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INCIDENTALOMI NADBUBREGA: UTICAJ VELIČINE INCIDENTALOMA NA SEKRECIJU KORTIZOLA I KLINIČKE KARAKTERISTIKE

Sažetak: Cilj ove studije je procena odnosa između veličine adrenalnih incidentaloma, kortizolske sekrecije, supresibilnosti hipotalamo-hipofizno-adrenalne osovine deksametazonom i kliničkih i laboratorijskih parametara. Metod: Ova retrospektivna studija je uključila sve pacijente sa dijagnozom adrenalnog incidentaloma koji su primljeni na jedno odeljenje Klinike za endokrinologiju, dijabetes i bolesti metabolizma u periodu 2012–2019. godina. Inkluzioni kriterijum je bio prisustvo asimptomatske adrenalne mase na vizualizaciji koja nije sprovedena zbog sumnje na bolest nadbubrega. Studija je uključila 197 osoba. Adrenalne mase su detektovane CT i MR snimanjem. Analizirana je korelacija između veličine tumora i relevantnih hormonskih i kliničkih parametara. Rezultati: Nađena je značajna pozitivna korelacija između veličine tumora i jutarnjeg kortizola, kortizola posle prekonoćnog deksametazona i značajna negativna korelacija između veličine incidentaloma i jutarnjeg ACTH i T skora kuka. Takođe, nađena je slaba, ali statistički značajna korelacija između veličine incidentaloma i sistolnog krvnog pritiska. Zaključak: Naša studija je pokazala da se prevalenca adrenalne autonomne kortizolske sekrecije povećava sa veličinom incidentaloma i da prevalenca hipertenzije i osteoporoze raste sa veličinom incidentaloma.

Ključne reči: Adrenalni incidentalomi, incidentalomi nadbubrega, adrenalna neoplazma, hipotalamo-hipofizno adrenalna osovina, Kušingov sindrom, hipertenzija, osteoporoza

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Uvod:

Incidentalomi nadbubrežne žlezde (adrenalni incidentalomi) su slučajno otkrivene adrenalne mase prilikom izvođenja vizualizacionih metoda koje nisu imale za svrhu vizualizaciju nadbubrega [1]. Korišćenjem CT-a visoke rezolucije, ukupna prevalenca adrenalnih lezija je 4.4% [2] i ona raste sa godinama, dosežući 10% kod starijih [3]. Bilateralni incidentalomi se mogu naći u oko 10% slučajeva [4], dok je dijagnoza supkliničkog Kušingovog sindroma postavljena u oko 20% pacijenata sa incidentalomom nadbubrega [5]. Pacijenti sa supkliničkim Kušingovim sindromom imaju veću ukupnu i kardiovaskularnu smrtnost, kao i veću prevalencu dijabetes melitusa tipa 2, osteoporoze, fraktura i infekcija [6]. Takođe je nađeno da veličina incidentaloma nadbubrega korelira sa insulinskom senzitivnošću. [7].

Cilj ove studije je procena odnosa između veličine adrenalnih incidentaloma, kortizolske sekrecije, supresibilnosti hipotalamo-hipofizno-adrenalne osovine deksametazonom i kliničkih i laboratorijskih parametara.

Materijal i metode

Ova retrospektivna studija je uključila sve pacijente sa dijagnozom incidentaloma nadbubrega koji su primljeni na jedno odeljenje Klinike za endokrinologiju, dijabetes i bolesti metabolizma u periodu od 2012. do kraja 2019. godine. Inkluzioni kriterijum je bio prisustvo asimptomatske adrenalne mase na vizualizaciji koja nije sprovedena zbog sumnje na bolest nadbubrega [1]. Pacijenti sa adrenalnim masama koje su otkrivene tokom praćenja u okviru maligne bolesti nisu bili uključeni u studiju. Studija je uključila 215 osoba, ali je 18 njih isključeno zbog nedostatka podataka, tako da je ostalo 197 osoba u studiji. Relevantni podaci učesnika studije prikazani su u Tabeli 1.

Tabela 1. Podaci o hormonskom statusu i klinički podaci učesnika.

	MALI	VELIKI	UKUPNO	P
Pol				0.104
muški	35 (31.0%)	17 (20.2%)	52 (26.4%)	
ženski	78 (69.0%)	67 (79.8%)	145 (73.6%)	
Godine				0.623
N	113	84	197	
Srednja vrednost (95% CI)	60.1 (58.1, 62.1)	59.3 (56.5, 62.1)	59.8 (58.1, 61.4)	
BMI (kg*m ²)				0.224
N	96	69	165	
Mean (95% CI)	29.9 (28.7, 31.0)	28.8 (27.4, 30.1)	29.4 (28.6, 30.3)	
Veličina (mm)				< 0.001
N	113	84	197	
Srednja vrednost (95% CI)	20.4 (19.4, 21.5)	40.9 (38.2, 43.5)	29.2 (27.3, 31.0)	
Adrenalektomija				< 0.001
Ne	107 (94.7%)	63 (75.0%)	170 (86.3%)	
Da	6 (5.3%)	21 (25.0%)	27 (13.7%)	
				0.463

Bilateralna	19 (16.8%)	18 (21.4%)	37 (18.8%)	
Unilateralna	94 (83.2%)	66 (78.6%)	160 (81.2%)	
Hipertenzija				0.624
Da	82 (72.6%)	64 (76.2%)	146 (74.1%)	
Ne	31 (27.4%)	20 (23.8%)	51 (25.9%)	
Sistolni pritisak (mmHg)				0.078
N	103	79	182	
Srednja vrednost (95% CI)	137.8 (133.5, 142.0)	143.9 (138.3, 149.5)	140.4 (137.0, 143.9)	
Dijastolni pritisak (mmHg)				0.099
N	103	79	182	
Srednja vrednost (95% CI)	83.4 (81.1, 85.7)	86.4 (83.6, 89.1)	84.7 (82.9, 86.4)	
Diabetes mellitus				0.885
Da	47 (41.6%)	34 (40.5%)	81 (41.1%)	
Ne	66 (58.4%)	50 (59.5%)	116 (58.9%)	
Glukoza (mmol/l)				0.266
N	96	75	171	
Srednja vrednost (95% CI)	6.3 (5.8, 6.8)	5.9 (5.6, 6.3)	6.1 (5.8, 6.5)	
HbA1C (%)				0.551
N	57	49	106	
Srednja vrednost (95% CI)	6.4 (6.0, 6.7)	6.2 (5.9, 6.5)	6.3 (6.0, 6.5)	
T skor lumbalne kičme				0.322
N	25	17	42	
Srednja vrednost (95% CI)	-1.7 (-2.0, -1.4)	-2.1 (-2.9, -1.2)	-1.8 (-2.2, -1.5)	
T skor kuka				0.151
N	25	17	42	
Srednja vrednost (95% CI)	-1.2 (-1.4, -0.9)	-1.6 (-2.2, -1.0)	-1.3 (-1.6, -1.0)	
Jutarnji kortizol (nmol/l)				0.005
N	97	75	172	
Srednja vrednost (95% CI)	397.9 (368.0, 427.8)	475.0 (427.1, 522.8)	431.5 (404.3, 458.6)	
Jutarnji ACTH (pmol/l)				0.068
N	85	66	151	
Srednja vrednost (95% CI)	4.0 (3.4, 4.6)	3.2 (2.6, 3.8)	3.7 (3.2, 4.1)	
Kortizol posle deksametazona (nmol/l)				< 0.001
N	113	84	197	
Srednja vrednost (95% CI)	53.0 (41.6, 64.3)	191.1 (128.7, 253.4)	111.9 (83.1, 140.6)	
Maksimalni kortizol posle ACTH stimulacije(nmol/l)				0.016
N	11	7	18	
Srednja vrednost (95% CI)	619.7 (546.8, 692.6)	846.4 (616.5, 1076.4)	707.9 (606.4, 809.4)	
Adrenalin (nmol/24 h)				0.168
N	34	38	72	
Srednja vrednost (95% CI)	16.2 (12.7, 19.6)	21.5 (14.8, 28.2)	19.0 (15.1, 22.8)	
Noradrenalin (nmol/24 h)				0.133
N	34	38	72	
Srednja vrednost (95% CI)	194.1 (154.4, 233.7)	241.5 (193.4, 289.6)	219.1 (187.8, 250.4)	
Aldosteron (pmol/l)				0.26
N	12	18	30	
Srednja vrednost (95% CI)	240.2 (114.9, 365.6)	163.4 (80.7, 246.1)	194.2 (126.9, 261.4)	

Tumori nadbubrega su viđeni CT i NMR pregledom abdomena. Snimanja su obavljena u različitim ustanovama i interpretirana od strane različitih radiologa. Kod svih osoba je merena bar jedna dimenzija. U 172 (87%) osobe su merene dve, a u 49 (25%) sve tri dimenzije. S obzirom na ovakvu varijabilnost podataka, odlučili smo da

koristimo maksimalni izmereni dijametar. Pearson-ova korelacija između maksimalnih merenih dijametara i izračunate površine je bila 0.91, dok je korelacija sa izračunatim volumenom iznosila 0.79.

Svim osobama je urađen prekonoćni (1 mg) deksametazonski test [1]. Hormonske i biohemijske karakteristike su prikazane u Tabeli 1. Koštana gustina je merena korišćenjem “dual-energy x-ray absorpcijometrije” (Hologic Discovery W). ACTH test je urađen kod 18 osoba.

Koncentracije kortizola posle deksametazona su transformisane logaritamski (log 10) zbog ekstremno desne raširenosti raspodele.

Da bi se našla optimalna “cut-off” vrednost za maksimalne dijetre korišćeni su Optimal Cutpoints R paketi [8, 9].

Kontinuirani podaci su prikazani kao srednja vrednost i 95% interval poverenja, a nominalni kao broj i procenat. Statistička analiza je urađena pomoću Pirsonove korelacije i linearne regresije and nominal data as count and percentages. Statistical analysis was done using Pearson correlation and linear regression, ANOVA an, ANOVA i Fišerovog testa tačne verovatnoće za nominalne podatke.

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Rezultati

Karakteristike pacijenata su date u Tabeli 1. Skoro tri četvrtine (73,6%) pacijenata su bile žene. Pacijenti su bili granično gojazni (body mass index – BMI 29,4 kg/m²), prosečne starosti 59.8 godina.

Bilateralni incidentalomi su nađeni kod 37 osoba (18,8%). Osobe sa bilateralnim incidentalomima su imale više vrednosti 24 h urinarnog adrenalina (bilateralni: N=12, 28.5; 95CI 13.7-43.3 nmol/24h, unilateralni: N=60, 17.1; 95CI 13.4-20.7 nmol/24h, p=0.027) i veću prevalencu dijabetesa (59.5% vs. 36.9% p=0.016). Podaci su prikazani u Dopunskoj tabeli 1.

Dopunska tabela 1. Karakteristike pacijenata, hormonske i biohemijske karakteristike kod bilateralnih i unilateralnih incidentaloma

	BILATERALNI	UNILATERALNI	UKUPNO	P
Pol				0.305
m	7 (18.9%)	45 (28.1%)	52 (26.4%)	
ž	30 (81.1%)	115 (71.9%)	145 (73.6%)	
Godine				0.832
N	37	160	197	
Srednja vrednost (95% CI)	59.4 (56.9, 62.0)	59.9 (57.9, 61.8)	59.8 (58.1, 61.4)	
BMI (kg/m ²)				0.263
N	32	133	165	
Srednja vrednost (95% CI)	28.4 (26.4, 30.4)	29.7 (28.7, 30.6)	29.4 (28.6, 30.3)	
Veličina (mm)				0.091

N	37	160	197	
Srednja vrednost (95% CI)	32.5 (27.6, 37.4)	28.4 (26.3, 30.4)	29.2 (27.3, 31.0)	
Grupe				0.463
Mali	19 (51.4%)	94 (58.8%)	113 (57.4%)	
Veliki	18 (48.6%)	66 (41.2%)	84 (42.6%)	
Adrenalektomija				0.181
Ne	29 (78.4%)	141 (88.1%)	170 (86.3%)	
Da	8 (21.6%)	19 (11.9%)	27 (13.7%)	
Hipertenzija				0.677
Da	29 (78.4%)	117 (73.1%)	146 (74.1%)	
Ne	8 (21.6%)	43 (26.9%)	51 (25.9%)	
Sistolni pritisak (mmHg)				0.337
N	36	146	182	
Srednja vrednost (95% CI)	137.1 (131.5, 142.7)	141.3 (137.2, 145.3)	140.4 (137.0, 143.9)	
Dijastolni pritisak (mmHg)				0.715
N	36	146	182	
Srednja vrednost (95% CI)	84.0 (80.1, 87.9)	84.8 (82.9, 86.8)	84.7 (82.9, 86.4)	
Diabetes mellitus				0.016
Da	22 (59.5%)	59 (36.9%)	81 (41.1%)	
Ne	15 (40.5%)	101 (63.1%)	116 (58.9%)	
Glukoza (mmol/l)				0.833
N	31	140	171	
Srednja vrednost (95% CI)	6.2 (5.3, 7.1)	6.1 (5.8, 6.5)	6.1 (5.8, 6.5)	
HbA1C (%)				0.943
N	25	81	106	
Srednja vrednost (95% CI)	6.3 (5.9, 6.7)	6.3 (6.0, 6.6)	6.3 (6.0, 6.5)	
T skor lumbalne kičme				0.925
N	8	34	42	
Srednja vrednost (95% CI)	-1.9 (-3.4, -0.4)	-1.8 (-2.2, -1.5)	-1.8 (-2.2, -1.5)	
T skor kuka				0.111
N	8	34	42	
Mean (95% CI)	-1.8 (-2.9, -0.7)	-1.2 (-1.5, -1.0)	-1.3 (-1.6, -1.0)	
Jutarnji kortizol (nmol/l)				0.790
N	33	139	172	
Srednja vrednost (95% CI)	423.9 (362.3, 485.6)	433.3 (402.7, 463.9)	431.5 (404.3, 458.6)	
Jutarnji ACTH (pmol/l)				0.139
N	28	123	151	
Srednja vrednost (95% CI)	3.0 (2.3, 3.7)	3.8 (3.3, 4.3)	3.7 (3.2, 4.1)	
Kortizol posle deksametazona (nmol/l)				0.410
N	37	160	197	
Srednja vrednost (95% CI)	136.9 (80.6, 193.2)	106.1 (73.0, 139.1)	111.9 (83.1, 140.6)	
Maksimalni kortizol posle ACTH stimulacije (nmol/l)				0.308
N	4	14	18	
Srednja vrednost (95% CI)	802.4 (451.1, 1153.7)	680.9 (565.8, 795.9)	707.9 (606.4, 809.4)	
Adrenalin (nmol/24 h)				0.027
N	12	60	72	
Srednja vrednost (95% CI)	28.5 (13.7, 43.3)	17.1 (13.4, 20.7)	19.0 (15.1, 22.8)	
Noradrenalin (nmol/24 h)				0.707
N	12	60	72	
Srednja vrednost (95% CI)	232.4 (126.2, 338.6)	216.4 (183.7, 249.2)	219.1 (187.8, 250.4)	
Aldosteron (pmol/l)				0.997
N	10	20	30	
Srednja vrednost (95% CI)	194.0 (71.8, 316.1)	194.2 (105.8, 282.7)	194.2 (126.9, 261.4)	

Kod dvadeset sedam pacijenata je izvršena adrenalektomija. Oni su imali veće tumore (28.0 mm; 95CI 26.0-30.1 mm vs. 36.2 mm; 95CI 31.1-41.3 mm, $p=0.003$) i viši kortizol posle deksametazona (87.3 nmol/L; 95CI 58.7- 115.8 nmol/l, vs. 266.8 nmol/L; 95CI 174.1-359.4 nmol/L, $p<0.001$). Operisani pacijenti su bile uglavnom žene (92.6% vs. 70.6% $p=0.017$). Podaci su prikazani u dopunskoj tabeli 2.

Dopunska tabela 2. Karakteristike pacijenata, hormonske i kliničke karakteristike adrenalektomisanih i neoperisanih pacijenata

	NEOPERISANI	ADRENALEKTOMI-SANI	UKUPNO	P
Pol				0.017
m	50 (29.4%)	2 (7.4%)	52 (26.4%)	
ž	120 (70.6%)	25 (92.6%)	145 (73.6%)	
Godine				0.048
N	170	27	197	
Srednja vrednost (95% CI)	60.4 (58.6, 62.2)	55.6 (51.9, 59.4)	59.8 (58.1, 61.4)	
BMI (kg*m ²)				0.002
N	143	22	165	
Srednja vrednost (95% CI)	29.9 (29.0, 30.9)	26.0 (24.8, 27.2)	29.4 (28.6, 30.3)	
Veličina (mm)				0.003
N	170	27	197	
Srednja vrednost (95% CI)	28.0 (26.0, 30.1)	36.2 (31.1, 41.3)	29.2 (27.3, 31.0)	
Grupa				< 0.001
Mali	107 (62.9%)	6 (22.2%)	113 (57.4%)	
Veliki	63 (37.1%)	21 (77.8%)	84 (42.6%)	
Bilateralni				0.181
Da	29 (17.1%)	8 (29.6%)	37 (18.8%)	
Ne	141 (82.9%)	19 (70.4%)	160 (81.2%)	
Hipertenzija				0.479
Da	124 (72.9%)	22 (81.5%)	146 (74.1%)	
Ne	46 (27.1%)	5 (18.5%)	51 (25.9%)	
Sistolni pritisak (mmHg)				0.06
N	155	27	182	
Srednja vrednost (95% CI)	139.1 (135.4, 142.7)	148.2 (138.7, 157.7)	140.4 (137.0, 143.9)	
Dijastolni pritisak (mmHg)				0.094
N	155	27	182	
Srednja vrednost (95% CI)	84.1 (82.2, 85.9)	88.3 (83.2, 93.3)	84.7 (82.9, 86.4)	
Diabetes mellitus				0.528
Da	68 (40.0%)	13 (48.1%)	81 (41.1%)	
Ne	102 (60.0%)	14 (51.9%)	116 (58.9%)	
Glukoza (mmol/l)				0.708
N	147	24	171	
Srednja vrednost (95% CI)	6.2 (5.8, 6.5)	6.0 (5.3, 6.7)	6.1 (5.8, 6.5)	
HbA1C (%)				0.525
N	89	17	106	
Srednja vrednost (95% CI)	6.2 (6.0, 6.5)	6.5 (5.9, 7.0)	6.3 (6.0, 6.5)	
T skor lumbalne kičme				0.952
N	36	6	42	
Srednja vrednost (95% CI)	-1.8 (-2.3, -1.4)	-1.8 (-2.6, -1.0)	-1.8 (-2.2, -1.5)	
T skor kuka				0.645
N	36	6	42	
Srednja vrednost (95% CI)	-1.3 (-1.6, -1.0)	-1.5 (-2.4, -0.6)	-1.3 (-1.6, -1.0)	
Jutarnji kortizol (nmol/l)				0.015
N	148	24	172	

Srednja vrednost (95% CI)	418.0 (389.0, 447.1)	514.4 (442.2, 586.7)	431.5 (404.3, 458.6)	
Jutarnji ACTH (pmol/l)				0.103
N	129	22	151	
Mean (95% CI)	3.8 (3.4, 4.3)	2.8 (1.7, 3.9)	3.7 (3.2, 4.1)	
Kortizol posle deksametazona (nmol/l)				< 0.001
N	170	27	197	
Srednja vrednost (95% CI)	87.3 (58.7, 115.8)	266.8 (174.1, 359.4)	111.9 (83.1, 140.6)	
Maksimalni kortizol posleACTH stimulacije (nmol/l)				0.005
N	15	3	18	
Srednja vrednost (95% CI)	652.1 (564.4, 739.8)	986.8 (497.9, 1475.7)	707.9 (606.4, 809.4)	
Adrenalin (nmol/24 h)				0.354
N	58	14	72	
Srednja vrednost (95% CI)	18.1 (13.9, 22.3)	22.7 (12.2, 33.1)	19.0 (15.1, 22.8)	
Noradrenalin (nmol/24 h)				0.004
N	58	14	72	
Srednja vrednost (95% CI)	197.2 (169.2, 225.1)	309.8 (199.9, 419.8)	219.1 (187.8, 250.4)	
Aldosteron (pmol/l)				0.359
N	23	7	30	
Srednja vrednost (95% CI)	211.1 (126.6, 295.5)	138.5 (36.0, 241.0)	194.2 (126.9, 261.4)	

Našli smo značajnu pozitivnu korelaciju između veličine incidentaloma i jutarnjeg kortizola i kortizola posle pi značajnu negativnu korelaciju između veličine incidentaloma i jutarnjeg ACTH i vrednosti T skora za kuk. Takođe je postojala slaba, ali statistički značajna korelacija između veličine incidentaloma i sistolnog pritiska (Tabela 2, Slika 1). Korelacija između veličine tumora i dijastolnog pritiska je bila na granici statističke značajnosti ($p=0.08$).

Tabela 2. Korelacija između veličine incidentaloma i ostalih analiziranih parametara

	VELIČINA INCIDENTALOMA		
	N	r	p
Kortizol	172	0.30	0.00
ACTH	151	-0.21	0.01
Kortizol posle deksametazona (log 10)	197	0.57	0.00
Adrenalin	72	0.35	0.00
Noradrenalin	72	0.23	0.05
Aldosteron	30	-0.33	0.07
Sistolni pritisak	182	0.17	0.02
Dijastolni pritisak	182	0.13	0.08
T skor kuka	42	-0.38	0.01
T skor lumbalne kičme	42	-0.13	0.42

Slika 1

Statistički značajna korelacija je takođe nađena između veličine tumora i 24 h urinarnog adrenalina i noradrenalina.

Aldosteron je bio u negativnoj korelaciji sa veličinom tumora, ali je statistička značajnost bila granična, a broj pacijenata mali ($n=30$, $r=-0.33$, $p=0.07$).

Nije bilo korelacije između veličine tumora i starosti, telesne mase, visine i BMI pacijenata.

Veličina incidentaloma nije bila u korelaciji ni sa koncentracijom glukoze ni sa vrednošću HbA1c.

Najbolji prediktor za nesupresibilnost kortizolske sekrecije nakon prekonoćnog 1 mg deksametazonskog testa (jutarnji kortizol > 50 nmol/L) bila je veličina tumora jednaka ili veća od 29 mm. Pacijenti su podeljeni u dve grupe: mali (M) incidentalomi, tumorske veličine manje od 29 mm i veliki (V), sa veličinom tumora jednakom ili većom od 29 mm. Odnos šanse za nesupresibilnost kortizola nakon 1 mg prekonoćnog deksametazonskog testa je bio 8.55 za V u odnosu na M incidentalome.

Osobe u V grupi su takođe imale višu koncentraciju jutarnjeg kortizola, kao i značajno jači odgovor kortizola na ACTH stimulaciju (Tabela 1).

Diskusija

U našoj studiji smo našli da je veličina incidentaloma povezana sa autonomnom sekrecijom kortizola. Ovo se manifestuje povećanjem jutarnjeg kortizola i smanjenjem jutarnjeg ACTH sa povećanjem veličine tumora i smanjenjem kortizolske supresije deksametazonom kod većih tumora.

Veličina tumora je takođe povezana sa porastom urinarnog (24h) adrenalina i noradrenalina. Kod svih pacijenata, i adrenalin i noradrenalin su bili unutar lokalnih referentnih opsega, a nijedan od pacijenata nije imao simptome ili znake feohromocitoma, iako su neki imali hipertenziju. Nijedan od adrenalektomisanih pacijenata nije imao feohromocitom. Na osnovu dosadašnjih saznanja može se pretpostaviti da su promene u sekreciji kateholamina i kortizola međusobno povezane i da su rezultat interakcija kortikalno-hromafinskih ćelija u nadbubrežnoj žlezdi [10–13].

Veza između veličine aldosterona i veličine incidentaloma ima graničnu statističku značajnost ($p=0,07$, $r=-0,33$, $N=30$). Međutim, ovi rezultati nisu pouzdani zbog malog broja pacijenata i činjenice da su neki pacijenti bili na terapiji lekovima koji bi mogli uticati na nivo aldosterona.

Glukokortikoidi su povezani sa pleiotrofnim efektima koji uključuju hipertenziju, gojaznost, smanjenje koštane mase i dijabetes [14]. Veza između incidentaloma nadbubrežne žlezde i osteoporoze i preloma pršljenova je dobro poznata [15]. Metaanaliza je pokazala da je prevalenca vertebralnih fraktura među pacijentima sa incidentalomom sa autonomnom sekrecijom kortizola (ACS) 63,6%, dok je kod pacijenata bez ACS prevalencija oko 28%, oba značajno veća nego kod kontrolnih ispitanika gde je prevalenca bila 16% [16]. Pronašli smo negativnu korelaciju između veličine incidentaloma i T skora kuka, ali ne i korelaciju sa T skorom lumbalne kičme (kuk $r=-0,38$, $p=0,01$, lumbalna kičma $r=-0,13$ $p=0,42$, $N=42$). Zanimljivo je da ni T skor kuka ni lumbalne kičme nisu korelirali sa jutarnjim kortizolom ili jutarnjim ACTH. Koncentracija kortizola posle deksametazonskog testa bila je u korelaciji sa T skorom kuka i granično u korelaciji sa T skorom lumbalne kičme (kuk $r=-0,28$, $p=0,07$, lumbalna kičma $r=-0,04$ $p=0,80$, $N=42$). Razlog za nedostatak povezanosti između veličine tumora i T skora lumbalne kičme u ovom trenutku nije jasan, ali jedan od razloga može biti nesistematski i pristrasni izbor pacijenata. Osobe kod kojih je urađena osteodensitometrija bile su starije ženske osobe (osteodensitometrija urađena vs osteodensitometrija nije urađena: starost 64,9; 95CI 62,4–67,4 vs 58,4; 95CI 56,4–60,3, $p=0,001$, Pol: žene 88,1% vs 69,7% $p=0,017$). Kako su ispitanici kojima je rađena osteodensitometrija bile starije žene, njihova osteoporoza može biti povezana i sa menopauzom.

Dobro je poznato da je višak glukokortikoida povezan sa hipertenzijom [17]. U ovoj studiji bila je prisutna slaba, ali statistički značajna korelacija između veličine incidentaloma i sistolnog krvnog pritiska (Tabela 2, Slika 1). Korelacija između dijastolnog pritiska i veličine incidentaloma bila je od granične statističke značajnosti ($r=0,13$, $p=0,08$). Ni sistolni ni dijastolni pritisak nisu bili u korelaciji ni sa jutarnjim kortizolom ni sa ACTH. Međutim, oba su bila u značajnoj korelaciji sa koncentracijom kortizola nakon deksametazona (sistolni $r=0,21$, $p<0,01$, dijastolni $r=0,23$, $p<0,01$). Međutim, svi hipertenzivni pacijenti su lečeni pa su dobijene slabije korelacije između veličine incidentaloma i koncentracije kortizola nakon deksametazona i krvnog pritiska i odražavaju efekte antihipertenzivnog lečenja.

Našli smo da je optimalna granična veličina tumora za supresibilnost kortizola u deksametazonskom testu 29 mm i shodno tome podelili naše pacijente. Odnos verovatnoće za nesupresibilnost kortizola nakon prekonoćnog (1 mg) deksametazonskog testa bio je 8,55 za V u odnosu na M incidentalome (Slika 2).

Slika 2.

Ispitanici iz V grupe imali su značajno viši jutarnji kortizol i intenzivniji odgovor kortizola na stimulaciju sinaktenom u poređenju sa M osobama. Prethodno je prikazan izdašniji odgovor kortizola na ACTH, posebno kod pacijenata sa incidentimalom i niskim bazalnim ACTH [18]. Jači odgovor na ACTH mogao bi biti mehanizam u razvoju autonomije i rastu incidentaloma nadbubrežne žlezde.

Prevalenca dijabetesa i dijabetesa lečenih insulinom bila je ista u M i V grupi.

Glavni nedostatak ove studije je retrospektivna priroda. Ova studija odražava klinički pristup pacijentima u našoj ustanovi. Međutim, kada je klinička sumnja na autonomno lučenje kortizola veća radi se više testova, što može uticati na rezultate naše studije. Takođe, testiranje u pravcu feohromocitoma je sprovedeno samo kod pacijenata sa kliničkom sumnjom na ovu bolest. Konačno, podaci koji nedostaju u

ovoj studiji nisu nasumični, već su uzrokovani dijagnostičkim pristupom, čime se onemogućava upotreba naprednijih statističkih metoda (analiza latentnih promenljivih, na primer). Međutim, naši podaci su dosledni i slažu se sa efektima glukokortikoida i ranijim studijama.

Drugi mogući nedostatak studije je taj što su vizualizacije rađene u različitim zdravstvenim ustanovama i tumačene od strane različitih radiologa. Ovo bi moglo smanjiti pouzdanost studije. Međutim, ovo je pragmatična studija. U kliničkoj praksi je uobičajeno da se snimanje vrši u različitim ustanovama i kod različitih radiologa. Stoga ne mislimo da ovo smanjuje pouzdanost studije, jer ovaj pristup odražava situaciju u stvarnom životu.

U ovoj studiji smo našli i da su u incidentalomima nadbubrežne žlezde prisutne i suptilne promene u sekreciji kateholamina, aldosterona i kortizola. Međutim, klinički značaj svih ovih promena nije jasan.

Naša studija pokazuje da se prevalenca autonomne sekrecije kortizola povećava sa veličinom incidentaloma nadbubrežne žlezde, kao i da se prevalenca hipertenzije i osteoporoze takođe povećavaju sa povećanjem veličine incidentaloma. U tumorima jednakim ili većim od 29 mm prevalenca autonomne sekrecije kortizola je veća, a komplikacije usled ovakve sekrecije su izraženije, što ukazuje na potrebu za agresivnijim pristupom ovim tumorima.

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ADRENAL INCIDENTALOMAS: EFFECT OF SIZE ON CORTISOL SECRETION AND CLINICAL FEATURES

Abstract: **Purpose:** The aim of this study was to assess the relationship between adrenal incidentaloma size, cortisol secretion suppressibility by dexamethasone and relevant clinical and laboratory parameters. **Methods:** This retrospective study included all patients diagnosed with adrenal incidentaloma and admitted to the single department of the Clinic of Endocrinology, Diabetes and Diseases of Metabolism during the period from 2012 till the end of 2019. The inclusion criterion was the presence of an asymptomatic adrenal mass on imaging not performed for suspected adrenal disease. The study group included 197 subjects. Adrenal masses were detected using CT or NMR scan. We analysed the correlation between tumour size and relevant hormonal and clinical parameters. **Results:** We found a significant positive correlation between incidentaloma size and morning cortisol, cortisol after overnight dexamethasone, and a significant negative correlation between incidentaloma size and morning ACTH, and hip T score. Also, there was a weak but statistically significant correlation between incidentaloma size and systolic blood pressure. **Conclusions:** Our study shows that the prevalence of adrenal autonomous cortisol secretion increases with incidentaloma size, and that prevalence of hypertension and osteoporosis also increases with an increase of incidentaloma size

Keywords: Adrenal incidentaloma, Adrenal Gland Neoplasms, Pituitary-Adrenal System, Adrenal Imaging, Cushing Syndrome, Hypertension, Osteoporosis

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Introduction

An adrenal incidentaloma is an adrenal mass detected on imaging not performed for suspected adrenal disease or the symptoms related to adrenal hormone excess [1]. Using high-resolution CT overall prevalence of adrenal lesions was 4.4% [2]. Prevalence increases with age, reaching 10% in the elderly [3]. Bilateral incidentalomas are found in about 10% of the cases [4]. Subclinical Cushing's syndrome is diagnosed in 20% of the adrenal incidentaloma patients [5]. Patients with subclinical Cushing's syndrome have increased all-cause mortality and cardiovascular-specific mortality, and a higher prevalence of type 2 diabetes, osteoporosis, fractures and infection [6]. It was also found, that size of adrenal incidentaloma correlates with insulin sensitivity [7].

The aim of this study was to assess the relationship between adrenal incidentaloma size, cortisol secretion suppressibility by dexamethasone and relevant clinical and laboratory parameters.

Materials and methods

This retrospective study included all patients diagnosed with adrenal incidentaloma and admitted to the single department of the Clinic of Endocrinology, Diabetes and Diseases of Metabolism during the period from 2012 till the end of 2019. The inclusion criterion was the presence of an asymptomatic adrenal mass on imaging not performed for suspected adrenal disease [1]. Patients with adrenal masses detected during staging for malignant conditions were excluded. The study group included 215 subjects, but 18 subjects were excluded due to missing data, leaving 197 subjects in the study. Relevant subject data are presented in Table 1.

Table1. Patient, hormonal and clinical data

	SMALL	LARGE	TOTAL	P VALUE
Sex				0.104
Male	35 (31.0%)	17 (20.2%)	52 (26.4%)	
female	78 (69.0%)	67 (79.8%)	145 (73.6%)	
Age				0.623
N	113	84	197	
Mean (95% CI)	60.1 (58.1, 62.1)	59.3 (56.5, 62.1)	59.8 (58.1, 61.4)	
BMI (kg*m ⁻²)				0.224
N	96	69	165	
Mean (95% CI)	29.9 (28.7, 31.0)	28.8 (27.4, 30.1)	29.4 (28.6, 30.3)	
Size (mm)				< 0.001
N	113	84	197	
Mean (95% CI)	20.4 (19.4, 21.5)	40.9 (38.2, 43.5)	29.2 (27.3, 31.0)	
Adrenalectomy				< 0.001
No	107 (94.7%)	63 (75.0%)	170 (86.3%)	
Yes	6 (5.3%)	21 (25.0%)	27 (13.7%)	
Bilateral				0.463
Bilateral	19 (16.8%)	18 (21.4%)	37 (18.8%)	
Unilateral	94 (83.2%)	66 (78.6%)	160 (81.2%)	

	SMALL	LARGE	TOTAL	P VALUE
Hypertension				0.624
Yes	82 (72.6%)	64 (76.2%)	146 (74.1%)	
No	31 (27.4%)	20 (23.8%)	51 (25.9%)	
Systolic Blood Pressure (mmHg)				0.078
N	103	79	182	
Mean (95% CI)	137.8 (133.5, 142.0)	143.9 (138.3, 149.5)	140.4 (137.0, 143.9)	
Diastolic Blood Pressure (mmHg)				0.099
N	103	79	182	
Mean (95% CI)	83.4 (81.1, 85.7)	86.4 (83.6, 89.1)	84.7 (82.9, 86.4)	
Diabetes mellitus				0.885
Yes	47 (41.6%)	34 (40.5%)	81 (41.1%)	
No	66 (58.4%)	50 (59.5%)	116 (58.9%)	
Blood glucose (mmol/l)				0.266
N	96	75	171	
Mean (95% CI)	6.3 (5.8, 6.8)	5.9 (5.6, 6.3)	6.1 (5.8, 6.5)	
HbA1C (%)				0.551
N	57	49	106	
Mean (95% CI)	6.4 (6.0, 6.7)	6.2 (5.9, 6.5)	6.3 (6.0, 6.5)	
Spine T score				0.322
N	25	17	42	
Mean (95% CI)	-1.7 (-2.0, -1.4)	-2.1 (-2.9, -1.2)	-1.8 (-2.2, -1.5)	
Hip T score				0.151
N	25	17	42	
Mean (95% CI)	-1.2 (-1.4, -0.9)	-1.6 (-2.2, -1.0)	-1.3 (-1.6, -1.0)	
Morning cortisol (nmol/l)				0.005
N	97	75	172	
Mean (95% CI)	397.9 (368.0, 427.8)	475.0 (427.1, 522.8)	431.5 (404.3, 458.6)	
Morning ACTH (pmol/l)				0.068
N	85	66	151	
Mean (95% CI)	4.0 (3.4, 4.6)	3.2 (2.6, 3.8)	3.7 (3.2, 4.1)	
Cortisol after dexametasone (nmol/l)				< 0.001
N	113	84	197	
Mean (95% CI)	53.0 (41.6, 64.3)	191.1 (128.7, 253.4)	111.9 (83.1, 140.6)	
Maximal cortisol after ACTH stimulation (nmol/l)				0.016
N	11	7	18	
Mean (95% CI)	619.7 (546.8, 692.6)	846.4 (616.5, 1076.4)	707.9 (606.4, 809.4)	
Adrenaline (nmol/24 h)				0.168
N	34	38	72	
Mean (95% CI)	16.2 (12.7, 19.6)	21.5 (14.8, 28.2)	19.0 (15.1, 22.8)	
Noradrenaline (nmol/24 h)				0.133
N	34	38	72	
Mean (95% CI)	194.1 (154.4, 233.7)	241.5 (193.4, 289.6)	219.1 (187.8, 250.4)	
Aldosterone (pmol/l)				0.26
N	12	18	30	
Mean (95% CI)	240.2 (114.9, 365.6)	163.4 (80.7, 246.1)	194.2 (126.9, 261.4)	

Adrenal masses were detected using CT or NMR scan. Imaging was done in different hospitals or imaging centres and interpreted by a different radiologist. In all subjects, at least one dimension was measured. In 172 (87%) subjects two dimensions were measured, and in 49 (25%) measurements of all three dimensions were reported. Because of the variety of image data reporting, we decided to use maximal reported diameter. Pearson correlation between the maximal reported diameter and the calculated surface was 0.91, while the correlation with calculated volume was 0.79.

In all subject overnight 1 mg dexamethasone test was done [1]. Hormonal and biochemical measurement are presented in Table 1. Bone mineral density was measured using dual-energy x-ray absorptiometry (Hologic Discovery W). ACTH test was performed in 18 subjects.

Post-dexamethasone cortisol concentrations were log 10 transformed because of the extreme right-skewed distribution.

To find optimal cut-off for the maximal reported diameter OptimalCutpoints R packages were used [8, 9].

Continuous data are presented as means and 95% confidence interval (95CI), and nominal data as count and percentages. Statistical analysis was done using Pearson correlation and linear regression, ANOVA and Fisher's exact test for nominal data.

Faculty of Medicine, University of Belgrade Ethics Committee (2650/XII-13) approved this study.

Results

Patient details are presented in Table 1. Almost three quarters (73.6%) of the patients were females. Patients were borderline obese (body mass index - BMI 29.4 kg/m²), with an average of 59.8 years.

Bilateral incidentalomas were present in 37 subjects (18.8%). Subjects with bilateral incidentalomas had higher 24 h urinary adrenaline (bilateral: N=12, 28.5 95CI 13.7-43.3 nmol/24h, unilateral: N=60, 17.1 95CI 13.4-20.7 nmol/24h, $p=0.027$) and increased prevalence of diabetes ((59.5% vs.36.9% $p=0.016$). Data are presented in Supplemental Table 1.

Supplemental Table 1. Patient, hormonal and clinical data in bilateral and unilateral incidentalomas

VARIABLE	BILATERAL	UNILATERAL	TOTAL	P VALUE
Sex				0.305
m	7 (18.9%)	45 (28.1%)	52 (26.4%)	
z	30 (81.1%)	115 (71.9%)	145 (73.6%)	
Age				0.832
N	37	160	197	
Mean (95% CI)	59.4 (56.9, 62.0)	59.9 (57.9, 61.8)	59.8 (58.1, 61.4)	

VARIABLE	BILATERAL	UNILATERAL	TOTAL	P VALUE
BMI (kg*m ²)				0.263
N	32	133	165	
Mean (95% CI)	28.4 (26.4, 30.4)	29.7 (28.7, 30.6)	29.4 (28.6, 30.3)	
Size (mm)				0.091
N	37	160	197	
Mean (95% CI)	32.5 (27.6, 37.4)	28.4 (26.3, 30.4)	29.2 (27.3, 31.0)	
Group1				0.463
Small	19 (51.4%)	94 (58.8%)	113 (57.4%)	
Large	18 (48.6%)	66 (41.2%)	84 (42.6%)	
Adrenalectomy				0.181
No	29 (78.4%)	141 (88.1%)	170 (86.3%)	
Yes	8 (21.6%)	19 (11.9%)	27 (13.7%)	
Hypertension				0.677
Yes	29 (78.4%)	117 (73.1%)	146 (74.1%)	
No	8 (21.6%)	43 (26.9%)	51 (25.9%)	
Systolic Blood Pressure (mmHg)				0.337
N	36	146	182	
Mean (95% CI)	137.1 (131.5, 142.7)	141.3 (137.2, 145.3)	140.4 (137.0, 143.9)	
Diastolic Blood Pressure (mmHg)				0.715
N	36	146	182	
Mean (95% CI)	84.0 (80.1, 87.9)	84.8 (82.9, 86.8)	84.7 (82.9, 86.4)	
Diabetes mellitus				0.016
Yes	22 (59.5%)	59 (36.9%)	81 (41.1%)	
No	15 (40.5%)	101 (63.1%)	116 (58.9%)	
Bloog glucose (mmol/l)				0.833
N	31	140	171	
Mean (95% CI)	6.2 (5.3, 7.1)	6.1 (5.8, 6.5)	6.1 (5.8, 6.5)	
HbA1C (%)				0.943
N	25	81	106	
Mean (95% CI)	6.3 (5.9, 6.7)	6.3 (6.0, 6.6)	6.3 (6.0, 6.5)	
Spine T score				0.925
N	8	34	42	
Mean (95% CI)	-1.9 (-3.4, -0.4)	-1.8 (-2.2, -1.5)	-1.8 (-2.2, -1.5)	
Hip T score				0.111
N	8	34	42	
Mean (95% CI)	-1.8 (-2.9, -0.7)	-1.2 (-1.5, -1.0)	-1.3 (-1.6, -1.0)	
Morning cortisol (nmol/l)				0.790
N	33	139	172	
Mean (95% CI)	423.9 (362.3, 485.6)	433.3 (402.7, 463.9)	431.5 (404.3, 458.6)	
Morning ACTH (pmol/l)				0.139
N	28	123	151	
Mean (95% CI)	3.0 (2.3, 3.7)	3.8 (3.3, 4.3)	3.7 (3.2, 4.1)	
Cortisol after dexametasone (nmol/l)				0.410
N	37	160	197	
Mean (95% CI)	136.9 (80.6, 193.2)	106.1 (73.0, 139.1)	111.9 (83.1, 140.6)	
Maximal cortisol after ACTH stimulation (nmol/l)				0.308
N	4	14	18	
Mean (95% CI)	802.4 (451.1, 1153.7)	680.9 (565.8, 795.9)	707.9 (606.4, 809.4)	
Adrenaline (nmol/24 h)				0.027
N	12	60	72	
Mean (95% CI)	28.5 (13.7, 43.3)	17.1 (13.4, 20.7)	19.0 (15.1, 22.8)	

VARIABLE	BILATERAL	UNILATERAL	TOTAL	P VALUE
Noradrenaline (nmol/24 h)				0.707
N	12	60	72	
Mean (95% CI)	232.4 (126.2, 338.6)	216.4 (183.7, 249.2)	219.1 (187.8, 250.4)	
Aldosterone (pmol/l)				0.997
N	10	20	30	
Mean (95% CI)	194.0 (71.8, 316.1)	194.2 (105.8, 282.7)	194.2 (126.9, 261.4)	

Twenty-seven patients were adrenalectomized. They had larger tumours (28.0 95CI 26.0-30.1 mm vs. 36.2 95CI 31.1-41.3 mm, $p=0.003$), and higher cortisol levels after dexamethasone (87.3 95CI 58.7- 115.8 nmol/l, vs. 266.8 95CI 174.1-359.4, $p<0.001$). Operated patients were dominantly females (92.6% vs. 70.6% $p=0.017$). Data are presented in Supplemental Table 2.

Supplemental Table 2. Patient, hormonal and clinical data in adrenalectomized and non-operated patients

VARIABLE	NON OPERATED	ADRENALECTOMY	TOTAL	P VALUE
Sex				0.017
m	50 (29.4%)	2 (7.4%)	52 (26.4%)	
z	120 (70.6%)	25 (92.6%)	145 (73.6%)	
Age				0.048
N	170	27	197	
Mean (95% CI)	60.4 (58.6, 62.2)	55.6 (51.9, 59.4)	59.8 (58.1, 61.4)	
BMI (kg*m ⁻²)				0.002
N	143	22	165	
Mean (95% CI)	29.9 (29.0, 30.9)	26.0 (24.8, 27.2)	29.4 (28.6, 30.3)	
Size (mm)				0.003
N	170	27	197	
Mean (95% CI)	28.0 (26.0, 30.1)	36.2 (31.1, 41.3)	29.2 (27.3, 31.0)	
Group				< 0.001
Small	107 (62.9%)	6 (22.2%)	113 (57.4%)	
Large	63 (37.1%)	21 (77.8%)	84 (42.6%)	
Bilateral				0.181
Yes	29 (17.1%)	8 (29.6%)	37 (18.8%)	
No	141 (82.9%)	19 (70.4%)	160 (81.2%)	
Hypertension				0.479
Yes	124 (72.9%)	22 (81.5%)	146 (74.1%)	
No	46 (27.1%)	5 (18.5%)	51 (25.9%)	
Systolic Blood Pressure (mmHg)				0.06
N	155	27	182	
Mean (95% CI)	139.1 (135.4, 142.7)	148.2 (138.7, 157.7)	140.4 (137.0, 143.9)	
Diastolic Blood Pressure (mmHg)				0.094
N	155	27	182	
Mean (95% CI)	84.1 (82.2, 85.9)	88.3 (83.2, 93.3)	84.7 (82.9, 86.4)	
Diabetes mellitus				0.528
Yes	68 (40.0%)	13 (48.1%)	81 (41.1%)	
No	102 (60.0%)	14 (51.9%)	116 (58.9%)	
Bloog glucose (mmol/l)				0.708
N	147	24	171	

VARIABLE	NON OPERATED	ADRENALECTOMY	TOTAL	P VALUE
Mean (95% CI)	6.2 (5.8, 6.5)	6.0 (5.3, 6.7)	6.1 (5.8, 6.5)	
HbA1C (%)				0.525
N	89	17	106	
Mean (95% CI)	6.2 (6.0, 6.5)	6.5 (5.9, 7.0)	6.3 (6.0, 6.5)	
Spine T score				0.952
N	36	6	42	
Mean (95% CI)	-1.8 (-2.3, -1.4)	-1.8 (-2.6, -1.0)	-1.8 (-2.2, -1.5)	
Hip T score				0.645
N	36	6	42	
Mean (95% CI)	-1.3 (-1.6, -1.0)	-1.5 (-2.4, -0.6)	-1.3 (-1.6, -1.0)	
Morning cortisol (nmol/l)				0.015
N	148	24	172	
Mean (95% CI)	418.0 (389.0, 447.1)	514.4 (442.2, 586.7)	431.5 (404.3, 458.6)	
Morning ACTH (pmol/l)				0.103
N	129	22	151	
Mean (95% CI)	3.8 (3.4, 4.3)	2.8 (1.7, 3.9)	3.7 (3.2, 4.1)	
Cortisol after dexametasone (nmol/l)				< 0.001
N	170	27	197	
Mean (95% CI)	87.3 (58.7, 115.8)	266.8 (174.1, 359.4)	111.9 (83.1, 140.6)	
Maximal cortisol after ACTH stimulation (nmol/l)				0.005
N	15	3	18	
Mean (95% CI)	652.1 (564.4, 739.8)	986.8 (497.9, 1475.7)	707.9 (606.4, 809.4)	
Adrenaline (nmol/24 h)				0.354
N	58	14	72	
Mean (95% CI)	18.1 (13.9, 22.3)	22.7 (12.2, 33.1)	19.0 (15.1, 22.8)	
Noradrenaline (nmol/24 h)				0.004
N	58	14	72	
Mean (95% CI)	197.2 (169.2, 225.1)	309.8 (199.9, 419.8)	219.1 (187.8, 250.4)	
Aldosterone (pmol/l)				0.359
N	23	7	30	
Mean (95% CI)	211.1 (126.6, 295.5)	138.5 (36.0, 241.0)	194.2 (126.9, 261.4)	

We found a significant positive correlation between incidentaloma size and morning cortisol, and cortisol after overnight dexamethasone, and a significant negative correlation between incidentaloma size and morning ACTH, and hip T score. Also, there was a weak but statistically significant correlation between incidentaloma size and systolic blood pressure (Table 2 and Figure 1). Correlation between diastolic pressure and tumour size was of borderline statistical significance ($p=0.08$).

Table 2. Correlation between incidentaloma size and other analyzed variables

	INCIDENTALOMA SIZE		
	N	r	p
Cortisol	172	0.30	0.00
ACTH	151	-0.21	0.01
Post-dexamethasone cortisol (log10)	197	0.57	0.00
Adrenaline	72	0.35	0.00
Noradrenaline	72	0.23	0.05
Aldosterone	30	-0.33	0.07
Systolic pressure	182	0.17	0.02
Diastolic pressure	182	0.13	0.08
Hip T score	42	-0.38	0.01
LS spine T score	42	-0.13	0.42

Figure 1.

Statistically, a significant correlation was also found between the incidentaloma size and 24 h urinary adrenaline, and noradrenaline.

Aldosterone was negatively correlated with the incidentaloma size, but statistical significance was borderline, and the number of patients was small ($n=30$, $r=-0.33$, $p=0.07$).

Age, body weight, body height or BMI were not correlated with the incidentaloma size.

Incidentaloma size was not correlated with blood glucose concentration or with HbA1c level.

The best predictor for the cortisol non-suppressibility after 1 mg overnight dexamethasone (morning cortisol > 50 nmol/l) was incidentaloma size equal or larger than 29 mm, and patients were divided into two groups: small (S) with the tumour size less than 29 mm and large (L) with the tumour size equal or larger than 29 mm. The odds ratio for the cortisol non-suppressibility after 1 mg overnight dexamethasone was 8.55 for L vs. S incidentalomas.

Subjects in the L group, also, had higher morning cortisol concentrations. Interestingly, L group had significantly larger cortisol response to ACTH stimulation (Table 1).

Discussion

We found that incidentaloma size is associated with the autonomous cortisol secretion. This manifests as an increase in morning cortisol and a decrease in morning ACTH related to an increase in tumour size, and reduced cortisol suppression by dexamethasone in larger incidentalomas.

Tumour size was also associated with the increase in 24 h urinary adrenaline and noradrenaline. In all patients, both adrenaline and noradrenaline were within local reference ranges, and none of the patients had symptoms or signs of pheochromocytoma, although some had hypertension. None of the adrenalectomized patients had pheochromocytoma. Based on the current knowledge, it can be hypothesized that changes in catecholamine and cortisol secretion are interrelated and due to cortical-chromaffin cell interactions in the adrenal gland [10–13].

Relation between aldosterone and incidentaloma size has borderline statistical significance ($p=0.07$, $r=-0.33$, $N=30$). However, these results are not reliable because of the small number of patients and the fact that some patients were on a drug therapy that could influence aldosterone levels.

Glucocorticoids are associated with pleiotropic effects that include hypertension, obesity, reduction in bone mass and diabetes [14]. Association between adrenal incidentalomas and osteoporosis and vertebral fractures is well known [15]. A meta-analysis showed that prevalence of vertebral fractures among incidentaloma patients with autonomous cortisol secretion (ACS) is 63.6%, while in the patients without ACS

fracture prevalence is about 28% both significantly higher than in control subjects where prevalence was 16% [16]. We found a negative correlation between incidentaloma size and hip T score, but not with LS spine T score (hip $r=-0.38$, $p=0.01$, LS spine $r=-0.13$ $p=0.42$, $N=42$). Interestingly, neither hip T score nor LS T score was correlated with morning cortisol or morning ACTH. Post-dexamethasone cortisol concentration was correlated with the hip T score and marginally correlated with LS spine T score (hip $r=-0.28$, $p=0.07$, LS spine $r=-0.04$ $p=0.80$, $N=42$). Reason for lack of association between tumour size and LS T score is not clear now, but it can be due to non-systematic and biased choice of patients. Subjects in which osteodensitometry was done were older females (osteodensitometry vs no osteodensitometry age: 64.9, 95CI 62.4-67.4 vs 58.4 95CI 56.4-60.3, $p=0.001$, sex females 88.1% vs 69.7% $p=0.017$). As the subjects in which osteodensitometry was performed were older females and their osteoporosis may be associated with menopause.

It is well known that glucocorticoid excess is associated with hypertension [17]. In this study, a weak, but statistically significant correlation between incidentaloma size and systolic blood pressure was present (Table 2 and Figure 1). Correlation between diastolic pressure and incidentaloma size was of borderline statistical significance ($r=0.13$, $p=0.08$). Neither systolic nor diastolic pressure was correlated with either morning cortisol or ACTH. However, both were significantly correlated with post-dexamethasone cortisol concentration (systolic $r=0.21$, $p<0.01$, diastolic $r=0.23$, $p<0.01$). However, all hypertensive patients were treated so correlations between incidentaloma size and post-dexamethasone cortisol concentration and blood pressure were probably reduced and reflects the effects of antihypertensive treatment.

We found that optimal tumour size cut-off for dexamethasone suppression was 29 mm and divided our patients accordingly. The odds ratio for the cortisol non-suppressibility after 1 mg overnight dexamethasone was 8.55 for L vs. S incidentalomas (Figure 2).

Figure 2.

Subjects in L group had significantly higher morning cortisol, and increased cortisol response to Synacthen stimulation compared to S subjects. The increased cortisol response to ACTH was previously shown, especially in patients with adrenal incidentalomas and low basal ACTH [18]. The increased response to ACTH could be a mechanism in the development of adrenal autonomy and adrenal incidentaloma growth.

Prevalence of diabetes and insulin-treated diabetes was the same in the S and L group.

The major drawback of this study is a retrospective nature. This study reflects a clinical approach to patients in our institution. However, when clinical suspicion of autonomous cortisol secretion is higher more tests are done and that biases results of our study. Also, a test for pheochromocytoma only in patients with clinical suspicion for this disease. Finally, missing data in this study are not random but caused by diagnostic approach, therefore precluding the use of more advanced statistical methods (latent variable analysis e.g.). However, our data are consistent and in agreement with glucocorticoid effects and previous studies.

Another possible drawback is that imaging has been done in different hospitals or imaging centres and interpreted by a different radiologist. This could reduce the reliability of the study. However, this is a pragmatic study. In clinical practice, it is common that imaging is done in different hospitals and by different radiologist. Therefore, we do not think that this reduces the reliability of the study, as this approach reflects the real-life situation.

This is a pragmatic study. In clinical practice, it is common that imaging is done in different hospitals and by different radiologist. Therefore, we do not think that this reduces the reliability of the study.

We found that in adrenal incidentalomas subtle alteration in the secretion of catecholamines, aldosterone and cortisol are present. However, the clinical significance of all these changes is not clear.

Our study shows that the prevalence of adrenal autonomous cortisol secretion increases with incidentaloma size, and that prevalence of hypertension and osteoporosis also increases with an increase of incidentaloma size. In tumours equal to or greater than 29 mm prevalence of autonomous cortisol secretion and its complications are increased, which suggest the need for a more aggressive approach for these tumours.

Declarations

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Conflicts of interest/Competing interests: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Availability of data and material: Anonymized data are available by request.

Code availability: Not applicable

Ethics approval: Faculty of Medicine, University of Belgrade Ethics Committee (2650/XII-13) approved this study.

Informed consent: Not applicable.

Consent to participate (include appropriate statements): Not applicable

Consent for publication (include appropriate statements): Not applicable

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