Premature adrenarche and metabolic risk: differences by gender

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DISCLOSURE:

Nothing to disclose

I. BACKGROUND

- ✓ Adrenarche is a progressive maturational process of the adrenal zona reticularis resulting in increased secretion of the adrenal androgen precursor DHEA and its sulphate ester DHEA, being clinically evident approximately 2 yr before the onset of puberty.
- ✓ Premature adrenarche (PA) is defined biochemically by increased levels of DHEA and DHEAS before the age of 8 yr in girls and 9 ys in boys and clinically recognized by the presence of signs of androgen action including adult-type body odour, oily skin and axillary and pubic hair growth.
- ✓ This is traditionally indicated by a DHEA-S level within normal limits for early puberty ~ 40 µg/dl (above average for 6 to 8 yr)
- ✓ Early infancy weight gain has been also associated with increased metabolic risk, earlier puberty, and premature adrenarche (PA).
- ✓ PA has been considered a benign condition until recently, where association to increased metabolic risk has arisen.
- ✓ This risk may depend on ethnic background and infancy weight gain, which could be different by gender.

II . Aim

To determine whether PA in children at pubertal onset (TII) determines a higher metabolic profile

III. SUBJECTS AND METHODS

✓A longitudinal Chilean cohort (~ 20% indigenous/Mapuche origin) the Growth and Obesity Cohort Study (GOCS, n=1052, 49.9%F) followed from 2006 (born in 2002), PA defined by DHEAS (RIA) > 75th percentile for each gender (45.1 M, 42.0 F microg/dl at mean age 6.8±0.6 yr) (*Corvalan, AJCN 2013,97(2):318-25)*

✓In these children we performed annual clinical examination including Tanner staging together with body composition (skinfolds and bioimpedanciometry) skeletal maturation. Bone age measurements were obtained from the left hand by using an ultrasound method (BonAge; Sunlight Co)

✓TII was defined by telarche in girls and testicular volume ≥3cc in boys.

✓At ~ age 7 y we measured serum DHEAS (RIA, DSL , Webster, TX, CVintra3.5% and Cvinter 5.1 %),IGF-I , insulin and leptin

✓At Tanner II : IGF-I concentration (locally developed RIA requiring sample extraction as a first step (sensitivity: 5 ng/mL; CVintra=8.6, CVinter=10.2),Insulin (RIA, Siemens Medical Solutions Diagnostics, Sens=0.5 mUI/ml, CVintra=8.6, CVinter=10.2, Leptin (RIA, Millipore, Sens=1.0 ng/ml, CVintra=3.8, CVinter=4. 7), glycemia (GOD-PAP), adiponectin (RIA; Sens=1.0 ng/ml, CVintra= 3.8 CVinter=4. 7) , usCRP % (Method: RIA; Sens=1.0 ng/ml, CVintra= 3.8 CVinter=4. 7) , and lipid profile (TG,HDL, LDL, total cholesterol) by dry analytic methodology (Vitros, Johnson & Johnson, Inc.)

✓Statistics: multiple regression lineal models were used to assess the relation between PA and anthropometric and metabolic profile at TII, adjusting by chronologic age at DHEAS sampling and body mass index (BMI). A survival analysis was used to estimate median age of Tanner attainment.

IV. RESULTS

Results in tables are presented as mean ± SD

Females

	Female			
	PA+	PA-	p	all
At age of DHEAS sampling				
n	143	361		504
Age yr	6.88±0.40	6.69±0.42	<0.001	6.74±0.43
Height SDS	0.31±0.97	0.15±0.87	0.09	0.19±0.90
BMI SDS	1.14±1.08	0.75±1.03	<0.001	0.86±1.06
Waist circunf. cm	61.2±7.08	58.1±6.08	<0.001	59.0±6.52
Obese n,%	27, 19	44, 12	<0.05	71, 14
Overweight n,%	49, 34	96, 27	<0.01	145, 29
At Tanner II				
n	101	297		398
Age yr	8.78 (CI 7.85- 9.26)	9.29 (CI 9.06- 9.26)		9.26 (CI 9.05- 9.26)
Height SDS	0.25±1.02	0.05±0.95	0.07	0.09±0.97
BMI SDS	1.09 ± 1.12	0.78±1.08	<0.05	0.86±1.10
Waist circumf. cm	66.1±8.7	65.7±8.8	0.69	65.7±8.7
Obese n,%	20, 20	38, 13	0.05	58, 15
Overweight n,%	33, 32	98, 33	ns	131, 33

Males

	Male			
	PA+	PA-	p	all
At age of DHEAS sampling				
n	126	378		504
Age yr	6.87±0.40	6.75±0.45	0.05	6.78±0.40
Height SDS	0.36±0.85	0.07±0.95	<0.001	0.14±0.93
BMI SDS	1.42±1.34	0.79±1.20	<0.005	0.95±1.27
Waist circunf. cm	61.7±7.6	58.1±6.06	<0.001	59.0±6.7
Obese n,%	42, 33	65, 17	<0.001	107, 21
Overweight n,%	30, 24	87, 24	ns	107, 21
At Tanner II				
n	100	301		401
Age yr	11.4 (CI 10.7- 11.9)	11.1 (CI 10.8- 11.6)		11.07 (CI 10.8-11.5)
Height SDS	0.39±0.89	0.03±0.97	<0.001	0.12±0.97
BMI	1.56 ± 1.14	1.05±1.24	<0.001	1.17±1.23
Waist circunf. cm	76,3±11.3	71.7±9.8	<0..01	65.7±8.7
Obese n,%	42, 42	77, 26	<0.005	119, 30
Overweight n,%	23, 23	81, 27	ns	104, 26

At age ~7 yr	PA+			PA-				Total		
	N	mean	SD	N	mean	SD	p-value	N	mean	SD
glycemia mg/dl	142	89,32	6,33	357	88,93	6,37	0,53	499	89,04	6,35
insulin uUI/ml	142	5,67	1,56	357	5,53	1,51	0,34	499	5,57	1,53
Total chol. mg/dl	142	167,56	23,58	359	168,39	26,52	0,73	501	168,16	25,70
LDL Cholesterol m	142	96,89	24,28	359	99,58	25,91	0,27	501	98,82	25,46
HDL cholesterol m	142	50,47	13,29	359	50,28	12,36	0,89	501	50,34	12,62
triglycerides mg/dl	142	101,01	49,63	359	92,64	37,64	0,07	501	95,01	41,51
leptin ng/ml	143	6,06	4,06	361	5,95	4,15	0,78	504	5,98	4,12
adiponectin ng/ml	143	17,37	5,91	361	17,56	6,37	0,76	504	17,50	6,24
IGF-1 ng/ml	143	186,28	47,34	361	172,83	40,88	0,00	504	176,65	43,19
us CRP mg/L	31	1,92	2,49	86	1,20	1,90	0,15	117	1,39	2,08

At age ~7 yr	PA+			PA-				Total		
	N	mean	SD	N	mean	SD	p-value	N	mean	SD
glycemia mg/dl	126	91,40	5,31	376	89,89	6,51	0,01	502	90,26	6,26
insulin uUI/ml	126	5,55	1,46	376	5,35	1,19	0,15	502	5,40	1,27
Total chol. mg/dl	126	168,87	30,25	378	163,96	26,41	0,11	504	165,19	27,47
LDL Cholesterol m	126	97,91	31,14	378	94,98	26,68	0,34	504	95,71	27,86
HDL cholesterol m	126	50,66	15,27	378	50,59	14,67	0,97	504	50,61	14,80
triglycerides mg/dl	126	101,46	48,62	378	91,94	45,13	0,05	504	94,32	46,16
leptin ng/ml	126	6,46	4,21	378	5,44	3,62	0,02	504	5,69	3,80
adiponectin ng/ml	126	17,95	6,88	378	18,49	7,26	0,46	504	18,35	7,17
IGF-1 ng/ml	126	200,49	64,60	378	184,19	60,71	0,01	504	188,27	62,05
us CRP mg/L	43	2,20	4,25	109	1,07	2,06	0,10	152	1,39	2,89

At Tanner II	PA+			PA-				Total		
	N	mean	SD	N	mean	SD	p-value	N	mean	SD
glycemia mg/dl	91	89,81	7,66	265	88,22	7,24	0,08	356	88,62	7,38
insulin uUI/ml	91	8,45	3,50	265	8,28	3,23	0,68	356	8,33	3,29
Total chol. mg/dl	93	157,92	28,21	272	156,61	28,62	0,70	365	156,95	28,48
LDL Chol. mg/dl	93	90,30	28,40	270	88,84	28,59	0,67	363	89,22	28,51
HDL chol. mg/dl	93	47,79	11,92	272	48,64	11,26	0,55	365	48,42	11,42
Triglycerides mg/d	93	99,16	44,91	270	97,02	47,65	0,70	363	97,57	46,91
Leptin ng/ml	92	13,00	8,97	272	12,72	8,09	0,79	364	12,79	8,31
Adiponectin ng/ml	92	17,46	7,50	272	17,39	7,46	0,93	364	17,41	7,46
IGF-1 ng/ml	88	242,98	61,60	256	232,75	70,11	0,20	344	235,36	68,09
us CRP mg/L	77	1,45	2,06	245	1,77	2,53	0,26	322	1,70	2,43

At Tanner II	PA+			PA-				Total		
	N	mean	SD	N	mean	SD	p-value	N	mean	SD
glycemia mg/dl	67	90,24	8,48	226	89,37	7,92	0,46	293	89,57	8,05
insulin uUI/ml	67	9,89	4,02	226	9,37	3,92	0,35	293	9,49	3,94
Total chol. mg/dl	79	152,03	28,13	249	151,24	26,00	0,83	328	151,43	26,48
LDL Chol. mg/dl	77	82,30	23,46	247	82,94	22,65	0,83	324	82,79	22,81
HDL chol. mg/dl	79	49,90	10,44	249	49,50	10,78	0,77	328	49,60	10,69
Triglycerides mg/d	77	99,62	48,41	247	94,23	47,70	0,39	324	95,51	47,85
Leptin ng/ml	79	15,34	8,71	249	12,19	8,57	0,01	328	12,94	8,70
Adiponectin ng/ml	79	209,65	59,32	249	200,29	57,76	0,22	328	202,54	58,19
IGF-1 ng/ml	79	13,86	5,96	249	14,69	7,17	0,30	328	14,49	6,90
us CRP mg/L	79	2,80	5,12	249	1,78	2,71	0,09	328	2,03	3,46

V. Summary

- ▪At TII, children who developed Premature adrenarche (PA) were taller and had a higher BMI vs those without PA (PA-).
- ▪ Boys PA+ had higher leptin levels and this persist after corrected by age at DHEAs sampling .
- ▪In girls, higher DHEAS levels were associated with higher IGF-I levels ($p<0.05$): For each unit increase of DHEAS, IGF-I increases 0.37 ng/ml after corrected by age at DHEAs sampling .
- ▪No differences were observed in insulin, glycemia, adiponectin, lipid profile, usCRP.

V. CONCLUSIONS

Children with PA were taller and had higher BMI; boys had higher leptin levels and girls higher IGF-I, but not to a disadvantageous metabolic profile at this early puberty. Follow-up of this cohort is necessary to address prospectively the interrelationships of Premature adrenarche, early growth and adiposity as markers of metabolic risk

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