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RESEARCH ARTICLE

Metabolic Syndrome and Type 2 Diabetes Mellitus in Overweight and Obese Children: A Single Centre Experience

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ABSTRACT

Objective: Childhood obesity is associated with various risks, including insulin resistance, type 2 diabetes mellitus (DM), hypertension, and metabolic syndrome (MetS). This study evaluated MetS and type 2 diabetes mellitus (DM) in overweight and obese children.
Methods: Between 2000 and 2013, 474 obese and overweight children aged <18 years were included in this study. The clinical characteristics of the patients with MetS and type 2 DM were evaluated.
Results: Of the patients, 50.4% (n = 239) were girls, and the mean age was 10.91±3.06 years. According to the body mass index, 20.5% (n=97) of the patients were overweight and 79.5% (n=377) were obese. Blood pressure, striae, and acanthosis nigricans were significantly higher in the obese group than in the overweight group (p <0.05). MetS was found in 30.8% (n=146) of the patients. The MetS rate was 37.7% (n=142) in the obese patients and 4.1% (n=4) in the overweight patients, and the difference between them was statistically significant (p<0.001) Based on the oral glucose tolerance test; 45 (9.5%) patients had impaired fasting glycaemia, 24 (5%) had impaired glucose tolerance and 4 (0.84%) had type 2 DM. One patient with normal glucose balance at admission, who was diagnosed with type 2 DM in the 4th year, was overweight and had a family history of diabetes, hyperinsulinemia, and high HOMA-IR.
Conclusions: The results of our study showed that both obese and overweight children are at risk of developing MetS and type 2 DM, particularly in the presence of risk factors. Close monitoring of these children is important to prevent complications.

Keywords: Childhood obesity, overweight, metabolic syndrome, type 2 diabetes mellitus

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INTRODUCTION

Obesity is defined by the World Health Organisation (WHO) as the unusual or excessive buildup of body fat tissue to the extent that it impairs health. Obesity, caused by genetic, environmental, metabolic, and hormonal factors, is a metabolic condition that can result in social, psychological, and medical complications (1). As 40 million children under the age of five were overweight as of 2011, the WHO prepared a global strategy plan to prevent and control obesity in the period 2008-2013, but by 2020, a total of 39 million children <5 years of age and 340 million children and adolescents between the ages of 5 and 19 years are obese or overweight.

The prevalence of obesity varies among countries. In the UK, an increase from 9.9% to 14.4% among 4-5 year olds and from 21% to 25.5% among 6 year olds was observed when comparing 2019/20 and 2020/21 school children (2). In Egypt, approximately one in six (17%) of 42,568 children under 5 years of age were overweight or obese. Severe obesity in children also increased 1.7-fold in a study comparing 2006-2017 and 1967-2007 (3). According to the Turkey Demographic and Health Surveys (TDHS), the rate of overweight increased from 5.3% in 1998 to 11.6% in 2013 (4). In a study in Turkey, 14.3% of children aged 6-10 were overweight and 6.5% were obese (5). In 2016, 9.9% of 7-8 year-olds were overweight and 14.6% were obese; in 2017, 19.5% of 10-14 year-olds were overweight and 10.5% were obese, and 15% and 5.6% of 15-18 year-olds were obese (6,7).

Childhood obesity is associated with various risks, including insulin resistance, type 2 diabetes mellitus (DM), hypertension, fatty liver disease, metabolic syndrome (MetS), and subclinical atherosclerosis, in early adulthood (1,8-11). Although there is no clear international definition of MetS for children and adolescents, obesity is an important cardiovascular risk factor associated with other metabolic problems. Considering that obesity is also an important risk factor for the development of type 2 diabetes and possible complications of MetS in children, the prevention of obesity at an early age is important in terms of complications that may develop and ensure a healthy adult life (12,13). In this study, we aimed to assess the prevalence of MetS and type 2 DM among overweight and obese children and identify the risk factors associated with these conditions. Additionally, we highlighted the shifts in the glucose balance that occurred during follow-up.

MATERIALS AND METHODS

Participant

This retrospective cohort study included 474 patients aged <18 years who were referred to the Department of Paediatric Endocrinology, Istanbul University Faculty of Medicine, between 2000 and 2013 with complaints of overweight and obesity. Patients with diseases, those taking medications that may affect body weight, or those with genetic syndromes were excluded. The demographic, physical examination, and laboratory data of the patients were retrospectively evaluated by analysing their medical records at admission, 6 months, and annually.

Definitions

According to Body Mass Index (BMI), overweight was defined 85-95 p (+1 and +2 SDS), and obesity was defined as >95 percentile (>+2 SDS). The WHO Health Organisation criteria adapted for children were used to define MetS (8). According to the defined criteria, patients with and without MetS in the patient population were compared in terms of demographic characteristics, physical examination results, and laboratory findings.

Definition of MetS (8)**;**

Three or more of the following;

- BMI> 95th p
- Abnormal glucose homoeostasis: Any of the following; a- fasting hyperinsulinemia; b- impaired fasting glucose; c- impaired glucose tolerance
- Hypertension: Systolic blood pressure (BP)> 95th p
- Dyslipidemia: Any of the following; a- high triglycerides [>105 mg/dL, <10 y; 136 mg/dL 10 y]; b- low HDL-cholesterol <35 mg/dL; c- high total cholesterol >(95th p)

Hyperinsulinism was defined based on the puberty stage. Impaired fasting glycaemia (IFG), Impaired Glucose Tolerance (IGT), and type 2 DM were defined according to the American Diabetes Association criteria (ADA) (8,14).

Abnormal glucose homoeostasis;

• Hyperinsulinism	Prepubertal> 15 mU/L Post-pubertal >20 mU/L
• IFG	Fasting plasma glucose (FPG) 100-126 mg/dL
• IGT	2nd hour glucose 140-199 mg/dL on the oral glucose tolerance test (OGTT).
• Type 2 DM	FGF > 126 mg/dL or 2nd hour plasma glucose 200 mg/dL on OGTT or plasma glucose level (random) 200 mg/dL or HbA1C >6.5%

HOMA-IR (homeostasis model assessment for insulin resistance: FPG (mg/dL)×fasting insulin level (µU/ml) /405) limit values above 2.16 and 5.2 in prepubertal/pubertal boys and above 2.22 and 3.83 in prepubertal/pubertal girls have been defined as insulin resistance (15).

The obese and overweight groups were compared in terms of demographic characteristics, physical examination results, laboratory results, frequency of metabolic syndrome, and differences in abnormal glucose balance.

Ethics committee

This study was approved by the Ethics Committee of Istanbul University, Faculty of Medicine on 02.10.2013 (File No:2013/1245). This article is based on my thesis entitled "Prevalence of Metabolic Syndrome and Type 2 Diabetes in Children with Exogenous Obesity", which was conducted under the supervision of Rüveyde Bundak at Istanbul University in 2014.

Statistical analysis

Statistical data were analysed using SPSS version 15 (SPSS Inc, Chicago, IL, USA). In addition to descriptive statistical methods (mean, standard deviation, etc.), the chi-square test and Fisher's exact test were used for categorical variables, and the Student's T-test and Mann-Whitney U test were used to compare means between the two groups. The results were evaluated at a 95% confidence interval (CI), and significance was set at $p<0.05$.

RESULTS

In total, 474 obese and overweight patients were included in this study. Of the patients, 50.4% (n:239) were girls and the mean age at presentation was 10.91±3.06 (0.90-17.20) years. The mean age of girls was 10.86±3.12 (0.9-17.5) years and the mean age of boys was 10.97±3.00 (1.25-17.2) years, and there was no statistically significant difference between them in terms of age. According to birth weight for gestational age; 88,6% (n=420) were appropriate for gestational age (AGA), 10.5% (n=50) were large for gestational age (LGA) and 0,84%(n=4) were small for gestational age.

Comparison of the obese and overweight groups

According to the BMI, 20.5% (n=97) of the patients were overweight and 79.5% (n=377) were obese. In the obese group, age was significantly younger (p=0.008), birth length was longer (p=0.041), and paternal weight was higher (p=0.033) than in the overweight group. The blood pressure percentiles (p=0.027), striae (p=0.002), and acanthosis nigricans (p=0.005) were significantly higher in the obese group. The FPG levels were significantly lower in the overweight group than in the obese group (p=0.027). There were no statistically significant differences between the other characteristics, physical examination results, and laboratory findings (Table 1).

Metabolic syndrome

MetS was found in 30.8% (n = 146) of the patients. The MetS rate was 37.7% (n = 142) in the obese patients and 4.1% (n = 4) in the overweight patients, and the difference between the two groups was statistically significant (p = 0.0001). Among the patients with MetS, 52.7% (n = 77) were girls, and the mean age was 11.30±2.82 (4.6-16.5) years. The incidence of heart disease in the family was significantly higher (p=0.014) in the MetS group; however, there were no statistically significant differences in terms of other parameters (Table 2).

Among the patients, 71.4% (n = 100) had dyslipidemia, 23.7% (n = 33) had high cholesterol, 55.7% (n = 78) had high triglycerides, 19.8% (n = 26) had low HDL cholesterol, 61.6% (n =90) had BP > 97p, 97.3% (n = 142) had BMI >95p, 91.1% (n = 133) had hyperinsulinemia, and 83.2% (n = 109) had high HOMA-IR levels (Figure 1).

Table 1. Family/medical history and laboratory parameters in obese and overweight children (mean±SD or N/%)

	Obese	Overweight	P
Age (year)	10.75±3.18	11.54±2.43	**0,008**
Sex Girl	198 (52.5)	41 (42.3)	0.072
Boy	179 (47.5)	56 (57.7)	
Birth weight (gr)	3429.10±640.5	3464.79±543.3	0.058
Birth height (cm)	50.83±2.5	49.91±3.0	**0,041**
Prematurity	24 (6.4)	4 (4.2)	0.403
CS	165 (45)	37 (37.4)	0.329
Maternal BMI (kg/m2)	31.63±9.8	32.50±9.05	0.389
Paternal BMI (kg/m2)	32.78±14.1	29.37±4.7	0.295
Paternal weight (kg)	93.6±17.04	85.19±13.5	**0.033**
Family history			
Obesity	205 (54.8)	47 (48.5)	0.263
Type 2 DM	133 (35.6)	37 (38.1)	0.637
Hypertension	62 (16.6)	14 (14.4)	0.602
Heart disease	19 (5.1)	3 (3.1)	0.590
Hyperlipidaemia	15(4)	8 (8.2)	0.109
Physical examination			
Acanthosis nigricans	72 (19.1)	7(7.2)	**0.005**
Striae	73 (19.4)	6(6.2)	**0.002**
BP >95 percentile	122 (32.4)	20(20.8)	**0.027**
Pubertal	188 (49.9)	41(42.3)	0.624
Prepubertal	189 (50.1)	56(57.7)	
Laboratory			
FPG (mg/dL)	90.30±10.7	84.40±14.62	**0.027**
Hyperinsulinemia	212 (59.4)	47 (52.2)	0.216
High HOMA-IR	193 (60.1)	34 (44.7)	**0.015**
High Cholesterol	47 (13.6)	17 (19.8)	0.152
HDL-cholesterol	48.39±16.2	54.45±14.4	**<0.001**
LDL- cholesterol	95.95±31.09	101.08±34.82	0.326
Hypertriglyceridaemia	120 (34.6)	22 (26.2)	0.142
Hepatosteatosis	47 (12.8)	8(8.2)	0.514

NSVD: normal spontaneous vaginal delivery, CS: Caesarean section, DM: diabetes mellitus, BMI: body mass index SDS: standard deviation score NS: non-significant, BP: blood pressure, FPG: fasting plasma glucose

Table 2. Comparison of family medical history and physical examination between the groups in MetS+/- (mean±SD or N/%)

	MetS+	MetS-	p
Age (year)	11.03±2.91	10.85±3.13	0.544
Sex Girl	77 (52.7)	162 (49.4)	0.501
Boy	69 (47.3)	166 (50.6)	
Birth weight (gr)	3403.82±632.74	3452.9±614.91	0.442
Birth height (cm)	50.76±2.61	50.55±2.7	0.570
Prematurity	9 (6.3)	19 (5.8)	0.865
CS	60 (42.6)	142 (44.4)	0.716
Maternal BMI (kg/m2)	32.09±9.5	31.66±9.8	0.820
Paternal BMI (kg/m2)	30.49±6.4	32.83±14.99	0.339
Gestational DM	2 (1.4)	6 (1.9)	0.999
Family history			
Obesity	81 (55.5)	171 (52.6)	0.564
Type 2 DM	55 (37.7)	115 (35.4)	0.633
Hypertension	29 (19.9)	47 (14.5)	0.144
Heart disease	12 (8.2)	10 (3.1)	**0.014**
Hyperlipidaemia	8 (5.5)	15 (4.6)	0.687
Physical examination			
BMI SDS	2.49±0.76	2.49±0.76	**<0.001**
BP>95 percentile	53 (16.2)	53 (16.2)	**<0.001**
Acanthosis nigricans	47 (14.3)	47 (14.3)	**0.041**
Striae	45(13.7)	45(13.7)	**0.010**

BP: blood pressure, BMI: body mass index, SDS: standard deviation score, CS: Caesarean section, DM: diabetes mellitus

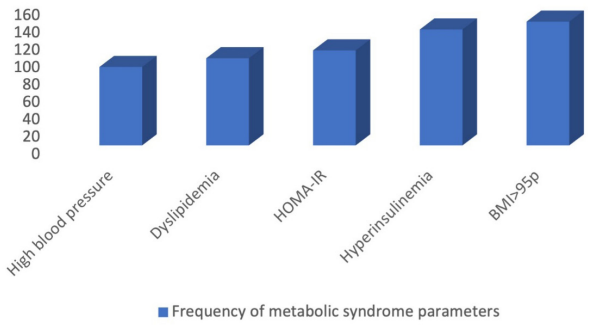

Figure 1: Frequency of metabolic syndrome parameters

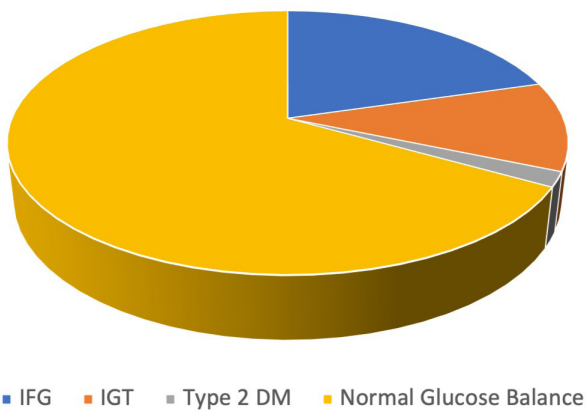

Figure 2: Distribution of glucose homeostasis

Comparison of physical examination and laboratory parameters between the MetS and non-MetS groups

Physical examination and laboratory parameters of the two groups at admission at 6th month, 1st year and 2nd year were compared (Table 3). BMI SDS, BP >95p, acanthosis, striae, FPG, HOMA-IR, insulin, total cholesterol, triglycerides, and LDL-cholesterol were significantly higher in the MetS group. In the 6th month of follow-up, BMI, SDS, and total cholesterol were significantly higher, and HLD-cholesterol was significantly lower in the MetS group. In the 1st year, BMI SDS, LDL-cholesterol, and HOMA-IR were statistically significantly higher in the MetS group.

Type 2 DM

OGTT was performed in 220 patients at the first presentation. According to the OGTT and FPG results, 45 (9.5%) patients had IFG, 24 (5%) had IGT, and four (0.84%) had type 2 DM (Figure 2).

IFG-IGT-type 2 DM was found in the obese (8.4%-6.3%-0.8%) and overweight (15.2%-1.1%-1.1%) groups, with no statistically significant difference between the two groups. In the patients who had type 2 DM, it was observed that two patients had a family history of type 2 DM and one patient had a history of low birth weight.

The incidences of IFG and IGT were significantly higher in the MetS group (11.7% and 11%, respectively) than in the non-MetS group (8.9% and 2.5%) (p<0.001).

Changes in glucose balance during follow-up

Among patients with normal glucose balance at admission (n = 387), IGT was found in three patients in the 2nd year, one

Table 3. Comparison of physical examination and laboratory parameters between the groups in MetS+/- (mean± SD or n/%)

	First examination			6th month			1st year		
	MetS+	MetS-	p	MetS+	MetS-	p	MetS+	MetS-	p
BMI SDS	2.86±0.7	2.49±0.76	**<0.001**	2.59±0.70	2.32±0.75	**0.001**	2.62±0.8	2.32±0.83	**0.017**
BP>95 percentile	90 (61)	53 (16.2)	**<0.001**	14 (38.9)	22 (6.7)	0.059	12(42.9)	27 (8.2)	0.064
Acanthosis nigricans	32 (21.9)	47 (14.3)	**0.041**	10(17.9)	14(4.3)	0.623	6(12.2)	16(4.9)	0.702
Striae	34 (23.3)	45(13.7)	**0.01**	10(17.9)	12 (3.7)	0.075	5(10.2)	15(4.6)	0.563
FPG (mg/dL)	93.1±11.2	89.89±10.1	**0.047**	91.97±8.95	91.85±7.9	0.403	88.86±12.4	88.89±11.8	0.673
Insulin (µU/ML)	26.6±12.04	17.4±13.4	**<0.001**	20.6±11.64	17.18±11.9	0.455	25.9±26.07	18.46±13.3	0.901
HOMA-IR	5.79±3.12	3.87±2.97	**<0.001**	4.63±2.52	3.86±2.72	0.067	6.15±7.2	4.31±3.4	0.045
Total-c (mg/dL)	175.8±37.7	168±78.3	**0.002**	164.55±26.8	168.48±39.4	0.681	180.79±35.62	167.13±32.1	0.367
Triglycerides (mg/dL)	139.7±67.6	103.95±54.8	**<0.001**	147.7±84.4	106.9±58.1	**0.026**	127.09±58	109.6±56.3	0.098
HDL-c (mg/dL)	45±11.1	50.9±13.2	**<0.001**	42.15±8.7	52.3±14.3	**0.02**	44.58±9.03	51.2±16.7	0.061
LDL-c (mg/dL)	103.34±36.4	95±29.7	**0.034**	98.45±32.4	92.52±33.46	0.516	106.96±26.4	93.2±26.02	**0.027**

c:cholesterol, FPG: fasting plasma glucose, BP: blood pressure, BMI: body mass index, SDS: standard deviation score

patient in the 3rd year, type 2 DM in two patients, and IFG in one patient in the 4th year (Table 4).

The patient diagnosed with type 2 DM in the 4th year was overweight and had a family history of diabetes, hyperinsulinemia, high HOMA-IR, and Polycystic Ovary Syndrome.

Table 4. IFG/IGT/Type 2 DM during follow-up (N/%)

	Type 2 DM	IGT	IFG	NGB	Total (n)
First examination	4 (0.84)	24 (5.06)	45 (9.5)	401 (84.6)	474
6**th** month	-	1 (0.9)	-	114 (99.1)	115
1**st** year	1 (0.8)	4 (3.2)	3 (2.4)	116 (93.5)	124
2**nd** year	1 (1.1)	3 (3.3)*	2 (2.2)	84 (93.3)	90
3**th** year	-	1 (1.5)*	1 (1.5)	63 (96.9)	65
4**th** year	1 (1.9)*	-	2 (3.9)*	48 (94.1)	51

IGT: Impaired glucose tolerance, IFG: Impaired fasting glucose, NGB: Normal glucose balance, DM: Diabetes Mellitus**,** * newly diagnosed patients

DISCUSSION

In this study, the prevalence of MetS was 30.8%, and it was shown to occur not only in obese individuals but also in overweight individuals. Type 2 DM has also been reported to develop during follow-up in the presence of risk factors.

The prevalence of MetS varies according to the criteria used and from community to community. Attempts have been made to modify and adapt the criteria used by adults for children. However, because blood pressure, lipid levels, and insulin levels change with puberty and age in children, there are problems with this definition. In a study of children aged 6-18 years, the prevalence of MetS in children aged 10 years was 14.3%-3.7% in obese and overweight children according to the International Diabetes Federation (IDF) 2007 criteria and 32.3%-8.4%; according to The National Cholesterol Education Programme's Adult Treatment Panel III (NCEP ATP) criteria. The prevalence of MetS in children aged less than 10 years was higher in the obese than in the overweight (16). Waist circumference, glucose, triglycerides, insulin, and HOMA-IR levels were higher and high-density lipoprotein (HDL) cholesterol levels were lower in the obese group than in the normal weight group. Between the ages of 10-18 years, 8.1% of the children were overweight, 9.2% were obese, 4.4% had MetS, and 43.9% had at least one component of MetS (17). The prevalence of MetS was found to be 28.7% by Cook et al., 38.7% by Weiss et al., and 38.7% by De Ferranti 10% and has been reported to increase 3-5-fold during puberty (18-20). In a study in Turkey, MetS was significantly more common in obese children than in overweight children and significantly more common in adolescents than in preadolescents (21). We also found that it was significantly higher in obese patients; however, no significant difference was observed in terms of puberty. In different studies in our country, the MetS rate was found to be 39%, 56.4%, and 38.8% according to the modified

WHO criteria (22-24) and a 1-point increase in BMI doubled the prevalence of MetS by two times (25).

A meta-analysis showed that the risk in children increased with the presence of MetS in parents (26). Children with a family history of diabetes and/or hypertension have a 4.7 times higher risk for MetS than those without a family history (27). In our study, the prevalence of heart disease in the family was found to be statistically significantly higher in the MetS group.

Acanthosis nigricans and striae are the manifestations of MetS. Acanthosis nigricans is used in the clinical evaluation of laboratory-proven insulin resistance, and the risk of type 2 diabetes is increased in those who are positive (28).

Children affected by obesity due to acanthosis nigricans were twice as likely to develop MetS after adjusting for sex, ethnicity, and strata (29). Additionally, serum insulin and HOMA-IR levels, which are parameters of MetS, were higher in obese children with acanthosis nigricans (30). We also found that the incidence of acanthosis nigricans was significantly higher in both the obese and MetS groups.

There is no consensus on the cutoff value for HOMA-IR in children. In a cohort study investigating metabolic proliferation and insulin resistance at the age of 6 years, when HOMA-IR ≥1.93, insulin resistance was significantly higher in obese/overweight children and 26% had at least one risk factor for MetS (31). In our study, HOMA-IR and FPG levels were significantly higher in obese children than in overweight children and in children with MetS than in those without MetS. The incidence of IFG-IGT was significantly higher in the MetS group (11.7% -11%) than in the non-MetS group (8.9%-2.5%). Insulin resistance is a known risk factor in later stages; although it can be reversible in the early stages, it can cause irreversible damage if left untreated. Morrison et al. found that 10-year-old girls diagnosed with both MetS and hyperinsulinemia had a higher frequency of progression to type 2 DM, 14 years later (32). Although many factors contribute to the development of type 2 DM, in a meta-analysis, the prevalence of type 2 DM in children was 75.27%, and obesity was found to be an important risk factor (33). The intermediate stages in the progression from normal glucose tolerance to type 2 DM include impaired fasting glucose and glucose tolerance. The factors-underlying the development of an abnormal glucose balance are multifactorial. In a multicenter study, the prevalence of IFG and IGT in obese children was 15.2%, hyperinsulinism was 57.1%, and 25% of children with type 2 DM had a family history of type 2 DM (34). A study found a high conversion rate of 27% from IGT to type 2 DM within an average of 1.7 years and 10% from normal glucose tolerance to type 2 DM within 2.5 years after the detection of abnormal glucose metabolism in obese adolescents, which was associated with BMI, severity of insulin resistance, and presence of non-alcoholic fatty liver disease (NAFLD) (35). In our case, we observed that an overweight girl with hyperinsulinemia developed type 2 DM in the 4th year.

The limitations of our study are that it was a retrospective and single centre study with some patients with a long-term follow-up. The WHO Health Organisation criteria adapted for children were used to define MetS. The WHO criteria adapted for children were used to define MetS, rather than the IDF 2007 criteria (36), because this consensus also suggests that MetS should not be diagnosed in children under 10 years of age and also because some of the patients in this retrospective study had missing waist circumference measurements.

In conclusion, both obese and overweight individuals are at risk for MetS and type 2 DM, and type 2 DM may develop during follow-up, even if not at admission. Considering that the foundations of many diseases encountered in adulthood are laid in childhood, attention should be paid to the warning signs of obesity and its complications and preventive measures should be taken.

Ethics Committee Approval: This study was approved by the Ethics Committee of Istanbul University, Faculty of Medicine (02.10.2013, File No:2013/1245).

Informed consent: The study was conducted retrospectively and was designed as an archived review of the files of all patients; it was neither necessary nor possible to acquire informed consent from the patients.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- R.B. ,A.D.; Data Analysis/Interpretation- A.D., .Ş.P; Drafting Manuscript- A.D.; Critical Revision of Manuscript- Ş.P., R.B.; Final Approval and Accountability A.D., Ş.P., R.B.

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