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NEW DIAGNOSTIC TEST WITH ACUTE APPENDICITIS FOR CHILDREN

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Abstract:
In the diagnosis of acute appendicitis, the most frequently-applied laboratory tests are blood leukocyte level (WBC) and serum C-reactive protein (CRP). In recent years, it has been thought that the leptin hormone level, which has been proven to be raised in acute inflammation, could be used diagnostically in patients with acute appendicitis.
In this study, we aimed to determine the relationship between WBC, CRP, and leptin levels with inflammation in acute appendicitis and to define the role of leptin in the mechanism underlying loss of appetite, which is the most frequently observed symptom.
The study comprised 40 patients diagnosed with acute appendicitis (AA) in the Pediatric Surgery Department and a control group of 20 age-matched patients. Blood samples were taken from all subjects in both groups and the levels of WBC, CRP and leptin were measured. Body mass index was calculated and all findings were compared.
In the AA group, the median leptin value was measured as 1.24 ng/ml preoperatively, 1.37 ng/ml peri-operatively, and 0.81 ng/ml 2 days postoperatively. The leptin value in the control group was 1.90 ng/ml. No statistically significant difference was found between the two groups with respect to the preoperative and perioperative leptin values ($p>0.05$). The postoperative 2nd day leptin values of the AA group were statistically significantly lower than those of the control group ($p<0.05$).
In cases of suspected acute appendicitis, leptin can be a useful diagnostic parameter since its levels increase during the early stages of inflammation.
Keywords: *Acute appendicitis; Inflammation; Leptin*

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1.0INTRODUCTION:

Acute appendicitis in childhood requires emergency surgery. Although the patient's history, physical examination, and laboratory tests are used in diagnosis, it can be complicated to make a conclusive diagnosis in every case. In addition, assistive diagnostic methods are being developed and new research is ongoing to reduce the rates of negative appendectomy and perforation. Laboratory tests are frequently used in the diagnosis of acute appendicitis. Currently, the most commonly-used of these tests are measurements of blood leukocyte (WBC) and serum C-reactive protein (CRP) levels. However, just as the results of these tests could also reach high levels in several similar diseases, normal values are insufficient to discount a diagnosis of acute appendicitis. Another criterion for diagnosis is the symptomology of the patient. A loss of appetite is prominent within this symptomology and is present in most acute appendicitis patients. The leptin hormone is known to have an effect on the development of loss of appetite by affecting the hypothalamus, which reduces appetite (Ayangil, Dorterler and Turan, 2016).

Leptin is a hormone expressed from fat tissue cells that plays an important role in natural and acquired immunity. In cases of infection and inflammation, the leptin levels of the host increase and show an anti-inflammatory effect. In addition to tumor necrotizing factor alpha (TNF-a), interleukin 1 (IL–1), and interleukin 6 (IL–6) in anorexia, the increasing leptin level observed during infections is believed to be expressive (Eric, 2008).

The aim of this study was to determine the relationship between WBC, CRP, and leptin levels with inflammation in cases of acute appendicitis, and to define the role of leptin in the mechanism underlying loss of appetite, which is the most frequently-observed symptom (Ayangil, Dorterler and Turan, 2016).

MATERIAL AND METHODS:

The study comprised 40 patients diagnosed with acute appendicitis in the Pediatric Surgery Department - the acute appendicitis group (AA) - and 20 age-matched children as a control group. The AA group had a mean age of 7.3 years (range: 2-10 years) and included patients considered to have acute appendicitis according to their medical history, as well as to clinical and ultrasonography (USG) examinations, and whose diagnosis was confirmed macroscopically during surgery. Patients were excluded from this group if they were considered to have acute appendicitis clinically and on USG, but were not confirmed by surgery, or if they were found to have another inflammatory disease as well as appendicitis (Ayangil, Dorterler and Turan, 2016). The control group had a mean age of 5.6 years (range: 2-10 years) and included patients who presented at the Pediatric Surgery Polyclinic complaining of constipation but who displayed no inflammatory disease on physical examination, or clinically at the time of enrolment into the study, or in the anamnesis (Ayangil, Dorterler and Turan, 2016).

Method

Patients in the AA group who presented at the Pediatric Emergency Polyclinic complaining of abdominal pain and who were considered to have acute appendicitis clinically and from their medical history, had a 10 cc venous blood sample withdrawn into a sterile biochemistry tube to allow the serum leptin and CRP levels to be examined and a 1ml sample withdrawn into an ethylenediaminetetraacetic acid (EDTA) tube to examine the WBC level at the time of presentation. Hen, a standing direct radiograph and abdominal USG were performed. Findings supporting a diagnosis of acute appendicitis were defined as an appendix of diameter>6 mm, target sign, distension or obstruction in the appendix lumen, thickening of the appendix wall>2 mm, loss of peristalsis in the appendix, free fluid in the surroundings, or fecalith in the appendix, and surgery was subsequently planned for these patients.

For the subjects in the control group, a blood sample was taken only once for the measurement of WBC, leptin, and CRP and these were stored in the same manner as before. Body mass index (BMI) was calculated for all patients in the AA and control groups, and the BMI values were compared with those of healthy children aged 2-10 years.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows Software with SPSS 18.0. A value of $p<0.05$ was accepted as statistically significant. Conformity to a normal distribution of continuous quantitative variables was examined with the Kolmogorov-Smirnov test. Data with a normal distribution were provided as means ± standard deviation (SD). To determine the dissimilarities between the two groups, Student's t-test was applied.

To assess divergence between time periods (preoperative, perioperative, postoperative), a repeated variance analysis was used.
Quantitative data not conforming to a normal distribution, such as CRP and leptin, were provided as median values (min-max). The Mann-Whitney U test was applied to determine the divergence between the two groups. The Friedman test was used to assess differences according to time period; to determine from which time period the differences originated, the Mann Whitney U-test was used with Bonferroni correction applied. The relationship between variables was examined by calculating the Spearman correlation coefficient and a regression curve was plotted. Qualitative data were provided as percentages. The Chi-square test was applied to assess difference between the two groups. When calculating the sensitivity and particular of the CRP and leukocyte values in the diagnosis of acute appendicitis, the standard formulae below were used:

Sensitivity=real positive/ (real positive + false negative) × 100 and
Specificity \ real positive/ (real negative + false positive) × 100

RESULTS:

The patients in the AA group comprised 27 (67.5%) males and 13 (32.5%) females, with a mean age of 7.3 ± 2.5 years, a mean body weight of 25.9 ± 9.1 kg, and a BMI of 17.1 ± 2.5 kg/m2. The patients in the control group comprised 15 (75%) males and 5 (25%) females, with a mean age of 5.6 ± 2.1 years, mean body weight of 20.2 ± 6.2 kg and a BMI of 16 ± 1.5 kg/m2. No statistically prominent difference was determined between the two groups in respect of BMI (p>0.05) mentioned in below Table 1.
The mean duration of a loss of appetite was determined as 37.6 ± 33.8 hours.

	Group I (AA) n=40 (x ± sd)	Group II (Control) n=20 (x ± sd)	t	p
Age (yr)	7.3 ± 2.5	5.6 ± 2.1	2.4	0.01
Weight (kg)	25.9 ± 9.1	20.2 ± 6.2	2.4	0.01
Height (cm)	121.4 ± 17.9	110.9 ± 12.7	2.3	0.02
BMI (kg/m^2)	17.1 ± 2.5	16 ± 1.5	1.6	0.1

Table 1: Age, weight, height, and BMI variables of the groups.

Source: Ayangil, Dorterler and Turan (2016)

Of the patients diagnosed with acute appendicitis, the appendix was found to be perforated in 26 (65%) cases and not perforated in 14 (35%). The mean body weight of the patients with a perforated appendix was determined as 23.5 ± 8.3 kg, the mean BMI as 16.6 ± 2.0 kg/m2, and the mean duration of the loss of appetite as 48.9 ± 36.7 hours. In patients with a non-perforated appendix, the mean body weight was determined to be 30.4 ± 9.2 kg, the mean BMI as 18.0 ± 3.3 kg/m2, and the mean duration of loss of appetite as 16.9 ± 11.7 hours.

	Perforated appendix n = 26 (x ± sd)	Non-perforated appendix n = 14 (x ± sd)	t	p
Age (yr)	6.9 ± 2.6	8.0 ± 2.3	1.2	0.2
Weight (kg)	23.5 ± 8.3	30.4 ± 9.2	2.4	0.02
Height (cm)	117.4 ± 19.2	128.9 ± 12.8	1.9	0.06
BMI (kg/m^2)	16.6 ± 2.0	18.0 ± 3.3	1.7	0.1
Loss of appetite (h)	48.9 ± 36.7	16.9 ± 11.7	3.1	0

Table 2: Distribution of variables between the two groups according to the appendix perforation status.

Source: Ayangil, Dorterler and Turan (2016)

The body weight of the children with perforated appendices was lower than those with non-perforated appendices and the duration of the loss of appetite was longer. These differences were determined to be statistically sufficient (p0.05) (Table 2) as mentioned above.

The WBC values of the patients were measured as 17,280 ± 5,009 mm^3 preoperatively, 162, 09 ± 4,258 mm^3 peri-operatively, and 11,362 ± 2,876 mm^3 on the 2nd day postoperatively. In the control group, the WBC value was measured as 7,697 ± 1,559 mm^3. The WBC values of the patient group were prominently higher than those of the control group and the difference was determined to be statistically significant ($p < 0.05$) according to Table 3 below:

	Group I (AA) n = 40 (x ± sd)	Group II (Control) n = 20 (x ± sd)	t	p
Preoperative WBC	17,280 ± 5009	7,697 ± 1559	8.3	0
Perioperative WBC	16,209 ± 4258	7,697 ± 1559	8.6	0
Postoperative Day 2 WBC	11,362 ± 2876	7,697 ± 1559	5.3	0

Table 3: Distribution of WBC values.

Source: Ayangil, Dorterler and Turan (2016)

The WBC values of the patients with a perforated appendix were measured as 17,290 ± 5,284 mm^3 preoperatively, 16,425 ± 4,311 mm^3 peri-operatively, and 11,839 ± 3,023 mm3 on the 2nd day postoperatively. The WBC values of the patients with a non-perforated appendix were measured as 17,262 ± 4,645 mm^3 preoperatively, 15,807 ± 4,288 mm^3 peri-operatively, and 10,476 ± 2,435 mm3 on the 2nd day postoperatively. No statistically prominent difference was found in WBC values between the patients with a perforated appendix and those without ($p>0.05$) as mentioned in below Table 4.

	Perforated appendix n = 26 (x ± sd)	Non-perforated appendix n = 14 (x ± sd)	t	p
Preoperative WBC	17,290 ± 5,284	17,262 ± 4,645	0.1	0.98
Perioperative WBC	16,425 ± 4,311	15,807 ± 4,288	0.4	0.66
Postoperative Day 2 WBC	11,839 ± 3,023	10,476 ± 2,435	1.4	0.15

Table 4: Distribution of WBC values in patients with and without a perforated appendix.

Source: Ayangil, Dorterler and Turan (2016)

According to the description of Ayangil, Dorterler and Turan (2016) the median CRP value of the patients in the AA group was determined as 96.3 mg/L preoperatively, 107 mg/L peri-operatively, and 111 mg/L on the 2nd day postoperatively. The median value of the patients in the control group was 3.17 mg/L, which was within normal limits. The CRP values of the patients were prominently\ higher than those of the control group and the difference was determined to be statistically prominent ($p<0.05$) as mentioned in Table 5 below:

		Group I (AA) n = 40 median (min-max)	Group II (Control) n = 20 median (min-max)	p
CRP	Preoperative	96.3 (5.6-618)	3.17 (3.17-4.49)	0
	Perioperative	107 (2.9-331)	3.17 (3.17-4.49)	0
	Postoperative Day 2	111 (7.6-288)	3.17 (3.17-4.49)	0
Leptin	Preoperative	1.24 (0.01-21.23)	1.90 (0.35-4.52)	0.52
	Perioperative	1.37 (0.01-20.05)	1.90 (0.35-4.52)	0.94
	Postoperative Day 2	0.81 (0.01-9.30)	1.90 (0.35-4.52)	0.01

Table 5: Distribution of CRP and leptin values.

Source: Ayangil, Dorterler and Turan (2016)

The median CRP value of the patients with a perforated appendix was determined as 149.5 mg/L preoperatively, 133 mg/L peri-operatively, and 132 mg/L on the 2nd day postoperatively. The median CRP value of the patients with a non-perforated appendix was determined as 32.3 mg/L preoperatively, 37.4 mg/L peri-operatively, and 55.75 mg/L on the 2nd day postoperatively. The CRP values of the patients with a perforated appendix were found to be prominently\ higher than those of the patients with a non-perforated appendix ($p<0.05$) as mentioned in Table 06 below:

		Perforated appendix n = 26 median (min-max)	Non-perforated appendix n = 14 median (min-max)	p
CRP	Preoperative	149.5 (30–618)	32.3 (5.64–138)	0
	Perioperative	133 (4.13–331)	37.4 (2.98–142)	0
	Postoperative Day 2	132 (57.3–288)	55.75 (7.63–160)	0
Leptin	Preoperative	0.79 (0.01–13.0)	3.32 (0.01–21.23)	0
	Perioperative	0.97 (0.01–9.07)	3.18 (0.01–20.05)	0.04
	Postoperative Day 2	0.51 (0.01–3.42)	2.02 (0.21–9.30)	0

Table 6: CRP and leptin values in patients with and without a perforated appendix.

Source: Ayangil, Dorterler and Turan (2016)

The median leptin value of the patients in the AA group was determined as 1.24 ng/l preoperatively, 1.37ng/l peri-operatively, and 0.811 ng/l on the 2nd day postoperatively. The median leptin value of the patients in the control group was 1.9 ng/l. No statistically prominent difference was determined between the two groups in respect of the preoperative and perioperative leptin values ($p>0.05$). The postoperative 2nd day leptin value of the patients was found to be lower than that of the control group and the difference was determined to be statistically prominent ($p<0.05$) as mentioned above in Table 5.

The leptin value of the patients with a perforated appendix was determined as 0.79 ng/l preoperatively, 0.97 ng/l peri-operatively, and 0.51 ng/l on the 2nd day postoperatively. The leptin values of the patients with a non-perforated appendix were determined as 3.32 ng/l preoperatively, 3.18 ng/l peri-operatively, and 2.02 ng/l on the 2nd day postoperatively. The leptin values of the patients with a non-perforated appendix were prominently\ higher than those of the patients with a perforated appendix ($p<0.05$) as mentioned above Table 6.

A statistically prominent positive correlation was determined between BMI and leptin in both the patient and the control groups (r: 0.35, p: 0.02) as Regression Curve Figure 1 below.

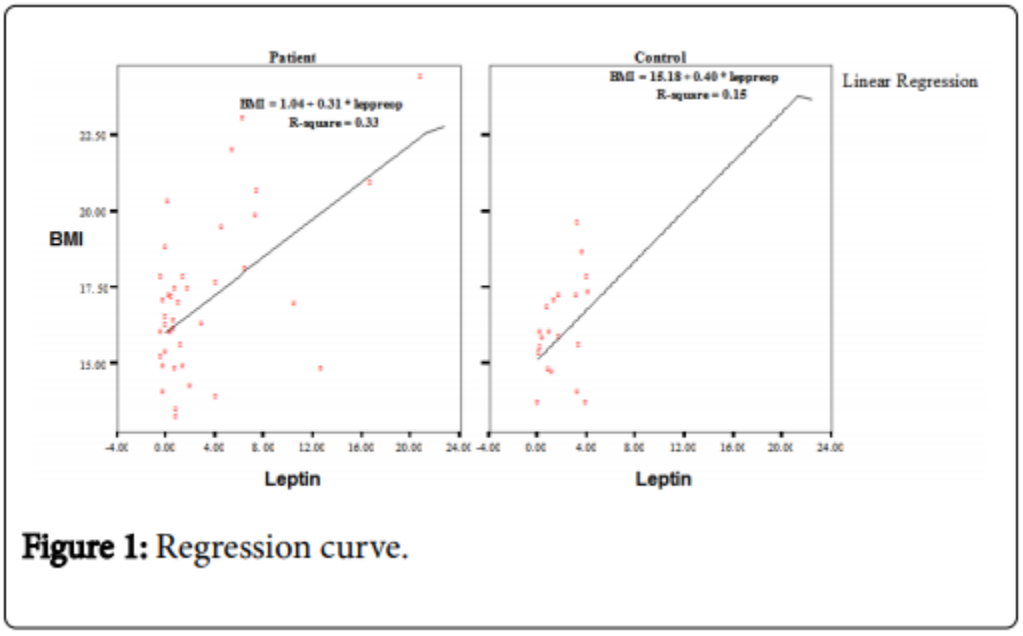

Figure 1: Regression curve.

Source: Ayangil, Dorterler and Turan (2016)

The WBC values were observed to decrease through the timed measurements preoperatively, peri-operatively, and 2 days postoperatively (17,280 mm^3, 16,209 mm^3 and 11,362 mm^3 respectively) and the divergence between the values was found to be statistically prominent (p0.05). The leptin values measured on the 2nd day postoperatively

were seen to be lower than the preoperative values (pre-operative 1.24 ng/ml, post-operative 2nd day 0.81 ng/ml) and the divergence was determined to be statistically prominent ($p<0.05$) as mentioned in below Table 7:

	Preoperative	Perioperative	Postoperative Day 2	p
	n=40	n=40	n=40	
WBC (x ± sd)	17,280 ± 5,000*bc	16,209 ± 4,258*ac	11,362 ± 2,876*ab	0
CRP median (min-max)	96.3 (5.64–618)	107 (2.98–331)	111 (7.63–288)	0.72
Leptin median (min-max)	1.24 (0.01–21.23)c	1.37 (0.01–20.05)c	0.81 (0.01–9.30)ab	0

Table 7: WBC, CRP, and leptin values measured at different times in the patient group. a: indicates a difference compared to the preoperative value, b: indicates a difference compared to the perioperative value, c: indicates a difference compared to the postoperative day 2 value, ∗: 0.05 was accepted as the level of statistical significance.

Source: Ayangil, Dorterler and Turan (2016)

DISCUSSION:

WBC and CRP are laboratory tests that are frequently applied to children suspected of having acute appendicitis. WBC, which increases in the early stages of the disease and before perforation occurs, has not been reported to show any statistically prominent difference between patients with perforated appendices and those without (Eric, 2008). However, the CRP level can reach a more expressively height, especially in acute appendicitis cases, which have a tendency to perforate or develop abscesses, and the measurement of CRP has been shown to provide more valuable data for patients with suspected acute appendicitis. The data obtained in the current study indicate a similar situation. Although no statistically effective difference was determined between patients with a perforated appendix and those with a non-perforated appendix in respect of the WBC values, the CRP values of patients with a perforated appendix were found to be higher than those of patients with a non-perforated appendix (Oestreich, 2011).

Serum leptin, which has been found in increased levels in experimental inflammation models, is another laboratory parameter that we investigated in the current study. Leptin is a hormone with a protein-like structure that contains 167 amino acids and resembles a cytokine. The primary role of leptin in the body is to reduce appetite via negative feedback to the hypothalamus region of the brain, to control food intake and, by regulating energy metabolism, to prevent the development of obesity. Leptin is known to play an exclusive role in natural and acquired immunity. It has been suggested that leptin is an important factor in the response to inflammation since the leptin level increases during inflammation and infection. Host anorexia is believed to be the acute phase response observed during the course of infections (Plus and Isaac, 2016).

In the current study, no statistically expressive difference was determined in preoperative and perioperative leptin values between the patients diagnosed with acute appendicitis and the control group. However, in the evaluation conducted within the patient group, the leptin values of the patients with a perforated appendix were observed to be higher than those of patients with a non-perforated appendix (Hamid, Mohamed and Salih, 2018).

When the data of postoperative 2nd day were examined, the leptin values of the patient group were determined to be expressively\ lowerthan those of the control group. There is known to be a positive correlation between BMI and leptin expression. In the current study, no statistically prominent difference was determined between the patient and control groups in BMI, nor between those patients with and without a perforated appendix. However, in both the patient and control groups a exclusively positive correlation between BMI and leptin was determined with a regression curve as referred in Figure 1 above. Of the 40 patients in the AA group, 3 had a BMI>95th percentile and were thus classified as obese (Plus and Isaac, 2016).

CONCLUSION:

In conclusion, leptin, which is initially defined as a satiety factor, is involved in the regulation of endocrine and immune functions in addition to energy regulation, and its acute increase as a result of stimuli, similar to other cytokines, shows that leptin is part of the acute phase inflammation response. The expression of leptin is increased due to the process of developing acute appendicitis. Due to the increase in leptin in the early phase of inflammation, it can be recommended as a useful diagnostic parameter in cases of suspected acute appendicitis. In addition, as the high level of leptin in a non-perforated acute appendicitis decreases together with perforation, it

can be useful in terms of identifying the course of the perforation.

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