ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Markers of Target Organ Damage in Children with Essential Hypertension

Esansiyel Hipertansiyonu Olan Çocuklarda Hedef Organ Hasarının Belirteçleri

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Abstract

Introduction: Hypertension (HT) is a common health problem that may cause target-organ damages (TOD). Our study aimed to investigate the clinical, laboratory and radiological findings associated with TOD.
Materials and Methods: The medical records of 102 patients diagnosed with essential HT were analyzed.
Results: A total of 102 patient were evaluated in this study. There was 53 girls (%52) and 49 boys (%48); the mean age was 13.7±1.97 years. Twenty-five patients (24.5%) were dipper and 77 (75.5%) were non-dipper. Sixty-three patients (64%) had single TOD, 22 (21.6%) had two TOD and 9 (8.8%) had three TOD. For obesity, there was a significant difference between patients without TOD and those with TOD in all groups. Serum uric acid, creatinine and sodium levels were significantly higher in all groups with TOD than those without TOD. Similarly, the WBC/lymphocyte ratio was significantly higher among the. RI values were higher in all groups with TOD.
Conclusion: The kidney is the first organ affected in essential HT and the earliest sign of TOD is microalbuminuria. Therefore, it may be possible to prevent other TOD that may occur if the kidney is well protected. In our study, the risk of developing TOD over time was found to be significantly higher in patients who did not have TOD at the time of diagnosis but had a high RI value. Reasonable adjustment of salt-protein balance and close monitoring of serum sodium, uric acid and creatine levels have prognostic importance in these patients.

Keywords
Essential hypertension, target organ damage, prognosis, child

Anahtar kelimeler
Esansiyel hipertansiyon, hedef organ hasarı, prognoz, çocuk

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Öz

Giriş: Hipertansiyon (HT), hedef organ hasarlarına neden olabilen yaygın bir sağlık sorunudur. Çalışmamız hedef organ hasarı ile ilişkili klinik, laboratuvar ve radyolojik bulguları araştırmayı amaçladık.
Gereç ve Yöntem: Esansiyel HT tanısı alan 102 hastanın tıbbi kayıtları analiz edildi.
Bulgular: Bu çalışmada toplam 102 hasta değerlendirildi. Elli üç kız (%52) ve 49 erkek (%48); ortalama yaş 13,7±1,97 yıl idi. Hastaların 25'i (%24,5) dipper, 77'si (%75,5) non-dipper idi. Altmış üç hastada (%64) tek hedef organ hasarı, 22 hastada (%21,6) iki hedef organ hasarı ve 9 hastada (%8,8) üç hedef organ hasarı vardı. Obezite için tüm gruplarda hedef organ hasarı olmayan ve olan hastalar arasında anlamlı bir fark vardı. Hedef organ hasarı olan tüm gruplarda serum ürik asit, kreatinin ve sodyum düzeyleri olmayanlara göre anlamlı derecede yüksekti. Hedef organ hasarı olan tüm gruplarda RI değerleri daha yüksekti.
Sonuç: Böbrek, esansiyel HT'den etkilenen ilk organdır ve hedef organ hasarının en erken belirtisi mikroalbüminüridir. Bu nedenle böbrek iyi korunursa oluşabilecek diğer organ hasarlarını önlemek mümkün olabilir. Çalışmamızda tanı anında hedef

organ hasarı olmayan ancak RI değeri yüksek olan hastalarda zamanla hedef organ hasarı gelişme riski anlamlı olarak daha yüksek bulundu. Tuz-protein dengesinin makul şekilde ayarlanması ve serum sodyum, ürik asit ve kreatin düzeylerinin yakından izlenmesi bu hastalarda prognostik öneme sahiptir.

Introduction

Hypertension (HT) is a common health problem that may cause target-organ damages (TOD) such as retinopathy, cardiovascular diseases, and, end-stage kidney disease. These mentioned TOD are the most important causes of morbidity and mortality in HT; therefore, it requires early, careful assessment and management (1,2). There are multiple risk factors identified for the risk of TOD, such as the severity of elevated blood pressure (BP), family history, duration of hypertension, and ethnicity (3). There are also many studies conducted on the presence of factors that may predict prognosis before the onset of TOD. Markers such as white blood cell (WBC)/lymphocyte ratio, serum amyloid protein, phospholipase level, renal resistive index (RI), blood sodium-uric acid level, and 24-hour blood pressure monitoring results (24-h ABPM) are among the prognostic factors in various studies (4-8).

Our study aimed to investigate the clinical, laboratory, and radiological findings associated with TOD in our patients who were followed up with the diagnosis of essential hypertension.

Materials and Methods

The medical records of 102 patients diagnosed with essential HT were analyzed. Necessary ethic permission was granted by The Mustafa Kemal University Ethics Committee. The definition of hypertension was made according to the American Academy of Pediatrics guideline (9). Office BP was measured using the standard auscultatory technique by a nephrologist with a stethoscope and a sphygmomanometer on at least three accurate systolic and diastolic readings. Office HT was determined when average systolic BP (SBP) or diastolic BP (DBP) levels were ≥95th percentiles for age, sex, and height. After hypertension was diagnosed, all patients were evaluated for secondary causes in a routine algorithm (renal Doppler ultrasonography, laboratory tests, eye examination for retinopathy, echocardiography, urine tests for microalbuminuria) to determine essential HT (10). In patients that met with HT definition, BP was confirmed by 24-h ABPM.

24-h-ABPM

24-h ABPM was performed with the oscillometric method using a portable automatic monitör (Spacelabs ABPM Model no: 90207; SpaceLabs Medical, Redmond, WA). An appropriate cuff was chosen from three available sizes and placed on the non-dominant arm. Measurements were taken every 20 minutes during the day and every 30 minutes at night. The day was defined as the hours from 08:00-20:00 and night as 00.00-07:00. Blood pressure load was defined as the percentage of total BP measurements exceeding the upper limit of normal according to age, sex, and height during awake and sleeping periods. A blood pressure load of 25% or more was accepted as hypertension. To calculate individual nocturnal BP falls, each patient had the mean nocturnal (00:00-07:00) values compared with the mean daytime values (08:00-20:00), and the difference was expressed as a percentage of the daytime mean value. Night dipping was defined as at least a 10% reduction in BP during sleep. According to the European reference standards, standard deviation scores (SDS) for SBP, DBP, mean arterial pressure (MAP), and heart rate were used to make height-, sex, and age-dependent corrections to BP (11).

Secondary HT,' white coat' HT, masked HT, renal artery stenosis, presence of Diabetes Mellitus (DM), familial hyperlipidemia, heart disease, urinary anomalies with HT, a history of nephrectomy, patients on drug treatment in the past 15 days were excluded from the study. Ethics committee approval was received from the Ethics Committee of Mustafa Kemal University Faculty of Medicine. Demographic data included age, gender, family history with HT, and preterm birth were noted. Weight and height were measured in all patients, and body mass index (BMI) was calculated as weight (kg)/height (m^2). BMI percentile was determined for patients, according to the 2000 center control and prevention growth charts (12). Obesity was defined as BMI>95th percentile for age and gender.

Target Organ Damage Decision

Retinopathy: A detailed eye ground examination was performed on all patients, and the diagnosis was confirmed by OCT (ocular tomography) in suspicious patients.

Left ventricular hypertrophy: All patients' evaluation were performed by the same pediatric cardiologist and the same echocardiography transducer. Interventricular septal thickness (IVSTd), left ventricular diameter at end-diastole (LVDd) and end-systole (LVDs), LV mass was calculated using the Devereux and Reichek formula (13). LV mass was indexed for height. LVH was defined as LV mass index (LVMI)>36.88 g/m$^{2.7}$ in girls and >39.36 g/m$^{2.7}$ in boys (95th percentile) (14).

Microalbuminuria: Microalbuminuria was measured by the nephelometric method by determining three separate 24-hour urine samples collected at least one week apart. 30-300 mg/day albumin excretion in urine in at least two of the three samples was accepted as microalbuminuria.

Renal Doppler and urinary ultrasonography: Ultrasonographic examinations were performed using duplex Doppler sonography. Kidney length (between upper and lower poles of the kidney), kidney size, parenchyma echogenicity, cortical thickness were measured for all patients. Intrarenal Doppler signals were obtained from three representative proximal segmental arteries. Peak systolic velocity (PSV) and minimum end-diastolic velocity (EDV) were determined using the angle correction menu of the apparatus. Resistive index (RI) was defined with (PSV-EDV)/PSV formula (15).

Statistical Analysis

The statistical analysis was performed by SPSS software version 21. The continuous data were described as mean and standard deviation, median and minimum-maximum where appropriate. The categorical data were described as percentages and compared with the chi-square test. The Kolmogorov-Smirnow test was used to determine the distribution of variables. Independent parametric and non-parametric variables were compared with Student's t-test and Mann-Whitney U test where appropriate. Parametric and non-parametric multiple groups were compared with one-way ANOVA and Kruskal-Wallis test. Bonferroni correction was performed in multiple group statistical analysis. P<0.05 was considered statistically significant.

Results

A total of 102 patients were evaluated in this study. There were 53 girls (52%) and 49 boys (48%); the mean age was 13.7±1.97 years (range 8-17 years). Fourteen patients (13.7%) had hypertension in their family history, and 57 (55.9%) patients had obesity. The mean daytime systolic blood pressure load (DSL) and nocturnal systolic blood pressure load (NSL) was 23.3±16.02% (range 1-90 %) and 24.17±22.7 % (range 1-90%) respectively. The mean daytime diastolic blood pressure load (DDL) and nocturnal diastolic blood pressure load (NDL) was 26.48±17.73% (range 3-85%) and 21.48±16.80% (range 1-74%) respectively. Twenty-five patients (24.5%) were dipper and 77 patients (75.5%) were non-dipper. The mean daytime systolic and diastolic blood pressure was 121±12 (range 96-160) mmHg and 73±11 (range 48-123) mmHg. The mean nocturnal systolic and diastolic blood pressure was 107±15 (range 79-156) mmHg and 62±10 (range 43-120) mmHg, respectively. The mean laboratory levels were as follows; BUN was 18.82±7.65 (range 8-45) mg/dL, creatinine was 0.73±0.43 (range 0, 43-8) mg/dL, uric acid was 5.89±1.13 (3.30-8.10) mg/dL, sodium was 137.16±13.84 mg/dL, potassium was 5.78±1.12 mg/dL, WBC to lymphocyte ratio was 2.69±1.07. The mean RI of left kidney was 0.64±0.13 (range 0, 42-1). Sixty-three patients (64%) had single TOD, 22 patients (21.6%) had two TOD and 9 patients (8.8%) had three TOD (Table 1). Microalbuminuria was the most seen TOD. TOD situation was divided into four groups: Patients with no TOD, patients with one TOD, patients with 2 TOD, and patients with 3 TOD. The comparative demographic, laboratory and radiological results were shown in Table 2.

For obesity, there was a significant difference between patients without TOD and those with at least two TOD (p<0.001), but there was no difference in terms of age and gender. In DSL, there was a significant difference between those without TOD and those with at least two TOD and between those with single TOD and those with 3 TOD (p=0.001, p=0.007, respectively). There was a significant difference in DDL between those with no TOD and 3 TOD (p=0.003). Among those without TOD and at least two TOD, there was a significant difference in NSL and NDL (p<0.001,

p=0.003). There is a significant difference between those without TOD and those with at least two TOD in terms of DSP and DDP (p=0.001, both). In terms of left RI, a significant difference was observed between those without TOD and all groups with TOD (p<0.001). There was no difference between groups in BUN levels, but patients with at least 2 or 3 TOD had significantly higher creatinine values (p<0.001). Serum uric acid levels were significantly higher in all groups with TOD than those without TOD (p=0.008 in 1 TOD, p=0.002 in 2 TOD, p<0.001 in 3 TOD). Similarly, the WBC/lymphocyte ratio was significantly higher among the groups (p<0.001). Contrary to many studies, it was observed that being dipper and non-dipper alone did not significantly affect retinopathy, left ventricle hypertrophy and microalbuminuria (p=0.194, p=0.058, p=0.166, respectively). However, RI was significantly higher in patients with non-dipper than in dipper patients (p=0.01).

Table 1. Patients with target organ damage

Target organ damage	n (%)
One TOD	50 (49%)
Microalbuminuria	36
Retinopathy	5
Left ventricul hypertrophy	9
Two TOD	22 (21.6%)
Microalbuminuria + retinopathy	21
Microalbuminuria + left ventricule hipertrophy	1
Retinopathy + left ventricule hypertrophy	-
Three TOD	9 (8.8%)
Microalbuminuria + retinopathy + left ventricule hypertrophy	9

TOD: Target organ damage

Discussion

Essential hypertension is a common health problem that needs to be treated early as it causes progressive TOD. Therefore, it is crucial to define the prognostic factors that may cause TOD and take precautions before chronic damage occurs. For this purpose, there are

Table 2. Demographic, clinical and radiological comparison of the group with target organ damage and the group without target organ damage

	Patients with TOD (n=50)			Patients with no TOD (n=52)	p
Target organ damage	Single TOD (n=19)	Two TOD (n=22)	Three TOD (n=9)	-	-
Gender (girl/boy)	9/10	9/13	1/8	34/18	>0.008
Age (year)	13.10±2.33	14.40±1.53	13.77±2.16	13.73±1.94	>0.008
Obesity	12	21	8	16	<0.001
DSL (%)	21.38±8.39	30.26±14.77	51.64±19.62	16.16±10.84	<0.001
DDL (%)	25.31±13.83	33.61±19.90	48.61±24.59	20.06±12.10	=0.003
NSL (%)	22.82±22.30	33.20±22.42	52.46±25.40	15.96±17.09	<0.001
NDL (%)	24.78±17.36	29.97±18.68	31.10±18.76	15.10±12.63	=0.003
DSP (mmHg)	118±9.5	126±11	140±9.5	117±10	=0.001
DDP (mmHg)	69±5	75±12	89±15	71±10	=0.001
NSP (mmHg)	105±15	117±17	126±14	103±10	>0.008
NDP (mmHg)	59±6	64±10	79±16	59±7	>0.008
Dipper/non-dipper (%)	4/16	5/17	0/9	16/36	<0.003
RI	0.62±0.12	0.73±0.11	0.84±0.14	0.57±0.08	<0.001
Urea (mg/dL)	19.47±8.61	22.18±8.12	23.88±9.26	16.28±5.7	>0.008
Creatinine (mg/dL)	0.67±0.11	1.07±1.55	0.81±0.95	0.58±0.11	<0.001
Sodium (mEq/L)	139±1.60	134±2.98	140±1.93	137±2.30	=0.002
Uric acid (mg/dL)	6.15±0.70	6.93±0.64	6.75±1.19	5.21±0.93	<0.001

DSL: Daytime systolic blood pressure load, DDL: Daytime diastolic blood pressure load, NSL: Nocturnal systolic blood pressure load, NDL: Nocturnal diastolic blood pressure load, RI: Resistive index, TOD: Target organ damage

many studies conducted in the literature. Early markers related to the risk of TOD identified up to now are; serum Na and uric acid levels, RI on Doppler USG, the severity of elevated BP values, family history, obesity, duration of hypertension, and ethnicity (3,5). In our study, we aimed to examine the clinical, demographic and radiological characteristics of patients followed up with essential HT and prognostic factors that play a role in TOD formation.

In the evaluation of our patients, in terms of socio-demographic and clinical risk factors, no significant relationship was found between age and gender with TOD in our study. However, obesity was significantly higher in patients with TOD ($p<0.005$). In 24h-ABPM results, daytime systolic-diastolic loading and non-dipper status of obese patients were significantly higher than non-obese patients. Since the risk of cardiovascular disease is increased in obese children diagnosed with hypertension, it is crucial to take precautions against obesity and to reach normal weight targets in obese children (16).

In the laboratory findings, serum creatine, sodium and uric acid values were significantly higher in all groups in patients with TOD. This demonstrates how nutrition and diet plays an important role in the development of hypertension and TOD. In many studies conducted on the subject, revealed that salt and protein intake should be balanced. Otherwise, the risk of TOD will increase (6,7).

In recent years, many studies were shown the relationship between increased RI value in the Doppler USG and TOD, and it was found to be significantly higher in patients with microalbuminuria (5). Similarly, in our study, RI values were higher in all groups with TOD (microalbuminuria + retinopathy, microalbuminuria + left ventricule hypertrophy or only one TOD). It was observed that TOD developed in the follow-up of patients who did not have TOD at the time of diagnosis but had a high RI. Even if RI is affected by factors such as increased vascular compliance, systemic pulse pressure, decreased GFR (glomerular filtration rate), urine microalbumin excretion, heart rate and rhythm, it is usually an indicator of renal vascular resistance and can be used in the diagnosis of renal vascular involvement because it is a non-invasive and easily accessible method. It was also considered that the RI value might be affected by age and pulse pressure, and normal RI values for age were defined in studies (17). In another study, as a result of 3.1 years of follow-up of 426 patients, the prognostic importance of the increase in the RI value was shown in patients with cardiorenal involvement, mainly when evaluated together with the decrease in GFR (18).

It has been shown that patients who received medical treatment regressed in RI value. Therefore, it has been suggested that the RI value can also be used for predicting the effect of treatment (19). In our study, unlike the literature, the RI value was found to be significantly higher in patients with isolated retinopathy or accompanying microalbuminuria. The relationship between RI and retinopathy has not been investigated in studies conducted so far. RI values were high in all 5 patients with isolated retinopathy. However, it would be wrong to say that this increase in RI is prognostic for retinopathy since most of our patients with retinopathy also had microalbuminuria. Likewise, 9 patients with isolated increased LVMI had higher RI values.

In our study, 36 patients had microalbuminuria, 5 patients had retinopathy, and 9 patients had left ventricular hypertrophy in patients with a single TOD. In other patients, 2 or more TOD were together. Interestingly, patients with 2 or more TOD had microalbuminuria. This made us think that the main trigger leading to TOD is renal parenchymal damage. Therefore, protecting the kidney should be the main goal in these patients. For this purpose, it will be beneficial for the long-term prognosis of the patients to determine the factors that will contribute to the development of microalbuminuria and to follow them more closely. RI can be used for this purpose because it is non-invasive and easily applicable. The significantly higher RI value in our patients with isolated retinopathy and isolated left ventricular hypertrophy supports this idea.

When the patients were examined in terms of 24h-ABPM results on admission, twenty-five patients (24.5%) were dipper, and 77 patients (75.5%) were non-dipper. Studies have found that the risk of TOD is significantly higher in patients with non-dipper and high DSL (20,21). Similarly, it was observed that there is a positive correlation between cardiac involvement and day and night systolic BP (22). When we evaluated our patients in two separate groups as dipper and non-dipper, there was no significant

difference between the groups in terms of TOD, unlike the literature. However, when we retrospectively examined patients who had no TOD at the time of diagnosis but developed TOD during follow-up, we found that patients with a high RI value who were non-dipper at the beginning developed significantly more TOD than patients with a normal RI (p=0.001. for microalbuminuria, p=0.003 for retinopathy, p=0.005 for left ventricular hypertrophy). Therefore, the RI value may be an important prognostic parameter in predicting the development of TOD along with the 24-h ABPM results.

Although our study was conducted with a limited number of patients, we think it will contribute to the literature since the clinical, laboratory, and radiological findings that may be prognostic in TOD have been investigated in detail and collectively.

Conclusion

In conclusion, the kidney is the first organ affected in essential HT, and the earliest sign of TOD is microalbuminuria. Therefore, it may be possible to prevent other TOD that may occur if the kidney is well protected. In our study, the significantly higher risk of developing TOD in the follow-up in patients with a high RI value before TOD occurs, suggesting that the use of RI measurements in early diagnosis may be beneficial in terms of prognosis. Thus, we think that the development of TOD can be prevented by closer monitoring and more aggressive treatment of patients with high RI values. Similarly, reasonable adjustment of salt-protein balance and close monitoring of serum sodium, uric acid and creatine levels have prognostic importance in these patients.

Ethics

Ethics Committee Approval: Ethical approval was received for this study from the Mustafa Kemal University Ethics Committee (decision number: 25, date: 18.02.2021).

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Lurbe E. Diagnosis and treatment of hypertension in children. Curr Hypertens Rep 2010;12:480-6.
2. Lurbe E. Hypertension and target organ damage in children and adolescents. J Hypertens 2007;25:1998-2000.
3. McCrindlle BW. Assessment and management of hypertension in children and adolescents. Nat Rev Cardiol 2010;7:155-63.
4. Lai CL, Xing JP, Liu XH, Qi J, Zhao JQ, Ji YR, et al. Relationships of Inflammatory Factors and Risk Factors with Different Target Organ Damage in Essential Hypertension Patients. Chin Med J (Engl). 2017;130:1296-302.
5. Viazzi F, Leoncini G, Derchi LE, Pontremoli R. Ultrasound Doppler renal resistive index: a useful tool for the management of the hypertensive patients. J Hyperts 2013;32:149-53.
6. Cailar Gd, Ribstein J, Mimran A. Dietary sodium and target organ damage in essential hypertension. Am J Hypertens 2002;15:222-9.
7. Ofori SN, Odia OJ. Serum uric acid and target organ damage in essential hypertension. Vasc Health Risk Manag 2014;2:253-61.
8. Andreadis EA, Agaliotis G, Kollias A, Kolyvas G, Achimastos A, Stergiou GS. Night time home versus ambulatory blood pressure in determining target organ damage. J Hypertens 2016;34:438-44.
9. Marcon D, Tagetti A, Fava C. Subclinical OrganDamage in Children and Adolescents with Hypertension: Current Guidelines and Beyond. High Blood Pressure&Cardiovascular Prevention 2019;26:361-73.
10. National High Blood Pressure Education Program Working Groupon High Blood Pressure in Children and Adolescents. The FourthReport on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics. 2004;114(2 Suppl 4th Report):555-6.
11. Dionne JM. Updated Guideline May Improve the Recognition and Diagnosisof Hypertension in Children and Adolescents; Review of the 2017 AAP Blood Pressure Clinical Practice Guideline. Curr Hypertens Rep 2017;19:84.
12. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. CDC growth charts for theUnited States: methods and development. Vital Health Stat 11 2000;246:1-190.
13. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, et al. Left ventricular massand body size in normotensive children and adults: assessment ofallometric relations and impact of overweight. J Am Coll Cardiol 1992;20:1251-60.
14. Daniels SR, Kimball TR, Morrison JA, Khoury P, Meyer RA. Indexing left ventricularmass to account for differences in body size in children and adolescents without cardiovascular disease. Am J Cardiol 1995;76:699-701.
15. Radermacher J. Ultrasonography of the kidney and renal vessels. I.Normal findings, inherited and parenchymal diseases. Urologe A 2005;44:1351-63.
16. Wühl E. Hypertension in childhood obesity. Acta Pediatr 2019;108:37-43.
17. Afsar B, Ozdemir NF, Elsurer R, Sezer S. Renal resistive index and nocturnal nondipping: is there an association in essential hypertension? Int Urol Nephrol 2009;41:383-91.
18. Doi Y, Iwashima Y, Yoshihara F, Kamide K, Hayashi S, Kubota Y, et al. Renal resistive index and cardiovascular and renal outcomes in essential hypertension. Hypertension 2012;60:770-7.
19. Erman C, Koc AS. Renal resistive index significantly increased in hypertensive children and it is independently related to the pulse pressure and left ventricular mass index. Clin Exp Hypertens 2019;41:607-14.

20. Conkar S, Yılmaz E, Hacıkara Ş, Bozabalı S, Mir S. Is Daytime Systolic Load an Important Risk Factor for Target Organ Damage in Pediatric Hypertension? The J Clin Hypertens 2015;17:760-6.
21. Mule G, Nardi E, Andronico G, Cottone S, Raspanti F, Piazza G, et al. Relationship between 24h blood pressure load and target organ damage in patients with mild to moderate essential hypertension. Blood Press Monit 2001;6:15-23.
22. Karpettas N, Nasothimiou E, Kollias A, Vazeou A, Stergiou SG. Ambulatory and home blood pressure monitoring in children and adolescents: diagnosis of hypertension and assessment of target organ damage. Hypertens Res 2013;36:285-92.