluation. Seven patients initially classified as overweight were subsequently found to have a normal weight at the subsequent evaluation. Three patients initially classified as normal weight were subsequently identified as underweight at the second evaluation.

The anthropometric parameters of the patients according to BMI percentiles in the first five years of age according to gender and anthropometric parameters according to BMI z-scores 9 years after the first evaluation are

presented in Figure 1. There was a statistically significant decrease in the mean WFH, WFA, HFA, and BMI z-scores in the girls during the follow-up period. In boys, a statistically significant reduction was found in the mean WFH, WFA, and HFA z-scores during the follow-up period. Although there was a decrease in the mean BMI z-score, statistical significance was not found (Table 2).

Anthropometric evaluations of the patients according to BMI percentiles in the first five years of age according to disease classification and anthropometric evaluations according to BMI z-scores 9 years after the first evaluation are presented in Figure 2. No statistically significant change was found in the mean WFH, WFA, HFA, and BMI z-scores of mPKU patients. However, the z-scores of all anthropometric indices (WFH, WFA, HFA, and BMI) decreased. A statistically significant decrease was found in the mean WFH, WFA, HFA, and BMI z-scores of cPKU patients during the follow-up period (Table 3).

DISCUSSION

Nutritional therapies are the primary treatment option for many inherited metabolic diseases, including PKU. It has long been hypothesised that the Phe-restricted diet followed by patients with PKU may lead to abdominal obesity and metabolic syndrome, which are chronic non-communicable diseases associated with nutrition in the long term (10, 11). The determination and monitoring of body composition changes in PKU plays a fundamental role in nutritional assessment and evaluation of the efficacy of nutritional therapy (12).

In the cohort of 102 patients enrolled in our study, there was a reduction in the mean z-score of WFA, HFA, WFH and BMI after nine years of follow-up. However, the mean z-scores were within the healthy reference range. According to the data obtained at the baseline and at the end

Table 1: Anthropometric data at the baseline and end of the follow-up period in all patient groups, anthropometric evaluation according to BMI

	WFH		WFA		HFA		BMI z-score		BMI evaluation			
	mean±SD	median	mean±SD	median	mean±SD	median	mean±SD	median	Underweight (n-%)	Normal (n-%)	Overweight (n-%)	Obese (n-%)
Baseline evaluation	0.8±1.1	0.8 (-1.8 - 4.4)	0.6±1.0	0.6 (-2.1-3.6)	0.1±1.0	0.1 (-2.0-2.2)	0.8±1.0	0.8 (-1.5-4.5)	0	65 (63.8%)	19 (18.6%)	18 (17.6%)
Second evaluation	0.2±1.2	0.3 (-2.6 - 3.1)	-0.1±1.4	-0.2 (-3.7-3.4)	-0.4±1.0	-0.5 (-3.6-2.6)	0.5±1.2	0.7 (-2.8-2.5)	3 (2.9%)	61 (59.8%)	29 (28.5%)	9 (8.8%)
p	0.000 ^{ps}		0.000 ^{ps}		0.000 ^{ps}		0.052 ^{ps}		0.140 ^w			

BMI: Body mass index, HFA: Height-for-age, SD: standard deviation, WFH: Weight-for-height, WFA: Weight-for-age, ^{ps}: paired samples t-test, ^w: wilcoxon test

Table 2: Anthropometric data at the baseline and at the end of the follow-up period according to gender groups, anthropometric evaluation according to BMI

	WFH		WFA		HFA		BMI z-score		BMI evaluation			
	mean±SD	median	mean±SD	median	mean±SD	median	mean±SD	median	Underweight (n-%)	Normal (n-%)	Overweight (n-%)	Obese (n-%)
Females	Baseline evaluation	0.8 (-1.7-3.2)	0.6 (-1.8-2.8)	0.0±0.7 (-2.0-1.1)	0.0	0.8±1.0 (-1.5-3.2)	0.8	0.8±1.0 (-1.5-3.2)	0	35 (64.8%)	9 (16.7%)	10 (18.5%)
	Second evaluation	0.4±1.4 (-2.6-3.1)	-0.1 (-3.7-3.4)	-0.5±0.9 (-2.2-1.4)	-0.7	0.5±1.2 (-2.1-2.5)	0.6	0.5±1.2 (-2.1-2.5)	2 (3.7%)	32 (59.3%)	12 (22.2%)	8 (14.8%)
	p	0.022^{ps}	0.001^{ps}	0.000^{ps}	0.000^{ps}	0.000^{ps}	0.000^{ps}	0.591^w				
Males	Baseline evaluation	0.8 (-1.8-4.4)	0.7 (-2.1-3.6)	0.1±0.9 (-1.8-2.2)	0.2	0.8±1.1 (-1.4-4.5)	0.8	0.8±1.1 (-1.4-4.5)	0	30 (62.5%)	10 (20.8%)	8 (16.8%)
	Second evaluation	0.1±1.0 (-2.0-2.2)	-0.7 (-2.2-1.4)	0.2±1.0 (-3.5-2.6)	-0.3	0.5±1.0 (-2.8-2.1)	0.7	0.5±1.0 (-2.8-2.1)	1 (2.1%)	29 (60.4%)	17 (35.4%)	1 (2.1%)
	p	0.001^{ps}	0.000^{ps}	0.025^{ps}	0.025^{ps}	0.392^{ps}	0.124^w					

BMI: Body mass index, HFA: Height-for-age, SD: standard deviation, WFH: Weight-for-height, WFA: Weight-for-age, ^{ps}: paired samples t-test, ^w: wilcoxon test

Table 3: Anthropometric data at the baseline and at the end of the follow-up period according to disease classification and anthropometric evaluation according to BMI

	WFH		WFA		HFA		BMI z-score		BMI evaluation			
	mean±SD	median	mean±SD	median	mean±SD	median	mean±SD	median	Underweight (n-%)	Normal (n-%)	Overweight (n-%)	Obese (n-%)
MPKU	Baseline evaluation	0.6±0.9 (-1.7-2.2)	0.5 (-1.7-2.2)	0.4±0.9 (-2.1-1.8)	0.6 (-2.1-1.8)	0.2±0.9 (-1.3-2.2)	0.2	0.6±0.9 (-1.5-2.1)	0	16 (72.8%)	4 (18.2%)	2 (9%)
	Second evaluation	0.2±1.1 (-1.2-2.5)	0.3 (-1.2-2.5)	0.0±1.1 (-1.5-2.7)	0.0 (-1.5-2.7)	-0.1±1.0 (-1.4-2.6)	-0.3	0.5±0.9 (-0.9-2.5)	0	16 (72.8%)	4 (18.2%)	2 (9%)
	p	0.200^{ps}	0.075^{ps}	0.131^{ps}	0.748^{ps}	1.000^w						
CPKU	Baseline evaluation	0.8±1.1 (-1.9-4.4)	0.9 (-1.9-4.4)	0.6±1.0 (-1.8-3.6)	0.6 (-1.8-3.6)	0.0±0.8 (-2.0-2.1)	0.0	0.9±1.1 (-1.4-4.5)	0	49 (61.3%)	15 (18.8%)	16 (19.9%)
	Second evaluation	0.2±1.3 (-2.6-3.1)	0.3 (-2.6-3.1)	-0.1±1.4 (-3.7-3.4)	-0.3 (-3.7-3.4)	-0.5±1.0 (-3.6-1.8)	-0.5	0.5±1.2 (-2.8-2.5)	3 (3.8%)	45 (56.3%)	25 (31.3%)	7 (9.6%)
	p	0.000^{ps}	0.000^{ps}	0.000^{ps}	0.000^{ps}	0.001^{ps}	0.108^w					

BMI: Body mass index, HFA: Height-for-age, SD: standard deviation, WFH: Weight-for-height, WFA: Weight-for-age, ^{ps}: paired samples t-test, ^w: wilcoxon test

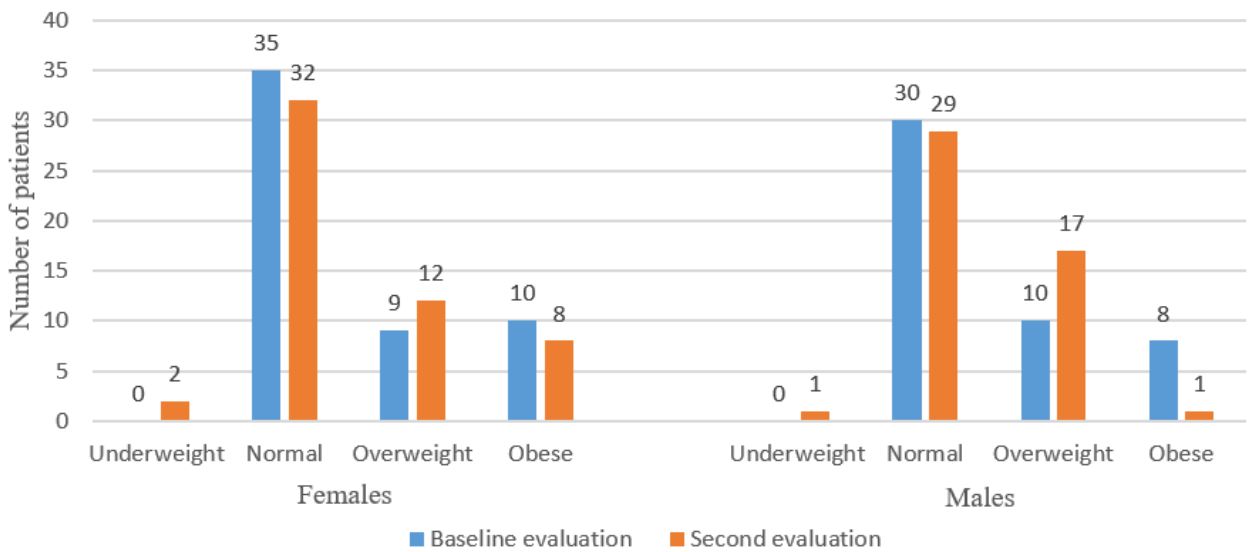


Figure 1: Anthropometric assessments of female and male patients at baseline and second evaluation

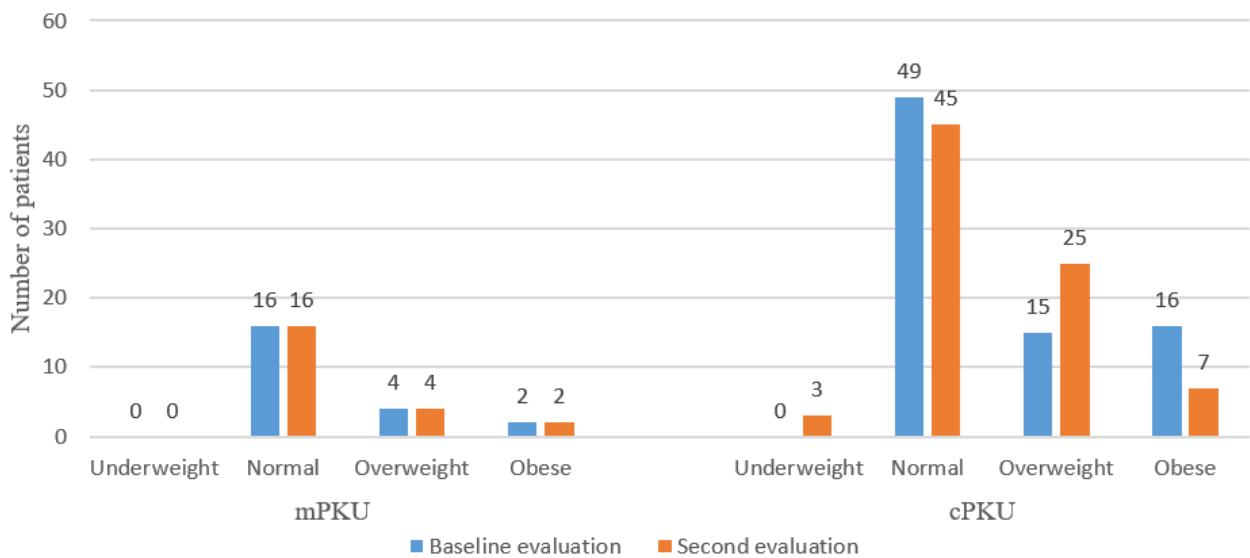


Figure 2: Anthropometric assessments of mPKU and cPKU patients at baseline and second evaluation
 cPKU: clasical phenylketonuria, mPKU: mild phenylketonuria

of the follow-up period, the rate of obesity in the PKU patient group was below the Turkish average. According to the data of the Turkish Statistical Institute, the rate of obesity among individuals aged 15 years and older in our country was 19.9% and the overweight rate was 33.7% in 2014, while the rate of obesity among individuals aged 15 years and older was 20.2% and the overweight rate was 35.7% in 2022 (13, 14). Some studies have found no difference in BMI, overweight and obesity prevalence between patients with PKU and healthy individuals (15, 16). A meta-analysis showed no significant association between PKU and overweight (1). However, there are many studies

showing that people with PKU have a higher BMI than the healthy population (10, 11, 17), especially in females (2, 18). Some studies have shown that the BMI and fat mass of female patients with PKU are higher than those of the control groups (19, 20). In our patient group, the obesity and overweight rates were found to be lower in both males and females than in the general population at both assessment periods. The reason for this result may be that the patients have acquired eating habits to achieve a more favourable body composition because of the special nutritional therapy. When the patients were grouped by sex, there was a decrease in anthropometric

measurements at the last assessment in both groups, and the z-score averages were within the healthy reference range at both assessments.

Grouping the patients according to disease classification, no difference was found in the WFH, WFA, HFA, and BMI of mPKU patients at the beginning and end of the follow-up period. In patients diagnosed with cPKU, a decrease was found in the mean WFH, WFA, HFA, and BMI z-scores at the last evaluation. The rate of obesity and overweight is below the Turkish mean rates (13, 14). In both the mPKU and cPKU groups, the mean and median values of WFH, WFA, HFA, and BMI z-scores during the first and second assessments were within the reference range considered normal. It has been reported that patients with cPKU have a significantly higher BMI than healthy controls (1). One reason for this is that more calories may be given to patients with cPKU to prevent catabolism, which causes higher blood Phe levels (1). This can lead to overweight development (1).

Studies assessing the prevalence of overweight and obesity in patients with PKU have reported different results (21-23). One of the reasons for these different results is that the studies were conducted with patient groups living in cultures with different dietary habits. Different treatment and follow-up principles of different centres may have caused such a result. Another reason is that changes in body composition that may occur during puberty may not be considered in the patient groups in the studies. In addition, caution should be taken when interpreting the results because of the different criteria used to classify overweight and obese individuals in the studies.

A comparison of the BMI z-scores of the patients revealed a shift in the distribution of BMI categories between the first and second assessments. A total of 14 patients were reclassified into a higher BMI category at the second assessment. A total of 23 patients were reclassified as belonging to a lower BMI group at the second assessment. This once again demonstrated the necessity of close follow-up of patients in terms of the results of special nutritional therapies.

The limitations of our study are that it did not include physical activity levels, dietary habits, Phe levels, which determine the metabolic control of the disease, and other parameters that provide information about body composition.

CONCLUSION

Monitoring anthropometric measurements and changes in body composition in all groups of patients receiving specific nutritional therapies is essential to determine and monitor treatment efficacy. In both evaluations of our patient group, the rates of overweight and obesity

were found to be low compared with the general population. This can be explained by the fact that researchers closely monitored patients by assessing their nutritional treatment and changes in body composition at each outpatient clinic visit. Multicenter studies with more advanced methodologies are needed to properly address the issues and guide clinical practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the İstanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 22.09.2023, No: 19).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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