



ABSTRACTS

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Leptin Resistance Is Independently Associated with a Low Academic Achievement in Healthy Chilean Adolescents

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Background: Leptin is a pleiotropic hormone, impinging on a variety of brain areas to influence satiety and also motivation, learning, memory and cognitive function. A low cognitive function associated with leptin resistance has been described in human and animal models.

Aim: To examine whether a dysregulation of leptin secretion in 371 healthy Chilean adolescents (16.8±0.3 years old) of low to middle-low socioeconomic status was associated with academic achievement (AA).

Methods: BMI, waist circumference (WC), % Fat and fat free mass (DEXA), glucose, insulin and leptin were measured. Leptin ≥75th p (18.6 ng/ml) defined leptin resistance. Academic achievement (AA) was evaluated using three national standardized tests, Mathematics (M), Language (L) and Science (Sc) for college admission (PSU). Two outcomes were considered: pass (≥450 score) and fail (<450 score), according to the Ministry of Education. We used bivariate and multivariate regression analysis to examine the association between leptin resistance and AA. Multiple logistic regressions assessed the relationship between leptin resistance (exposure) and the odds of AA (outcome). Models were adjusted for potential confounders.

Results: 48.2% of adolescents were male, 13.5% had Obesity and 30.2% abdominal Obesity. 56.6%, 52.8% and 59.1% of adolescent approved the M, L and Sc test, respectively. Adolescents that fail PSU test showed higher mean values of BMI z-score and leptin (significantly for M, L and S), WC and % fat mass (significantly for M and Sc), glucose, insulin and HOMA-IR (significantly for M) and significantly lower mean values of % fat free mass (significantly for M and Sc). We found a significant association between pass M and Sc test with female sex (crude OR: 0.652 [0.43–0.98] and crude OR: 0.413 [0.21–0.81] respectively and with abdominal obesity (crude OR: 0.615 [0.39–0.96] and crude OR: 0.514 [0.26–0.99]) respectively. Whereas, we found a significant association between pass M, L and Sc test with Leptin resistance (crude OR: 0.367 [0.23–0.58], crude OR: 0.613 [0.39–0.96] and crude OR: *0.432 [0.21–0.89]) respectively. *Leptin resistance remained a significantly association with academic achievement (evaluated through M and L) after adjustment for sex and abdominal obesity (OR: 0.398 [0.24–0.67] and OR: 0.582 [0.35–0.96] respectively).

Conclusions: Leptin resistance is independently associated with a low academic achievement in healthy Chilean adolescents. A low cognitive function associated with deregulation in leptin secretion is discussed. *Funding:* NHLBI/NIH (grant n° R01HL088530).

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Low Lean Mass and Low Physical Activity Are Independently Associated to Metabolic Syndrome in Healthy Chilean Adolescents of Mid-Low to Low Socioeconomic Level

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Background: The association of sarcopenia, low physical fitness and low physical activity (PA) with cardiovascular risk has been widely demonstrated.

Aim: We analyzed the association between muscle mass and the cardiovascular and metabolic (CVM) profile in healthy Chilean adolescents to study the influence of low lean mass and physical inactivity over the risk of MetS.

Methods: In a cohort of 668 adolescents BMI, waist circumference (WC), blood pressure (BP), fat mass (FM) and fat free mass (FFM) (DEXA), Lipid profile, glucose, insulin, HOMA-IR, hs-CRP, adiponectin and lifestyle habits (intake and PA) were measured. MetS was diagnosed using IDF criteria, insulin resistance (IR) using HOMA-IR (≥3.3) and inflammation using usPCR (≥1.5 mg/L). PA was assessed by a validated test and lean mass by % of FFM. Low PA, Low Lean Mass (LM) and low adiponectin were diagnosed according to percentilar distribution (≤25th). Bivariate and multivariate regression analyses examined the association between MetS (outcome) and Low PA and Low LM (exposures) after adjusting for obesity, IR, low adiponectin and inflammation.

Results: There was a significantly CVM risk profile in adolescent with Low LM and Low PA. Low PA, Low LM, Obesity, IR, Low adiponectin and inflammation were significantly associated to MetS. Low LM and Low PA, significantly increased the risk of MetS after adjusted for obesity, IR, low adiponectin and inflammations.

Conclusions: Low LM and Low PA were independently associated to MetS in healthy adolescents of middle low and low SEL. *Funding:* NHLBI/NIH (grant n° R01HL088530).

Serum Estrogenic Activity Is Diminished in Adolescents with Type 1 Diabetes and Is Affected by Hyperglycemia

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Introduction: Clinical studies in pre-menopausal women with Type 1 diabetes mellitus (T1D) show an increase incidence of cardiovascular disease and osteoporosis. These conditions usually occur in healthy women during the post-menopausal years associated with low estrogen levels. We postulate that women with T1D exhibit a loss of the physiological protection provided by estrogen. The aim of this study is to evaluate the estrogenic activity of the serum of adolescents with T1D and the effect of hyperglycemia on the growth of estrogen-sensitive cells.

Materials and Methods: Patients with T1D (N = 71) and healthy controls (C, N = 61) were studied. The adolescents were grouped according to pubertal stage and time that has occurred after menarche. One blood sample was obtained in premenarcheal subjects. Post-menarcheal girls were evaluated during follicular (FP) and luteal phase (LP) with one serum sample in each period. The overall estrogenic activity (EA) of the serum was assessed with a modified in vitro bioassay *E-screen*, which evaluates the proliferation of estrogen-sensitive MCF-7 BUS cells in response to blood serum. The proliferation was measured by fluorometry (CyQuant kit) the serum estrogenic activity (EA) is shown compared to a pool of sera obtained from healthy women. In order to evaluate the effect of hyperglycemia, the rate of cell proliferation under chronic hyperglycemia and normoglycemia was evaluated using hyperglycemic conditions (4.5 g/L glucose) and normoglycemia (1 g/L glucose).

Results: Postmenarchal adolescents with T1D have lower EA during LP compared to C ($p < 0.01$, Table). The T1D adolescents with more than 2 years since menarche had lower EA than C in both phases of the menstrual cycle (FP: 76 versus 94, LP: 94 versus 131, $p < 0.01$), which remained significantly lower after adjusting for 17β -estradiol and estrone levels and body mass index. EA was similar in T1D and C girls who were premenarcheal.

Cells growth under hyperglycemia showed a slower proliferation than that observed under normoglycemia that reached borderline significance (192,000 cells/day versus 261,000 cells/day. N = 10, $p = 0.07$).

Conclusions: Postmenarchal adolescents with T1D have a lower proliferative estrogenic activity compared with healthy controls, which could have an impact on the development of chronic cardiovascular or bone complications in these patients.

Hyperglycemia appears to have a role in decreasing estrogenic activity observed in these patients. We report the development of a modified assay for evaluating estrogen activity that represents the integrated activity of estrogen and its circulating metabolites.

Fondecyt 1100123.

Importance of Molecular Identification in Type 1 VHL

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Introduction: von Hippel-Lindau disease is an autosomal dominant cancer syndrome characterized by the development of SNC and retina hemangioblastomas, renal tumours or cysts, pheochromocytoma, pancreatic tumours or cysts and epididymal cysts. Its incidence is 1 in 35000 live births. The disease is classified into two subtypes according to the absence (type 1) or presence (type 2) of pheochromocytoma. In non-mosaic patients with classical VHL disease germline mutation detection is 95%. In 10–40% of patients with apparently sporadic hemangioblastomas *VHL* gene mutations have been detected. Recently, our laboratory has implemented the analysis of large deletions, that together with point mutations and small deletions analysis enables the complete study of the gene, and thus the molecular identification of type 1 VHL disease.

Aim: To detect alterations in the *VHL* gene in patients with clinical diagnostic criteria of type 1 VHL or any of its characteristic manifestations.

Patients: In this study 24 unrelated patients were included, ages 3–55 years (median = 26.5), at clinical manifestation. 11 of them fulfilled the clinical diagnostic criteria of type 1 VHL, while 13 presented a single type 1 VHL typical tumour. Furthermore, 25 first grade relatives were studied.

Methods: Genomic DNA was extracted from peripheral blood leukocytes. Complete genetic analysis of the *VHL* gene was performed using the PCR amplification techniques and automatic sequencing for the study of point mutations and small deletions. MLPA and UPQFM-PCR for the study of large deletions. In those

Table 1. Estrogenic activity assessed by *E-screen* (for Abstract 3)

	Tanner 2–3	Tanner 4–5 PreM	Tanner 4–5 PostM	
			FP	LP
T1D	82.3±28 (n = 21)	94.5±21 (n = 12)	81.3±16 (n = 38)	95.8±28 (n = 38)
Control	79±16 (n = 16)	96.9±20 (n = 13)	90.3±23 (n = 32)	125.3±28 (n = 32)

Values represent % relative cell proliferation ± standard deviation.

with positive results, the study was extended to their first grade relatives. All patients signed an informed consent.

Results: In 9/11 patients who fulfilled the clinical diagnostic criteria of type 1 VHL the following mutations we found: p.R161*(n = 3), p.W88*(n = 1), p.G144*(n = 1), p.C162W (n = 1), and the deletion IVS1_Ex3del (c.554-?_c.810+?) (n = 1), previously described by other groups, and two novel mutations: p.Q73Pfs*58 (n = 1), and c219_232del GGTCATCTTCTGCA (n = 1). After the identification of index cases, the genetic study was extended to 25 relatives, of which 5 were positive for the corresponding mutation. In the group of patients with a single manifestation of disease (n = 13), p.W88* mutation was detected in one patient with cerebellar hemangioblastoma.

Conclusions: Our results underline the importance of the complete genetic study of the *VHL* gene for the confirmation of von Hippel-Lindau disease, not only in patients with clinical diagnostic criteria, but also in those patients presenting a single typical manifestation, enabling their correct diagnosis and follow-up. Two novel germ line mutations were detected in VHL patients with no family history of VHL disease.

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Mini-Puberty in Daughters Born After Pregnancies with Diabetes. Preliminary Report of Hormonal and Clinical Profile

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Background: Patients with diabetes mellitus (DM) may exhibit a wide array of reproductive abnormalities, including hypogonadotropic hypogonadism and PCOS. Diabetes during pregnancy is an endocrine disruptor and studies performed in animal models have shown abnormalities in ovarian function in the offspring, but it is unknown whether gestational (GDM) and pre-gestational diabetes (PGDM) may affect gonadal function in daughters of women with diabetes mellitus in the short or long term.

Objective: To evaluate serum concentration of anti-Müllerian hormone (AMH), testosterone, SHBG and weight in infant girls born to women who had diabetes during pregnancy (GDM or PGDM) at the time of mini-puberty.

Population and Methods: Female infants born to mothers who had diabetes during pregnancy (DM, N = 17), and healthy girls born product of a normal pregnancy in non-diabetic mothers (N = 21) [1] were studied. Anthropometry and blood sample was obtained. Circulating concentrations of testosterone, SHBG and AMH were determined by specific assays.

Results: Daughters of DM mothers had higher SHBG and AMH levels (Table), but similar testosterone levels.

Discussion: AMH is produced by the granulosa cells and their serum levels are correlated with the development of preantral and small antral follicles. Elevated AMH levels suggest that abnormalities in folliculogenesis that have been reported in offsprings of diabetic animals may be observed also in daughters of DM women.

Conclusions: This preliminary report shows higher AMH and SHBG levels measured in mini-puberty in a group of girls born after a pregnancy with diabetes, suggesting that these girls may show evidence of an altered follicular development during infancy. Proyecto Fondecyt N° 11121460.

Reference

- 1 The control group was previously studied by Sir-Petermann T, Codner E, Maliqueo M, et al. Increased Anti-Müllerian Hormone Serum Concentrations in Prepubertal Daughters of Women with Polycystic Ovary Syndrome. *J Clin Endocrinol Metab* 2006;91:3105–3109.

6

Instability of Pseudoautosomal Region 1 in Patients with Y-Chromosome Terminal AZF-b+c Deletions

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Background: Infertile men with microdeletions of the Y chromosome (Y-MD) may present abnormalities in the Pseudoautosomal Regions (PARs), which may affect genes involved in long-bone growth (*SHOX*), or psychiatric diseases (*ASMT*, *VAMP7* and *ILR9*).

Table 1. (for Abstract 5)

	Daughters of DM Mothers (N = 17)		Daughters of Non-DM mothers (N = 21)	
	Mean	SD	Mean	SD
Age (month)	3.24	0.53***	2.4	0.6
Weight (SDS)	0.53	0.76	0.37	0.11
Testosterone (ng/ml)	0.17	0.29	0.3	0.2
SHBG (nM/l)	251.15	76***	95.8	42.3
AMH (pM/l)	39.3	32.8***	9.16	8.6

*** p < 0.0001.

Objective: To study whether patients with classical AZF-deletions have PARs abnormalities, and their possible association with linear growth and neuropsychological development.

Methods: We studied 33 patients (from 9 to 43 years), who were diagnosed with Y-MD (4 AZF-a; 3 AZF-b; 16 AZF-c; 2 AZF-b+c; 2 distal AZF-b+c and 6 terminal AZF-b+c) by the Multiplex Ligation-dependent Probe Amplification (MLPA) Kit P018-F1-SHOX to search for PAR gene copy variations. The MLPA results with PARs aberrations were further studied by FISH (*SRY*) and quantitative PCR for *SHOX*, *ZBED1*, *SRY*, *DDX3Y*, *SRY* and *IL9R*.

Results: Only those patients with terminal AZF-b+c Y-MD had PARs abnormalities. In agreement with their terminal Y-MD, these patients had only one copy of PAR2. Regarding PAR1, 2 patients had a loss and 4 patients a gain of one copy. In the last patients quantitative PCR analysis showed *SRY* and *DDX3Y* duplication with a gain of *SHOX* not reaching duplication. In addition, we documented that 3 patients had a history of learning disabilities and 3 of mood disorders; 2 of major depressive disorders (with one or three copies of PAR1), and 1 with a bipolar disorder (with one copy of PAR1). Two patients had growth disorders, one with PAR1 deletion had severe short stature (Z score for height: -2.89), and one with very tall stature (Z score for height: +2.58) had global loss of PAR1 and Y-mosaicism (*SRY*+/+/*SRY*+ and *SRY*-).

Conclusions: Only patients with terminal AZFb+c Y-MD have additional sex-chromosomal abnormalities, including iso-Yq and PAR1 instability associated with growth disorders, learning disabilities and/or psychiatric dysfunction, in addition to their fertility problems.

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Estrogen Profile and Growth Factors Serum Levels During the Menstrual Cycle in Adolescents with Type 1 Diabetes (T1D)

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Introduction: Patients with type 1 diabetes (T1D) may display diminished growth and abnormalities in their ovarian function. A positive correlation between the levels of IGF1 and estradiol has been described in healthy adolescents, but it is not known how the menstrual cycle may affect the growth hormone axis and estrogen metabolism in adolescents with T1D. Estrogens are metabolized by the liver to metabolites that affect estrogen action. The main metabolite is to 2-hydroxyestrone (2OHE), a weak estrogenic compound, which has protective cardiovascular effects.

Objective: To determine how the menstrual cycle affects estrogens, IGF1 and estrogenic metabolites in adolescents with T1D compared to healthy adolescents.

Methods: Postmenarcheal adolescents with T1D (N = 45) and healthy controls (C, N = 43) were evaluated during follicular phase

(FP, days 3–7) and luteal phase (LP, 21–23) of one menstrual cycle. A blood sample was obtained to measure estradiol (E2), estrone (E1), IGF1 and IGFBP3. Free and bioavailable E2 was calculated. An overnight 12-hr urine collection was obtained to measure 2OHE and 16-hydroxyestrone (16OHE). Nonparametric statistics and linear regression analysis was used to determine the relationship between the GH-IGF1 axis and estrogen levels.

Results: Adolescents with T1D had lower levels of E2, free and bioavailable E2 in FP, and higher levels of E1 in LP ($p < 0.05$). T1D group had higher levels of SHBG levels in LP compared with FP ($p < 0.0001$).

2OHE and 16OHE levels were similar in both phases of menstrual cycle in C vs T1D, but only T1D showed an elevation of 2OHE levels (9.0 ± 7.4 to 17.6 ± 17.0 ng/mg-creat, $p < 0.01$) and 16OHE levels (7.4 ± 6.0 to 11.1 ± 9.5 ng/mg-creat, $p < 0.01$) in LP compared to FP, respectively, which was not observed in C.

Adolescents with T1D compared with C exhibit lower levels of IGF1 in FP (287 ± 65 vs 331 ± 45 ng/ml, $p < 0.01$) and LP (293 ± 64 vs 341 ± 55 ng/ml, $p < 0.001$). Higher levels of IGFBP3 were observed in both phases of the menstrual cycle in adolescents with T1D compared with C (In FP: 2.7 ± 0.5 vs 2.5 ± 0.3 ng/ml, $p < 0.001$ and LP 2.7 ± 0.5 vs 2.4 ± 0.3 ng/ml, $p < 0.01$, T1D vs C, respectively). IGF1 levels were similar in LP and FP in T1D and C adolescents. No association between estrogens and IGF1 and IGFBP-3 was observed.

Conclusion: Adolescents with T1D show lower levels of estradiol in follicular phase, and higher levels of estrone and estrogen metabolites in luteal phase compared to healthy adolescents. T1D patients display abnormalities of the GH-IGF1 axis in both phases of the menstrual cycle. This is the first report of differences in estrogen metabolism in adolescents with T1D. (Fondecyt 1100123).

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Estrogen Effect on Anti-Müllerian Hormone (AMH) Promoter Activity in a Prepubertal Sertoli Cell Line

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Background: Sertoli cells of the prepubertal testis produce high amounts of AMH. FSH stimulates testicular AMH output, whereas androgens inhibit it at puberty. In patients with androgen insensitivity syndrome or with Peutz-Jeghers syndrome, AMH testicular production is increased, concomitantly with the rise in FSH, testosterone and estradiol. The AMH promoter contains an estrogen response element hemi-palindrome ($\frac{1}{2}$ -ERE) at position -1772. The aim of this work is to assess whether estrogens are involved in the increase of AMH expression in a prepubertal Sertoli cell line, SMAT1.

Three ALS Deficient Patients in a Non Consanguineous Family Presenting Four Different *IGFALS* Gene Variants

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Methods and Results: Reporter assays were performed using an AMH promoter-luciferase vector transfected to SMAT1 cells. Luciferase activity was used to estimate the AMH promoter activity, and results were expressed as % of the respective control (mean \pm SEM). One sample t-tests were used to compare them to a 100% value corresponding to the basal activity; a $p < 0.05$ value was considered statistically significant. To select the most adequate dose of 17β -estradiol (E_2), we performed dose-response curves. SMAT1 cells were co-transfected with 3068 bp of the AMH promoter-luciferase vector (AMH-3068) and with expression vectors for human estrogen receptor α (hER α) and/or β (hER β), and incubated with E_2 from 10^{-12} to 10^{-6} M for 24 h. The expression of hER in transfected SMAT1 cells was verified by immunofluorescence and Western blotting. Maximum response was observed with E_2 between 10^{-10} and 10^{-8} M; we performed subsequent experiments with E_2 10^{-9} M since it is a physiologic concentration within the testis. In presence of hER α and E_2 , we observed a significant increase of the AMH-3068 promoter ($288.6 \pm 12.2\%$, $p < 0.05$). Conversely, with the hER β no significant changes were observed ($129.9 \pm 29.7\%$, NS). Co-transfection of both hER showed results similar to those obtained with the hER α ($202.9 \pm 48.7\%$, $p < 0.05$). The effect obtained with E_2 was abolished in presence of the antiestrogen ICI 182,780 (10^{-6} M) ($118.8 \pm 24.2\%$, NS). To verify that the effect observed was mediated by hER α on the AMH promoter, SMAT1 cells were co-transfected with a mutated AMH promoter at the $\frac{1}{2}$ -ERE at -1772 or with a shorter AMH promoter (423 bp) not containing the $\frac{1}{2}$ -ERE. In both cases, the effect produced by E_2 was abolished ($105.3 \pm 47.7\%$, NS and $109.4 \pm 35.1\%$, NS, respectively).

Discussion and Conclusions: E_2 stimulates the transcriptional activity of the AMH promoter transfected in SMAT1 cells in presence of hER α , but not hER β . The effect is abolished by the antiestrogen ICI 182,780 and by the absence of the normal $\frac{1}{2}$ -ERE present at -1772 of the AMH promoter. These results indicate that estrogens are involved in the activation of the AMH promoter in SMAT1 cells, at least in part through the $\frac{1}{2}$ -ERE present at -1772, suggesting that this mechanism may be involved in the increase of AMH in conditions like androgen insensitivity and Peutz-Jeghers syndrome.

Introduction: Complete ALS deficiency (ALS-D), caused by inactivating mutations in both *IGFALS* gene alleles, presents severe IGF-I and IGFBP-3 deficiencies associated with moderate growth retardation.

Aim: To characterize the molecular defect in a family where the index case and his father presented short stature and IGF-I and IGFBP-3 deficiencies.

Subjects and Methods: We studied a 2.4 y old boy (A, index case) and his father (B), mother (C), brother (D), paternal aunt (E) and grandmother (F). IGF-I, IGFBP-3 and GH serum levels were determined by CLIA (Immulite, Siemens), ALS by ELISA (Mediagnost) and Western immunoblot (WIB). *In vitro* ternary complex formation [$TCF = (\text{peak cpm}/\text{total cpm}) \times 100$] was evaluated by size exclusion chromatography (Superdex column, GE Healthcare) after incubating patients' sera with ^{125}I -IGF-I. *IGFALS* gene was PCR amplified and automatically sequenced. *In silico* bioinformatic tools were used to predict the gene variants effects on protein function. Three out of 4 *IGFALS* gene variants found were expressed *in vitro* in CHO cells and ALS expression was evaluated by WIB.

Results: *IGFALS* sequencing in the index case (A), who presented short stature with normal GH secretion (GHmax: 15.3 ng/ml) and undetectable IGF-I, IGFBP-3 and ALS serum levels, revealed he was compound heterozygous for a frameshift mutation (c.103dupG, p.E35Gfs*17) and a novel missense variant (c.1469C>G, p.S490W). His father was compound heterozygous for the novel p.S490W variant and p.[L409F; A475V], previously described in an ALS-D consanguineous family. The patient's mother and brother, who presented normal/low levels of IGFBP-3

Table 1. (for Abstract 9)

Subject	Age (years)	Height cm (SDS)	IGF-I (ng/ml)	IGFBP-3 ($\mu\text{g}/\text{ml}$)	ALS (mU/ml)	TCF (%)	<i>IGFALS</i> Genotype	
							Allele 1	Allele 2
A	2.4	81.5 (-2.90)	<25	<0.5	<100	1.6	c.103dupG (p.E35Gfs*17)	c.1469C>G (p.S490W)
B	30.4	156.5 (-2.40)	29	<0.5	<100	2.7	p.[L409F; A475V] (c.[1225C>T; 1424C>T])	c.1469C>G (p.S490W)
C	25.8	162.3 (0.26)	128	2.6	800	17.9	c.103dupG (p.E35Gfs*17)	WT
D	6.0	116.5 (0.41)	126	2.0	700	-	c.1469C>G (p.S490W)	WT
E	24.8	153.0 (-1.26)	27	<0.5	<100	2.5	p.[L409F; A475V] (c.[1225C>T; 1424C>T])	c.1469C>G (p.S490W)
F	56.5	156.4 (-0.70)	133	2.7	1,044	10.4	p.[L409F; A475V] (c.[1225C>T; 1424C>T])	WT

and ALS, were heterozygous carriers for p.E35Gfs*17 and p.S490W variants, respectively. His paternal aunt presented the same genotype as the father while the paternal grandmother was heterozygous carrier for p.[L409F; A475V].

The p.S490W, p.L409F and p.E35Gfs*17 were predicted to be pathogenic while p.A475V was predicted as benign by *in silico* bioinformatic tools. *In vitro* expression in CHO cells demonstrated that p.L409F and p.E35Gfs*17 mutants are not expressed, while p.A475V was normally expressed and secreted.

Conclusions: The finding of undiagnosed ALS-D adult subjects, compound heterozygous for *IGFALS* gene mutations (with either short or normal height) and the appearance of heterozygous carriers in a non consanguineous family, support that these genetic variants are present in the population and are not under a strong negative selection pressure. Functional evaluation of these variants by *in vitro* cell culture expression suggests that p.E35Gfs*17 and p.L409F are loss-of-function mutations. Remarkably, this is the first report showing fertility is preserved in an adult ALS-D patient.

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Renal Tubular Acidosis and Silver Russell Syndrome

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Aims: Demonstrate the prevalence of renal tubular acidosis in patients with Silver Russell syndrome.

Material and Method: Observational, cross-sectional, analytical, comparative and retrospective study in 28 patients seen during the period from 1998–2009, with the following inclusion criteria (both genders, age under 18 years, diagnosis of Silver Russell elaborated by the Genetic Department. Exclusion criteria were: treatment with human growth hormone, other genetic syndromes or chromosome abnormalities. Renal tubular acidosis was defined only when all the following were presents: hyperchloremic metabolic acidosis (serum Cl \geq 110 mEq/L, pH \leq 7.36), decrease in proximal re-absorption of bicarbonate with hipercarbonaturia (urinary HCO $_3^-$ \geq 3 mEq/L), decreased serum bicarbonate (HCO $_3^-$ \leq 19 mEq/L), normal serum anion gap and negative urine anion gap.

Results: 28 patients (15 males, 13 females), 18 with renal tubular acidosis (64.3%), 12 males and 6 females. The characteristics of age and physical examination were shown in table 1.

Only 30% of the patients showed postnatal catch up growth.

Analysis: There are not differences between weight, height, BMI or weight/height in patients with Silver Russell syndrome with or without renal tubular acidosis. At the contrary that in other causes of intrauterine growth retardation, only 30% of this group has complete postnatal catch up growth, and consequently 57% had short stature (<3rd centile) during infancy. Males were diagnosed younger than females, and their height Z punctuation was lower. The patients with RTA and good metabolic control showed catch up of weight and height.

Conclusions: Because of the high prevalence of RTA, it is essential to discard it in every child with Silver Russell syndrome, and when it is present, is necessary to achieve good metabolic control to promote the recovery of weight and height.

Table 1. (for Abstract 10)

		n	Age (months)	Weight (Kg)	Height (cm)	BMI (kg/m ²)
No ATR	Males	3	21.0 \pm 20.2	6.5 \pm 2.7	70.5 \pm 15.1	12.8 \pm 0.6
	Females	7	55.2 \pm 39.5	10.1 \pm 4.3	88.0 \pm 19.9	12.7 \pm 1.2
ATR	Males	12	26.0 \pm 20.7	7.5 \pm 2.4	74.3 \pm 13.4	13.4 \pm 1.3
	Females	6	35.8 \pm 33.7	7.9 \pm 4.1	78.1 \pm 17.1	12.5 \pm 1.4
		n	Z weight	Z height	Z w/h	Z fam height
No ATR	Males	3	-2.9 \pm 0.8	-3.6 \pm 0.7	-2.9 \pm 0.8	-9.0 \pm 7.7
	Females	7	-3.4 \pm 0.8	-3.5 \pm 0.6	-2.9 \pm 0.8	-10.5 \pm 2.9
ATR	Males	12	-3.7 \pm 0.6	-3.9 \pm 1.0	-2.3 \pm 1.2	-11.7 \pm 11.2
	Females	6	-3.7 \pm 1.3	-3.8 \pm 1.0	-3.1 \pm 1.6	-20.0 \pm 13.1

Metabolic control in patients with Renal Tubular Acidosis

		n	Z weight	Z height	Z BMI	Z w/h
Metabolic control	Males	8	-3.1 \pm 1.7	-3.4 \pm 1.5	-2.4 \pm 0.7	-2.5 \pm 1.0
	Females	3	-2.5 \pm 0.0	-3.7 \pm 1.2	-0.8 \pm 0.7	-1.2 \pm 0.6
No metabolic control	Males	4	-3.5 \pm 0.4	-4.0 \pm 1.6	-2.4 \pm 0.8	-2.7 \pm 0.7
	Females	3	-4.8 \pm 1.0	-4.2 \pm 1.2	-3.5 \pm 1.4	-3.9 \pm 1.2

Pediatric Non Autoimmune Hyperthyrotropinemia and TSH Receptor Gene (*TSHR*) Variants

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Introduction: Mild TSH resistance characterized by non autoimmune hyperthyrotropinemia (NAH) has been described associated with heterozygous variants in *TSHR* gene. The prevalence of this condition varies in different reports and its occurrence is considered when subclinical hypothyroidism is assessed.

Objective: To study the prevalence of *TSHR* gene variants in a pediatric population with NAH.

Subjects and Methods: Thirty five non obese unrelated children with NAH (18 girls), aged 1 to 19 years, were enrolled. Eighteen patients were born small for gestational age (SGA). All presented at least two TSH measurements >5 mIU/L (median 8.8, range 5.7–14.0 mIU/L), with normal total (T4) and free thyroxine (FT4) and negative ATPO and ATG anti-thyroid antibodies. Serum levels of TSH, T4 and FT4 were measured by ECLIA method and ATPO and ATG antibodies by ICMA (Immulite). The whole coding sequence of *TSHR* gene (exons 1 to 10 and intronic flanking regions) was PCR amplified from genomic DNA and automatically sequenced. Polyphen 2, SIFT and Mutation Taster softwares were used for *in silico* prediction of gene variants effects.

Results: Several known polymorphic variants were found (allelic frequency): p.Pro52Thr (4.3%), p.Asn187Asn (14.3%), p.Ala459Ala (1.4%), p.Asp727Glu (15.7%) and p.Asn744Lys (1.4%). In two patients, both non SGA, two uncommon heterozygous variants were found in exon 10. Both variants were predicted as pathogenic by three different prediction softwares. Patient 1 and his father carried the novel p.Pro407Leu (c.1220C>T) missense variant, present with very low allelic frequency (1/13005) only in Exome variant server database [1]. Patient 2, his father and brother carried the p.Ile583Thr (c.1748T>C) variant, absent in available population databases but already reported in one NAH patient and described as less responsive to TSH stimulation *in vitro* than the wild type receptor. *In vitro* expression of the novel p.Pro407Leu variant is required to establish its role in thyroid pathogenesis.

Conclusions: In a relatively small cohort of pediatric patients with NAH we were able to find ~6% of potential pathogenic *TSHR* gene variants. Nevertheless, further investigation is needed to assess their deleterious effect on thyroid function and to apply this knowledge to the clinical management of pediatric subclinical hypothyroidism.

References

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Association of Intramyocellular (IMCL) Lipid Content with Insulin Resistance in Obese Adolescents

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Background: The prevalence of overweight and obesity in children and adolescents has increased in recent decades. The exogenous obesity is associated with increased cardiovascular risk, especially in patients with ectopic fat (pericardial, hepatic and intramyocellular).

Aim: To evaluate anthropometric, laboratory and intramyocellular lipid content data in obese adolescents.

Methods: 66 pubertal overweight patients, 25 boys and 41 girls, were evaluated, the mean (SD) chronological age was of 12.8 (2.5) years. The study included: weight, height (to calculate BMI-WHO), waist circumference (WC), percentage of fat by bioelectrical impedance (BIA), total cholesterol (TC) and fractions, glucose oral tolerance test with measurement of glycemia and insulin. The data of height and BMI were expressed in SDS score. The WC/Height, triglyceride/HDL-C, HOMA-IR ratios were evaluated. Intramyocellular (IMCL) and extramyocellular (EMCL) lipid content ratings were obtained by: spectroscopic 1.5T.

Results: The mean (SD) BMI SDS was +2.5 (0.7), the WC/height 0.6 (0.05) and the percentage of body fat 37.8% (6.3). We found the inadequacy values of 36.4% of TC, 75.7% of HDL, 34.8% of LDL and 53% of TG. The mean (SD) of fasting insulin was 19.1 (10.8) and IMCL = 4.6 (4.7). None of the patients have diabetes mellitus type 2 and 3 were intolerant to glucose. We found a positive correlation of IMCL with HOMA-IR ($r = 0.339$, $p < 0.005$) and IMCL with triglyceride/HDL-c ($r = 0.251$, $p < 0.042$). Another positive correlation found was between IMCL/EMCL ratio and HOMA-IR ($r = 0.513$, $p < 0.001$).

Discussion and Conclusion: We found a high percentage of inadequacy of the lipid profile, suggesting that this population may be at cardiovascular risk. There was no association between IMCL lipid content and anthropometric data, but there was a positive association between ectopic fat assessed by the presence of IMCL lipid content with higher levels of insulin and the TG/HDL-c, suggesting the importance of ectopic fat in the pathophysiology of insulin resistance. Therefore, we suggest that the analysis of IMCL lipid content may be useful on the assessment of the metabolic risk in overweight patients.

Insulin Resistance Index (HOMA-IR) and Triglyceride/HDL-Cholesterol Ratio as Cardiovascular Risk Markers in Obese Prepubertal and Pubertal Children

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Introduction: The HOMA-IR has been traditionally used as a marker of metabolic and cardiovascular risk (CVR) in obese children and adolescents. However in recent years the triglyceride/high density lipoprotein cholesterol (TG/HDL-C) ratio is reported as a marker of greater utility. Our aim was to compare the association between HOMA-IR and TG/HDL-C ratio with clinical and biochemical CVR factors in obese prepubertal and pubertal children.

Methods: We included 118 prepubertal and 77 pubertal obese children (3–14 years, 114 M/81 F). Anthropometric measurements, waist circumference, pubertal stage, blood pressure, glucose, lipid profile, insulin, the TG/HDL-C ratio and HOMA-IR were evaluated. We performed bivariate analysis and multivariate logistic regression.

Results: The TG/HDL-C ratio showed association with CVR (OR = 6.7, 95% CI: 3.3–13.4, $p = 0.001$), increasing to higher number of CVR factors. Adjusted to pubertal stage, gender and age no significant association between HOMA-IR and CVR factors (OR = 1.1, 95% CI: 0.9–1.4, $p = 0.299$) was found. The correlation between HOMA-IR and TG/HDL-C ratio was low ($r = 0.16$, $p = 0.03$). From the second tertile of TG/HDL-C ratio greater association was found with CVR.

Discussion: TG/HDL-C ratio is better correlated to HOMA-IR for predicting CVR in obese children and adolescents, however the cutoff points of tertiles TG/HDL-C ratio in obese differ in other studies.

Conclusions: TG/HDL-C ratio showed higher association to predict CVR compared with HOMA-IR. We therefore recommend its use in the evaluation of CVR in obese children and adolescents.

Table 1. (for Abstract 13)

	OR*	95% CI	p
Cardiovascular risk			
TG/HDL-C	6.7	3.3–13.4	0.001
HOMA-IR	1.1	0.9–1.4	0.299
Tanner**	0.9	0.5–1.8	0.934
Sex***	1.8	0.6–4.9	0.260
Age	0.8	0.6–1.1	0.122
1 and 2 cardiovascular risk factors			
TG/HDL-C	6.9	3.2–14.5	0.001
HOMA-IR	1.1	0.9–1.3	0.581
Tanner**	1.0	0.5–1.9	0.970
Sex***	1.9	0.7–5.5	0.193
Age	0.8	0.6–1.1	0.168
≥3 cardiovascular risk factors			
TG/HDL-C	21.7	3.5–132.7	0.001
HOMA-IR	1.4	0.9–2.4	0.157
Tanner**	0.8	0.2–3.4	0.788
Sex***	1.2	0.1–14.2	0.885
Age	0.5	0.2–1.0	0.054

* OR adjusted to Tanner, sex and age.

** Prepubertal reference.

*** Male reference.

Table 2. (for Abstract 13)

	Tertiles of TG/HDL-C ratio						P
	<2.32		2.32–3.96		>3.96		
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	9.3	2.4	9.7	2.6	10.3	2.3	0.051
BMI (kg/m ²)	26.3	3.3	26.7	3.5	28.2	4.5	0.014
BMI Z score	2.3	0.4	2.2	0.4	2.3	0.5	0.983
WC (cm)	82.7	9.6	85.8	10.9	87.9	10.7	0.017*
SBP (mm Hg)	104.3	10.3	103.9	10.2	107.1	10.8	0.154
DBP (mm Hg)	66.9	9.1	67.3	7.3	69.3	9.9	0.237
Glucose (mg/dl)	91.4	8.4	90.4	8.6	91.7	9.8	0.695
Insulin (uU/ml)	15.8	9.8	24.6	19.3	24.9	28.6	0.043*
HOMA-IR	3.5	2.3	5.3	3.9	5.7	7.2	0.037*
Cholesterol (mg/dl)	159.4	35.6	173.1	25.6	167.7	30.2	0.04**
LDL (mg/dl)	95.4	36.9	105.2	23.6	91.9	28.4	0.04***
HDL (mg/dl)	49.8	13.9	42.8	6.9	34.9	6.8	0.001**
Triglyceride (mg/dl)	74.9	20.7	127.7	25.0	209.7	61.8	0.001**

Significant values by post-hoc * 3rd tertile vs 1st tertile; ** 3rd tertile vs 2nd tertile; *** 2nd tertile vs 1st tertile.

Anovulatory Adolescents Display an Elevation of C-Reactive Protein in Luteal Phase

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Introduction: The menstrual cycle is characterised by cyclical changes in the hormonal levels. Studies performed in adult women have shown that chronic anovulation is associated with an increased risk of coronary heart disease and stroke and type 2 diabetes, but it is not known whether anovulatory cycles frequently observed in adolescence, are associated with higher C-reactive protein (usCRP) and lower 2-hydroxyestrone (2OHE) levels, an estrogen metabolite with cardioprotective actions.

Aim: To evaluate usCRP levels during the menstrual cycle and to determine its association with ovulation and variations in estrogen metabolites (2OHE and 16 α -hydroxyestrone (16OHE)) in healthy adolescents.

Methods: Healthy postmenarcheal adolescents (N = 37) were studied during one menstrual cycle in follicular (FP, days 3–7) and luteal phases (LP, days 21–23). An early-morning blood sample was obtained during FP and LP to measure usCRP, sex steroids, IGF1 and IGFBP3. An overnight 12-hr urine collection was obtained to measure 2OHE and 16OHE. Ovulation was determined by a serum progesterone level >4 ng/ml in LP. Non-parametric statistical tests were used (Mann-Whitney and Wilcoxon). The association of clinical characteristics and hormonal profile with usCRP was evaluated with regression analysis.

Results: Luteal phase showed higher levels of usCRP, estrone, estradiol (E2), free and bioavailable E2, 2OHE, testosterone and FAI levels compared to the FP ($p < 0.01$). A borderline elevation in IGF1 levels ($P = 0.06$) was observed in LP. The levels of IGFBP-3, SHBG, 16OHE and the 2OHE/16OHE ratio were similar in the two stages of the menstrual cycle.

Ovulation was detected in 32% of the cycles. Serum usPCR concentrations increased from 1.9 \pm 1.1 mg/L in the FP to 2.5 \pm 1.8 mg/L in the LP ($P < 0.0001$) in anovulatory cycles. Ovulatory cycles had similar usCRP levels in both phases (1.6 \pm 0.5 mg/L in the FP and 2.0 \pm 1.1 mg/L in the LP; $P > 0.05$). The elevation in sex steroids seen in the entire group was observed in LP in ovulatory and anovulatory cycles, but anovulatory cycles reached lower levels of these steroids in the LP compared to ovulatory cycles ($p < 0.01$). The elevation of 2OHE levels seen in the whole group was not observed by dividing by ovulation ($p > 0.05$).

Regression analysis showed that BMI, gynecological age and luteal E2, SHBG and testosterone levels were not associated with follicular or luteal usCRP. Follicular usCRP was significantly associated with follicular estrone ($\beta = 0.43$, SEM = 0.004, $p = 0.004$) and IGF1 levels ($\beta = -0.41$, SEM = 0.003, $p = 0.006$), even after adjustment for BMI (Model ANOVA $p = 0.001$). Luteal usCRP had a borderline association with luteal progesterone level ($\beta = -0.38$, SE = 0.07, $p = 0.025$; ANOVA $p = 0.05$). No association was ob-

served between usCRP serum levels and urinary estrogen metabolites (2OHE and 16 OHE).

Conclusions: We report an elevation of usCRP and 2OHE levels during the luteal phase in healthy adolescents. Anovulatory adolescents exhibit an elevation of usCRP without an increase in 2OHE, suggesting an inflammatory milieu and lack of protective effect of estrogen metabolites. Ovulatory girls did not display an elevation of usCRP in LP. The adverse profile observed in anovulatory girls may play a role in the pathophysiology of the long-term metabolic and cardiovascular risks that have been associated with chronic menstrual disorders. (Fond-ecyt 1100123).

Testosterone and IGF-1 Levels in Pregnant Women with Diabetes and Relationship with Birth Weight

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Introduction: Diabetes mellitus (DM) is associated with hyperandrogenism in non-pregnant women, but it is not known whether hyperandrogenism is observed in these patients during pregnancy.

Objective: To study testosterone, estradiol, SHBG and IGF-1 levels in pregnant women with DM during the second (2ndT) third trimester (3rdT) and at the time of delivery (TOD) and its association with the metabolic control and birth weight (BW) of the offspring.

Methods: Pregnant women were studied (N = 48). Patients with diabetes (PDM, N = 38, type 2 DM (n = 17) and with gestational DM (n = 21). Non-diabetic pregnant women were included if they had normal blood glucose during the first trimester and normal oral glucose tolerance test in the 3rdT (C, n = 10). Clinical and hormonal assessment (sexual steroids, SHBG, HbA1c and IGF-1 levels) were performed during 24–28 and 32–34 weeks of gestation and at the time of delivery (TOD). Association of T levels with HbA1c levels and birth weight (BW) of the offspring was determined. Data analysis: ANOVA and Dunnett post test and Pearson's r correlation coefficient.

Results: Age and BMI was higher in PDM compared with C ($P = 0.007$). PDM group had higher T and IGF-1 levels than C at 32–34 weeks (0.97 \pm 0.09 ng/ml; 0.62 \pm 0.01 ng/ml; 0.56 \pm 0.04, $P = 0.048$; 775.1 \pm 93.1 ng/ml; 467.4 \pm 54.1 ng/ml; 374.2 \pm 58.9 ng/ml; $P = 0.03$ respectively) and at TOD (1.1 \pm 0.1 ng/ml; 0.8 \pm 0.1 ng/ml; 0.7 \pm 0.1 ng/ml; $P = 0.038$; 673.5 \pm 53.1 ng/ml; 529.9 \pm 51.1 ng/ml; 355.4 \pm 54.3 ng/ml; $P = 0.05$ respectively). PDM had lower SHBG and E2 levels than C in the 2ndT (683.4 \pm 44.1 nmol/l; 629.2 \pm 66.0 nmol/l; 1110.0 \pm 137.3 nmol/l; $P = 0.001$; 7244.1 \pm 779.3 pg/ml; 9837.1 \pm 846.5 pg/ml; 14385.3 \pm 4025.1 pg/ml; $P = 0.01$, respectively) and 3rdT (902.7 \pm 63.9 nmol/l; 677.9 \pm 74.2 nmol/l; 1070 \pm 86.0 nmol/l; $P = 0.07$; 19527 \pm 1805 pg/ml; 20606 \pm 1879 pg/ml; 23713 \pm 3403 pg/ml; $P = 0.04$, respectively). T levels correlated with

HbA1c ($r = 0.11$; $P = 0.009$) and with IGF-1 levels ($r = 0.10$; $P = 0.01$). BW correlated with maternal IGF-1 ($r = 0.3$; $P = 0.03$) and HbA1c levels ($r = 0.3$; $P = 0.03$) at TOD.

Conclusions: Hyperandrogenism is observed in pregnant women with diabetes, in association with deteriorating metabolic control. The birth weight of offspring with diabetes is correlated with maternal IGF-1 levels at the time of delivery, but not with sex steroid. FONDECYT grant No 11121460.

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Assessment of Intima-Media Thickness of the Carotid Artery and Intraluminal Diameter of the Brachial as Cardiovascular Risk Markers in Obese Adolescents

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Background: It is known that increased intima-media thickness of the carotid artery is considered to be a marker for early onset of atherosclerosis, being found in overweight children and adolescents. Furthermore, the presence of endothelial dysfunction is also associated with cardiovascular risk.

Aim: Evaluate anthropometric, laboratory and ultrasonographic intima-media thickness of the carotid and brachial intraluminal diameter data in obese adolescents.

Methods: 77 pubertal overweight patients were evaluated, 29 boys and 48 girls, with the mean (SD) chronological age of 12.9 (2.5) years. Weight, height (to calculate BMI), waist circumference (WC), percentage of abdominal fat by bioelectrical impedance (BIA), serum total cholesterol (TC) and fractions, triglycerides (TG) and glucose oral tolerance test with glucose and insulin dosages were evaluated. BMI was expressed in SDS score (BMI SDS-WHO) and the ratios WC/Height, TG/HDL-C, HOMA-IR and sum of insulin values were made. The image data were obtained through the ultrasound to obtain the intima-media thickness (IMT) of the carotid and in the longitudinal axis of the brachial artery, 3 inches from the antecubital fold for analysis of the intraluminal diameter of the brachial artery. We also evaluated the arterial blood velocity of the brachia arterial in the first 15 seconds of reactive hyperemia after inflating the cuff on the patient's arm up to 30 mm Hg above their systolic BP for 5 minutes.

Results: The mean BMI SDS was +2.5 (0.7), the WC/height 0.6 (0.05) and the percentage of fat (BIA) of 38% (6.6). We found 36.4% of inadequacy values of TC, 72.7% of HDL, 36.4% of LDL and 53.2% of TG. The mean (SD) fasting insulin was 20 (10.9) and carotid IMT = 0.5 (0.08). None of the patients have diabetes mellitus type 2 and four were intolerant to glucose. There was a positive correlation between the TG/HDL-C ratio with the sum of insulin ($r = 240$, $p < 0.036$) and the zIMC with carotid IMT ($r = 0.226$, $p < 0.049$). There was an inverse correlation between the arterial blood velocity rate and the sum of insulin ($r = -0.297$, $p < 0.009$).

Discussion and Conclusion: In the literature, carotid IMT increased is described as above 0.4 mm. In the population studied, we observed that the average carotid IMT was above this threshold value, and the higher the BMI, the greater the IMT, suggesting that this population may be at cardiovascular risk. Moreover, there was a high percentage of inadequacy of the lipid profile in this group. The relation between TG/HDL-c and the sum of insulin values suggests that it can be used as a marker of insulin resistance. Finally, the negative correlation between brachial artery blood velocity rate with the sum of insulin shows the change of the response of the endothelium to vasoconstriction (mediated by nitric oxide) in patients with insulin resistance.

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Gestational Age Versus Birth Weight as Parameters to Stratify Cutoff Levels in the Newborn Screening of Congenital Adrenal Hyperplasia of Premature Babies

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Introduction: The newborn screening (NS) of congenital adrenal hyperplasia (CAH) is a major challenge, which involves rapid detection and confirmation of suspected cases in the context of a high number of false-positive cases, especially prevalent in the population of preterm newborns (PN). In order to limit the number of false positives, NS programs usually stratify the cutoffs levels of 17 OH progesterone (17OHP) either by Gestational age (GA) or Birth Weight (BW). In the USA, Canada and New Zealand, cut-off levels are usually based on BW, while in Europe and Japan GA is used to establish cut-off levels.

Objective: The aim of this study was to determine whether BW and GA are equivalent to discriminate suspected cases, or if one of these parameters is more suitable than the other.

Materials and Methods: NS for CAH was performed by measuring 17OHP (DELFA kit 024) in dried blood samples (paper Whatman 903) in 9374 newborns. From them, 8414 samples were taken from 48 to 72 hs of life, so GA and BW was registered and considered for analysis. BW was registered in grams & by group (1: ≤ 1000 gr, 2: ≤ 1500 gr, 3: ≤ 2000 gr, 4: ≤ 2500 gr, 5: ≤ 3000 gr, 6: ≤ 3500 gr, 7: ≤ 4000 gr, 8: 4000 gr). 17OHP mean, SD, CV% were calculated in groups by GA and BW and compared. Distribution of BW according to GA was plotted. Arbitrary cut-off values at 97 percentile for GA and BW groups were established, and Cohen's kappa statistic (κ) was used as a measure of agreement between GA and BW as alternative methods of categorical assessment. The 17OHP mean concentrations were plotted, simultaneously, according to the groups of GA and BW, and a multiple regression analysis was performed.

Results: 17OHP mean concentrations were found to be significantly negatively associated with both GA and BW ($r = -0.9117$; $p < 0.0001$ and $r = -0.8616$; $p = 0.0127$); The intra-class coefficient of variation (CV%) was not associated to the groups by GA and BW ($R^2 = 0.0194$ and 0.0973). CV% did not differ sig-

nificantly between GA and BW: CV%= 87.61% (95% CI [74.79, 100.44]) vs 75.92% (95% CI [62.13, 89.71]) t-test: p = ns. When 97 centil cutoff values were used for GA and BW groups, the strength of agreement was good ($\kappa = 0.6764$ (95% CI [0.637, 0.7158])), but the proportion of agreement for the positive cases was 0.5291 (95% CI [0.4857, 0.5720]). 17OHP plotted by GA and BW and multiple regression analysis, showed that GA ($p < 0.0001$) is the main factor with influence on 17OHP rather than BW (p :ns).

Discussion: Our data showed that BW follows the influence of GA to predict 17OHP, but it is not a factor with intrinsic influence. Besides, only a weak correlation between BW and GA ($R^2 = 0.438$) is found and almost half of the 'suspected cases' were not detected simultaneously by both approaches.

Conclusions: GA predict 17OHP values more accurately than BW, therefore it would result a better parameter to stratify cutoff levels in a screening program for CAH.

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Cardiovascular Diseases in Turner Syndrome

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Aim: To evaluate the prevalence of cardiovascular abnormalities in Turner syndrome (TS).

Background: TS is the most common chromosomal abnormality, affecting 1/2000 live female birth. Congenital heart disease (CHD) affects approximately 50% of TS individuals and it is the major cause of premature morbidity and mortality in TS adults. Recent data report an association of TS with a generalised vasculopathy and aortic abnormalities such as aortic dilatation (AoDil) and dissection. The higher risk of CHD is associated with severe dysmorphic features. Bicuspid aortic valve (BAV), aortic coarctation (CoA), aortic root dilatation (ARD) and arterial hypertension (AH) are the risk factors for aortic dissection. Risk of the aortic dissection is increased in young women particularly during pregnancy. Accurate data on prevalence of aortic valve abnormalities, AH and ARD are not available yet.

Patients and Methods: Forty four individuals with TS (18 with karyotype 45,X) age 7.4 (0.1 to 19.0) years underwent complete cardiologic examination including ECG, echocardiography, 24 hours monitoring of arterial blood pressure and 38 of them also magnetic resonance imaging (MRI). The median of age at first cardiologic evaluation was 12.3 (0.1–19.0) years.

Results: BAV or dysplastic aortic valve was found in 29% of subjects, CoA was found in 2% of patients, aortic stenosis in 2% of subjects, AoDil in 18% and AH in 11% of subjects. Ascending/descending aortic diameter ratio >95th percentile was found in 21% individuals. The cardiac abnormalities had 61% of all TS patients (78% of 45,X).

Conclusion: One third of our patients had at least one risk factor for aortic dissection, but 44.5% in the group of 45,X individuals. Our data confirm the high risk for cardiovascular diseases in TS. The patients should be carefully examined just after diagnosis of TS to detect the cardiovascular abnormalities and to identify many asymptomatic individuals with risk factors. Regularly follow-up by experienced cardiologist is necessary for early detection of cardiac abnormalities to prevent cardiovascular morbidity and mortality. MRI is recommended in all TS girls at an age when it may be performed without sedation.

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Functional Characterization of Three Novel Mutations in the IGF1R Gene

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Background: IGF1R gene mutations have been associated with varying degrees of intrauterine and postnatal growth retardation, and microcephaly. We have previously reported three novel variants in the IGF1R gene: *de novo* p.Arg1256Ser, *de novo* p.Asn359Tyr and p.Tyr865Cys (ENDO 2013, OR20-2).

Aim: To characterize the functional effects of the novel IGF1R gene allelic variants.

Methods: *In silico* tools were used to predict the pathogenicity of the variations. Functional effects were evaluated by two *in vitro* assays: 1) IGF-1 dependent DNA synthesis in fibroblast cell primary cultures from patients and two control subjects (C1, C2) were analyzed by ³[H]thymidine incorporation into DNA treated with IGF-1 (50 ng/ml) for 16, 20 and 24 hs. 2) PI3K/Akt pathway was evaluated with phospho Akt (Ser473) STAR ELISA Kit (Millipore) in fibroblast cultures from patients and controls stimulated with 50 ng/ml of IGF-1 for 10 minutes. Protein concentration for each well was measured by Bradford assay.

Results: *In silico* prediction models indicated that the substitutions probably affect protein function. Proliferation assay showed that IGF-1 significantly induced DNA synthesis in C1 and C2 after 20 hs vs 16 and 24 hs of treatment (5.15±0.67 and 6.37±1.00 fold increase over basal respectively, $p < 0.05$ by ANOVA and Bonferroni Tests) and also Akt phosphorylation was significantly stimulated in controls after 10 minutes of treatment with IGF-1 ($p < 0.05$ by ANOVA and Bonferroni Tests). However, no significant increase was observed in any of the three patients in both functional studies (figures A and B).

Conclusion: These mutations led to failure of the IGF1R function causing pre and postnatal growth retardation and microcephaly. Microcephaly should be considered in the evaluation of SGA patients, since it seems to favor the frequency of detection of IGF1R mutations.

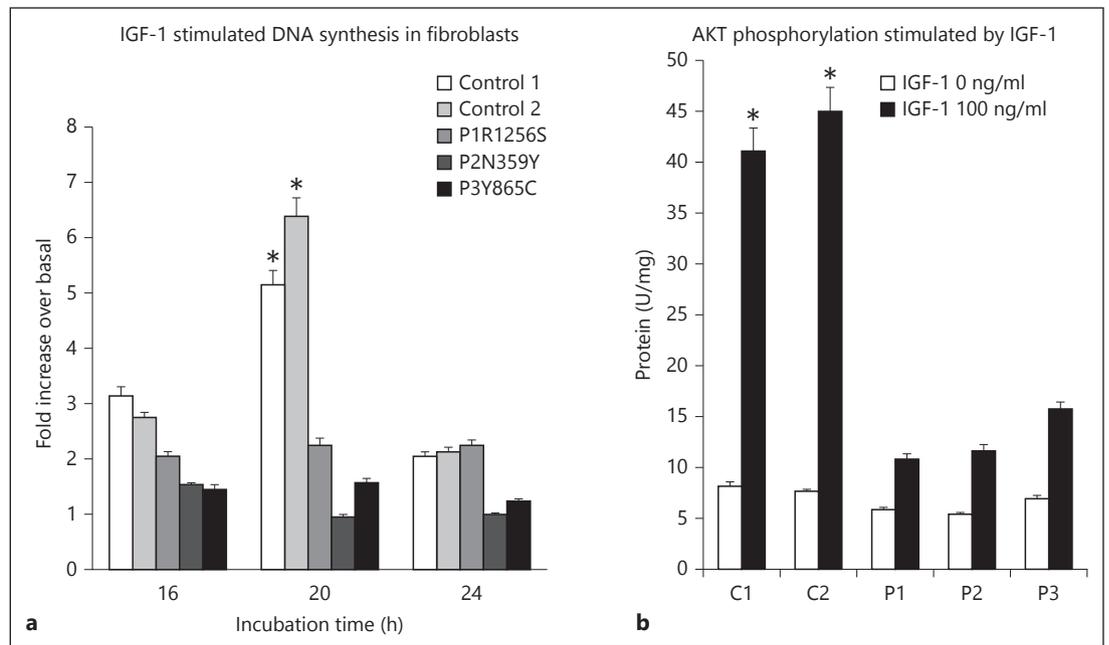


Fig. 1. (for Abstract 19).

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Surveillance of rhGH Therapy: Monitoring Serum IGF-I and IGF-I/IGFBP3 Molar Ratio on a IGF-I Based Dosing Titration Strategy for Optimizing rhGH Therapy in Children

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Introduction: Elevated serum IGF-I and probably IGF-I/IGFBP-3 molar ratio levels are frequently found in children throughout rhGH therapy. Whether sustained elevated serum IGF-I is a harbinger for serious long term adverse events (AE) requires further follow up. Meanwhile surveillance of circulating IGF-I and IGFBP-3 may be useful to identify those children in whom rhGH dose titration might improve safety.

Objective: To determine IGF-I and IGF-I/IGFBP-3 ratio in children on rhGH and dose titration in those with persistently elevated IGF-I to achieve serum IGF-I concentrations within the normal range.

Subjects and Methods: Prospective and interventional study, including prepubertal patients with either growth hormone deficiency (GHD), or born small for gestational age (SGA) without catch up growth, or Turner Syndrome (TS), naïve for rhGH ther-

apy. rhGH dosing: conventional weight based. IGF-I and IGFBP-3 were determined basally and every 3 months (IMMULITE 2000, Siemens). rhGH dose titration was conducted (10% reduction) when IGF-I was above + 2 SDS in two consecutive controls. IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio are expressed as SDS according to local data. Fostering other clinical and biochemical tools of pharmacovigilance serum anti-GH antibodies were analyzed by an in-house ELISA and AE occurrence on rhGH were obtained.

Results: Thirty five patients were enrolled (26 boys and 9 girls) aged 7.0±3.5 years: 14 GHD, 17 SGA and 4 TS. Three patients were excluded from the study, two due to poor compliance and one with a serious AE probably not related to rhGH. Basal IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratios (mean ± SD), were as follows: in GHD -3.02±2.81, -2.15±1.02, -0.8±0.17 respectively; in SGA -0.55±0.73, -0.62±0.88, -0.22±0.65, respectively and in TS 0.53±1.08, -0.35±2.61, 0.17±0.14, respectively. Median follow up was 12 months (range 0 to 20 months). Considering those patients with follow up ≥6 months, the proportion of patients that required rhGH dose titration was 30% (3/10) in GHD, 50% (6/12) in SGA and 66% (2/3) in TS at a median (range) time of 12 (9–20), 9 (6–12) and 7.5 (6–9) months, respectively. The time of occurrence of the event (need to titrate) was not significantly different for GHD and SGA (Kaplan Meier). The need to titrate according to dichotomized (positive or negative) basal IGF-I SDS had a hazard ratio of 8.87 (CI: 1.4–55.0, p = 0.0204) adjusted for pathology, age and dose of rhGH. The overall proportion of IGF-I/IGFBP3 molar ratios above + 2 SDS in basal, 6 and 12 months was 0%, 20% and 7%, respectively. At titration indication, IGF-I and IGF-I/IGFBP3 molar ratio were concomitantly elevated in all GHD, 2/6 SGA and 1/2 TS. Anti-GH antibodies were negative in all but one patient. Prevalence of mild probably related AE was 25.7% (most ≤6

months and 1 concurrent with need of titration); mild not related AE 8.5% and one serious AE.

Conclusions: We confirm a marked proportion of patients with elevated IGF-I throughout conventional rhGH weight based dosing. Therefore rhGH titration appears necessary for a more safe approach. We also found an increment in IGF-I/IGFBP-3 molar ratios in many patients; however their value as a safety measurement remains unclear. The variability in response to a given dose of rhGH reflects not only different sensitivity to treatment among different pathologies but also individual variability. Continuous surveillance of GH dependent biomarkers will provide useful information regarding the long term safety and efficacy of individualized IGF-I based rhGH therapy.

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Osteoporosis-Pseudoglioma Syndrome in a Girl with a Novel Mutation in LRP5 Gene: Clinical Presentation and Response to Oral Bisphosphonate Treatment

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Background: Osteoporosis-Pseudoglioma (OPPG) syndrome is a rare autosomal recessive disorder characterized by severe juvenile-onset osteoporosis with fragility fractures of long bones and vertebrae, and congenital or early-onset blindness. OPPG syndrome is caused by inactivating mutations in the low-density lipoprotein receptor-related protein 5 gene (LRP5). We report a novel frameshift mutation identified in a 7 year-old Mapuche ethnicity girl of a no consanguineous parents, along with clinical phenotype and response to treatment with oral bisphosphonates.

Clinical Case: Product of term pregnancy (37 weeks), vaginal delivery, SGA. Ophthalmologic evaluation at 2 month of age di-

Table 1. DXA at baseline and 1.5 years of treatment with Alendronate (for Abstract 21)

Age (years)	L2-L4 BMD (gr/cm ²)	Z-score	L2-L4 BMD (gr/cm ³)	Z-score
7	0.106	-7.4	0.052	-4.9
8.5	0.413	-3.3	0.187	-3.8
% increase over baseline	389		359	

BMD = Bone mineral density.

agnosed congenital cataract. At 2 years of age, eye examination revealed bilateral microphthalmia, retinal detachment, intraocular hemorrhage, persistent hyperplastic primary vitreous, total bilateral cataract and bilateral vision loss. Since age 6, she had multiple and recurrent fractures in long bones (femur, humerus, tibia) with minimal trauma. She was in a wheelchair not able to walk due to constant pain. Anthropometry at 7 years old: Weight: 15.7 kg (-2.9 DS), Height: 103 cm (-3.6 DS) and BMI: 14.1 kg/m² (-0.42 DS). She had bilateral sunken eyes, with microphthalmia, bilateral corneal leukoma, thoracic kyphosis, and barrel chest. Radiological examinations revealed generalized bone demineralization, severe platyspondyly with biconcave vertebral bodies (compression fractures), thin long and tubular bones and narrow diaphysis with new and old fractures. Laboratory test: normal renal function, Ca: 9 mg/dL, P: 5 mg/dL, alkaline phosphatase: 236 U/L, Ca/Creat urinary index = 0.18, PTH 18.6 pg/mL and 25-hydroxyvitamin D 11.4 ng/mL. DXA was performed at 7 years, showing a severe decrease in bone mineral density Z-score (table 1).

Genetic Analysis: All 23 exons of the LRP5 gene were analyzed by direct sequencing after PCR amplification. Mutation screening for LRP5 gene revealed homozygous mutation in exon 18 (RS3736228) with aminoacid change Ala-Val. Furthermore, a new mutation was found in the patient. She was homozygous for a new mutation at the end of exon 10 (location C.2393+1G>T according to cDNA). A G to T change at the end of LRP5 exon 10 in this patient can change the splicing site GT and delete one base (G) of exon 10 causing a cDNA frameshift. Mother is heterozygous for the same mutation (G/T at this site).

Treatment and Outcome: The patient began supplementation with calcium and vitamin D in doses of 40.000 IU/wk for 2 months. She also started treatment with alendronate 70 mg/wk. Currently she has completed 1.5 years of treatment, with significant clinical improvement (able to stand, walk and is painless) and radiologic (no new fractures, increased of bone mineralization), as well in DXA (table 1).

Conclusions: OPPG syndrome should be suspected in the presence of primary osteoporosis associated with blindness. We have described a new mutation of the LRP5 gene and as well as a favorable response to oral bisphosphonates, with decreased pain, increased BMD and improved quality of life for the patient.

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In Vitro Impairment of Protein Synthesis and/or Secretion of IGFALS Gene Variants Characterized in ALS Deficient or Idiopathic Short Stature Children

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Background: ALS is essential for the stabilization of IGF-I and IGFBP-3 in ternary complexes in the vascular system. ALS deficient (ALS-D) patients, homozygous or compound heterozygous for IGFALS gene mutations present severe IGF-I and IGFBP-3 de-

iciencies and variable degree of growth retardation. In addition, heterozygous carriers for these mutations, either first degree relatives of ALS-D patients or a subset of children with idiopathic short stature (ISS), have levels of IGFBP-3 and ALS intermediate between ALS-D and wildtype (WT) subjects. These findings suggest that *IGFALS* gene variants affect ALS synthesis, secretion and/or function and are responsible for the phenotype observed (height and biochemical parameters).

Aim: To study the impact of ten *IGFALS* gene variants we identified in ALS-D or ISS children (p.E35Kfs*87, p.E35Gfs*17, p.L213F, p.N276S, p.P287L, p.A330D, p.L409F, p.A475V, p.C540R, and p.R548W) on ALS protein synthesis and secretion through cell culture transient transfections.

Methods: *IGFALS* gene variants were introduced by site-directed mutagenesis into a commercial vector containing the entire human *IGFALS* cDNA (pCMV6-XL5-IGFALS). CHO cells (lacking ALS expression) were transiently transfected with wildtype *IGFALS* on each of the 10 variants using lipofectamine and harvested at 48 hours. Both lysates and conditioned media were analyzed by Western immunoblots using a mouse anti ALS antibody to detect protein localization.

Results: Western immunoblots showed that WT-ALS was found mostly secreted into the culture medium at 48 hours. This assay was able to discriminate between variants that affect protein synthesis (absence or diminished levels of protein in both lysates and culture medium: p.E35Kfs*87, p.E35Gfs*17, p.N276S, p.L409F and p.C540R), defects in protein secretion (presence of protein in lysates but absence in culture medium: p.L213F) and neutral variants that do not affect protein synthesis and/or secretion (similar levels of protein in lysates and culture medium as WT-ALS: p.P287L, p.A330D, p.A475V and p.R548W).

Conclusions: The majority of the *IGFALS* gene variants analyzed impaired the biosynthesis of the protein and only p.L213F affected its secretion. Whether the normally synthesized and secreted protein variants retain complete functional capacity for ternary complex formation remains to be characterized.

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Distress and Association Between Serum Levels of Hemoglobin Glycosylated in Adolescents with Type 1 Diabetes Mellitus

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Introduction: It has been reported that adolescents with type 1 diabetes mellitus (DM1), is an especially complicated for adherence period intervening factors such as depression, stress associated with treatment compliance and the changes brought about in their social and family environment. The Diabetes Distress (DD) is defined as the emotional distress that comes from living with diabetes and has been reported in 18–35% of cases. High levels of DD was significantly associated with increased HbA1c, poor self-care and poor quality of life.

Objective:

- To determine the frequency of emotional distress in adolescents with Type 1 Diabetes Mellitus.
- Meet the correlation between diabetes distress and serum level of glycosylated hemoglobin in adolescents with Type 1 Diabetes Mellitus.

Methods: A cross-sectional, prospective study was conducted in adolescents with DM1 attending the outpatient pediatric endocrinology in high specialty Hospital in Mexico City. We included adolescents of both sexes, aged 9 to 16 years 11 months, excluding those in antidepressant drug treatment and less time evolution of one year. Weight, height, BMI and mean glycosylated hemoglobin (HbA1c) in the last year, as well as the outline of insulin treatment were recorded. Emotional stress, related to the doctor, and interpersonal therapy: the Diabetes Distress Scale Test 17 (DDS 17) (validated in Hispanic population) that includes 4 subscales to identify areas where intervention is required is given. With this tool, you get a total score and four subscales: less than 2 indicate little or no distress, between 2.1 to 2.9 moderate and >3 severe.

Analysis: Description: mean and standard deviation for quantitative variables and percentage frequencies for qualitative variables. Inference: the Pearson correlation was used to assess the correlation of HbA1c and emotional distress.

Results: 80 patients, 48.7% (39) females and 51.3% (41) males, with a mean age 12.2 +2.2 years were studied. HbA1c was 9 +1.9% last year, with evolution time 4.6 +3.2 years and BMI 20 PC 65, with 92.5% with intensive or semi-intensive scheme with multiple doses of insulin. 51.3% (41) presented mild or no distress, 27.5% (22) moderate and 21.3% (17) severe. For moderate and severe emotional distress, 41% and 82% of cases occurred in males respectively. The correlation of DDS17 full and HbA1c was $r = 0.24$, $p = 0.03$ and subscales, the correlation was significant stress treatment in both sexes ($r = 0.42$ and $r = 0.36$, $p = 0.005$) and emotional stress ($r = 0.32$, $p = 0.04$) only in the case of men.

Conclusions:

- In our study we found that the frequency of severe distress is 21.3% and male sex were the most affected (82%).
- It is a slight correlation DDS17 and HbA1c, associated mainly in males and in the subscales emotional stress and stress treatment found.

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Oxidative Desoxic Ribonucleic Acid (DNA) Damage in Obese Children

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Background: 8-OHdG is considered as the most sensitive and useful marker of oxidative DNA damage. It is important that cell injury, mitochondrial and nuclear DNA damage by free radicals, should be repaired. The antioxidant system is blocked with high blood glucose and obesity, which leads to increased activity of free radicals and increased tissue damage, mutagenesis, carcinogenesis

and atherosclerosis. The aim of our study was to measure the serum levels of 8-OHdG in a group of obese children and to compare with children with normal body mass index (BMI). Also to assess whether if there is correlation between metabolic values and serum levels of 8-OHdG.

Methods: Cross-sectional comparative study. A total of 58 children with exogenous obesity and 10 children with a normal BMI, were investigated. All subjects were given a questionnaire for familial history of obesity, type 2 diabetes mellitus (DM2), arterial hypertension and premature coronary disease, in addition to anthropometry and physical examination. An oral glucose tolerance test were performed, along with basal and 120 minutes insulin and glucose measures. The concentrations of total cholesterol, C-HDL, C-LDL, triglycerides, C-RP and total adiponectin were measured as well. Serum concentrations of 8-OHdG were determined using an EIA kit, a competitive assay that utilize anti-mouse IgG coated plate and a tracer consisting of an 8-OHdG enzyme conjugated. Descriptive statistics were performed, Student's t test for independent samples, χ^2 test, Pearson correlation.

Results: The obese children had higher weight, BMI and waist circumference ($p < 0.001$), compared with those with normal BMI, also obese children had a higher frequency of family history of first or second degree with DM2 ($p = 0.004$). Regarding the metabolic profile, obese children had higher baseline insulin levels ($p = 0.008$), insulin at 120 minutes ($p = 0.016$), triglycerides ($p = 0.049$), C-RP ($p = 0.016$) and serum 8-OHdG ($p = 0.01$). We found a positive correlation between 8-OHdG concentrations ($r = 0.315$, $p = 0.009$) and blood pressure ($r = 0.429$, $p < 0.001$) with BMI, and a negative correlation of adiponectin and C-HDL with BMI ($r = -0.489$, $p = 0.007$, $r = -0.328$, $p = 0.007$ respectively).

Discussion: Higher levels of 8-OHdG found in obese pediatric patients compared with children with normal BMI may reflect oxidative damage. Obesity phenomenon favors and accelerates the oxidative stress by means of increased insulin resistance, and decrease in the protective factors such as adiponectin.

Conclusions: Obese children have higher concentrations of 8-OHdG, compared with children with normal BMI. It is the first study in pediatric patients with obesity where oxidative damage to DNA is determined by measuring serum 8OHdG by a more sensitive assay with little variability.

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Novel Sex-Specific Visceral Adiposity Index for Mexican Pediatric Population

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Background: Visceral Adiposity Index (VAI) has been used as a surrogate indicator of visceral adipose function in adult population. VAI has been strongly associated to adipocytokine synthesis, pro-inflammatory activity, insulin resistance, dyslipidemia, hyper-

tension and atherosclerosis. Anthropometric and metabolic abnormalities including waist circumference (WC), body mass index (BMI), triglycerides and HDL-cholesterol have been considered as classical markers of cardiometabolic disease. VAI has been constructed as a model that includes and correlates these anthropometric and metabolic markers and has been proposed as a risk factor index associated to final outcomes such as coronary heart disease, myocardial infarction and transient ischemic stroke in adult population. Some studies conducted in pediatric population have extrapolated VAI calculation in order to predict these abnormalities in children. Nonetheless, visceral adipose deposition, absolute values of BMI, waist circumference-BMI correlation, as well as reference triglycerides and HDL-cholesterol levels might be different for pediatric population.

Aim: The aim of the present study was to design a new sex-specific VAI model adjusted for pediatric population and based on the original VAI formulation.

Subjects and Methods: 549 children (289 males and 260 females) aged 3–17 years were included for analysis. Eutrophic children ($n = 223$) were recruited from elementary schools nearby the hospital. Overweight and obese subjects ($n = 89$ and $n = 237$, respectively) were patients that regularly attended pediatric obesity clinic at the pediatric department in General Hospital of México. Anthropometric evaluation included weight, height and waist circumference (measured at the midpoint between the lowest rib and the immediately above point of iliac crest). BMI was calculated and triglycerides and HDL-cholesterol measured in a 12 hrs fasting condition (mMol/L).

Results: A mathematical regression model was used to correlate waist-circumference and BMI variables in order to calculate the first VAI formula component. Eutrophic, overweight and obesity spectrum of individuals were considered for first analysis. A non-linear quadratic regression model accurately explained the relationship between waist circumference and BMI in pediatric population. Triglyceride and HDL-cholesterol means were calculated from eutrophic population and included in the second formula component.

$$\text{Females: VAI} = [\text{WC}/-0.012\text{BMI}^2 + 3.05\text{BMI} + 10.81] [\text{Tg}/0.97* 1.35/\text{HDL}]$$

$$\text{Males: VAI} = [\text{WC}/-0.023\text{BMI}^2 + 3.83\text{BMI} + 00.65] [\text{Tg}/0.90* 1.39/\text{HDL}]$$

Discussion: VAI formula construction seemed to be different in children compared to adults. In the present study we propose a new sex-specific visceral adipose index for pediatric Mexican population living in urban areas that could be further used to predict abnormal cardio-metabolic outcomes. This index must be validated in our clinic as well as in others states of the country.

Growth and Puberty in Obese Patients and Their Not Obese Brothers

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Aims: Demonstrate if obesity modify growth, bone maturation and puberty in normal and obese brothers and sisters.

Material and Method: Observational, cross-sectional, analytical, comparative and prospective study in 264 patients (116 males, 148 females) with obesity and 390 non obese brothers (196 males, 194 females), selected in public and private schools.

Although not at the same time, all the patients were followed since 8.5 ± 4.0 years old until the end of growth, and every 6 months were collected height (1 mm range stadimeter), weight (0.1 k range mechanic weighing machine), body mass index, height velocity, and Tanner stages; X ray in no dominant hand for bone age was performed yearly. The patients with obesity remain with BMI higher than 90 percentile during all the study, and their brothers/sisters between 10 and 50 centiles.

Inclusion criteria was: one patient with obesity and one or more brother with normal BMI (gender match in every case), no chronic disease, no pharmacological treatment for more than 2 weeks/year, no use of oral or dermal steroids, no changes in more than 10% in BMI during the study. Growth charts used were from CDC for height, weight and BDM, Tanner & Davis for growth velocity and Tanner & Marshall stages for puberty progression.

Results: Obese and not obese showed concordance with familiar target height ± 4 cm, but obese males were 3.5 ± 1.2 cm taller than their brothers and obese females 2.3 ± 1.7 cm taller than their sisters, during childhood.

Puberty start at bone age equivalent to 12.5 years old in males and 10.5 years old in females, obese and not obese, but obese males and females showed advances bone age (6 ± 3 months and 9 ± 4 months, respectively).

Pubertal growth spur was higher in growth velocity (2.2 ± 1.6 cm/year in males, 1.1 ± 0.8 cm/year in females) but shorter in duration (6 ± 3 months in males and 8 ± 4 months in females), in obese patients of both genders.

According bone age (BA) maturation, the classification of the growth pattern was Intrinsic (BA = chronological age), delayed (BA < chronological age), advanced (BA > chronological age).

Analysis: Inside the same family, assuming very close correlation with genetic conditions, the obese males and females are taller than their brothers/sisters at the same age, and although bone maturation is advanced since childhood, the final height is taller than the no obese brothers/sisters. Growth velocity spur during puberty start in the same Tanner stage and bone age in boys and girls, with or without obesity.

Conclusions: Advanced growth pattern (bone age > chronological age) is more frequent in obese than in no obese, and final height is taller in obese than in not obese boys and girls.

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Phenotypic Variability in Patients with P450 Oxidoreductase Deficiency

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Background: P450 oxidoreductase (POR) is a flavoprotein that transfers electrons from NADPH to all microsomal cytochrome P450 enzymes (including 17 α -hydroxylase/17-20 lyase, 21 hydroxylase and aromatase enzymes). The clinical presentation of POR deficiency shows broad phenotypic variability regarding glucocorticoid sufficiency, sexual differentiation in 46,XY and 46,XX, and the presence of skeletal malformations characteristic of Antley-

Table 1. (for Abstract 26)

	Males		Females	
	No obese	Obese	No obese	Obese
Childhood height	± 4 cm PH	>3.2 cm	± 4 cm PH	>2.8 cm
Puberty start	Normal	-6 ± 3 months	Normal	-9 ± 4 months
Growth velocity	Tanner 3-4	Tanner 3-4	Tanner 2-3	Tanner 2-3
Puberty duration	Normal	-3 months	Normal	-8 months
Final height	± 4 cm PH	>3.5 cm	± 4 cm PH	>2.3 cm
	Males		Females	
	No obese	Obese	No obese	Obese
Intrinsic	70%	20%	68%	30%
Delayed	20%	15%	10%	6%
Advanced	10%	65%	26%	64%

Bixler syndrome (ABS). The phenotypic complexity derives not only from the variable degree of enzymatic deficiency but also from the capacity of different mutations to affect the various enzymes differentially.

Aim: To describe the clinical phenotype and biochemical and molecular alterations in a 46, XY patient (P1) and five 46, XX patients (P2-6) with POR deficiency.

Results: P1 presented with ABS phenotype, micropenis and glucocorticoid deficiency. Four 46, XX patients (P2-P5) were evaluated in the prepubertal period (chronological age 0.7–7.4 years). All of them showed signs of prenatal virilization. P2 presented with ABS phenotype and history of maternal virilization during pregnancy. P6 consulted at 16.5 years for lack of pubertal development and primary amenorrhea, with a history of discrete fetal virilization. All six patients presented increased basal and/or ACTH-stimulated 17OHP and P serum levels associated with low or undetectable levels of androgens (A4, T and DHEAS) suggesting impaired 17.20 lyase activity of the P450c17. P2, P5 and P6 presented insufficient cortisol response after ACTH supporting involvement of both P450c21 and P450c17. In P6, the clinical phenotype with serum T and A4 within the normal range suggests the impairment of P450 aromatase activity. Mutations in the P450 oxidoreductase gene were found in all patients: p.S379Cfs*24/p.P399_E401dup (P1), p.A287P/p.A287P (P2), p.V492M/p.A91V (P3), p.V492M/IVS6-2A>T (P4), p.R550W/p.G539R (P5), and p.H473P/p.[R457_Y458delinsH; A503V] (P6). Variations p.V492M, p.A91V, H473P, p.R457_Y458delinsH, and p.S379Cfs*24;

p.P399_E401dup were not previously described and *in silico* studies showed pathogenicity.

Conclusion: The spectrum of clinical and biochemical manifestations associated with mutations in POR is complex and variable. Although the molecular study is required for a definitive diagnosis, detailed steroid profile after ACTH stimulation is useful not only for the diagnosis but also to identify those patients with glucocorticoid insufficiency. The comprehension of the pathophysiology and the consequences of the deficiency would help to better understand the clinical and biochemical findings.

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Absence of Leptin-Melatonin Correlation in Obese Pediatric Patients of Both Genders from Childhood to the End of Puberty

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Introduction: Previous studies have shown contradictory results about the relationship between melatonin and leptin during the onset and progression of puberty. Our objective, in this pre-

Table 1. (for Abstract 27)

Patient	1	2	3	4	5	6
Chronological age (years)	1.5	7.4	0.7	2.9	3.5	16.5
Karyotype	46,XY	46,XX	46,XX	46,XX	46,XX	46,XX
ACTH (pg/ml)	293	35.4	25.5	21.8	32.8	83.1
Cortisol (mcg/dl)	Basal	12.5	16.7	12.8	19.7	13.4
	Peak	12.6	16.7	24.2	24.8	5.8
17OHP4 (ng/ml)	Basal	>9.5	5.9	3.8	0.8–8.1	0.6–5.9
	Peak	>9.5	16.2	16	15.2	4.8
P4 (ng/ml)	Basal	27	13.7	3.4	0.4–5.1	0.2–3.3
	Peak	115	64.4	16	7.6	8.2
Testosterone (ng/ml)	<0.05	<0.05	<0.2	<0.05	<0.05	0.15
Androstenedione (ng/ml)	<0.10	0.3	<0.30	<0.10	<0.10	0.61
SDHEA (ng/ml)	149	182	<150	11.5	36–91	1206

Table 1. (for Abstract 28)

	6-SMn (µg)	6-SMd (µg)	Δ 6-SM (µg)	Leptin (ng/mL)
Females G1	2.90 (0.74–20.4)	0.54 (0.21–2.44)	2.42 (0.42–19.0)	16.8 (4.80–36.0)
Females G2	1.45 (0.25–7.98)	0.83 (0.11–2.52)	0.61 (0.07–6.17)	36.0 (22.8–72.0)
Females G3	0.70 (0.16–4.95)	0.45 (0.07–1.20)	0.31 (–0.45–4.43)	50.3 (24.6–90.0)
Males G1	2.01 (0.25–18.0)	0.54 (0.08–5.61)	1.46 (0.14–12.4)	22.0 (4.80–57.0)
Males G2	1.48 (0.32–6.76)	0.36 (0.15–2.97)	1.22 (0.12–4.67)	20.0 (3.00–60.0)
Males G3	1.25 (0.22–7.13)	0.46 (0.11–1.41)	0.25 (0.13–6.18)	19.4 (10.4–60.0)

liminary study, was to evaluate in a pathophysiological model, such as obesity associated with cardiovascular risk factors, the potential role of both hormones.

Material and Methods: We evaluated 97 obese patients (BMI >2 SDS) classified into: G1 (prepubertal) 17 females: 5–10.4 years, 18 males: 5–12.2 years, G2 (Tanner II and III) 16 females: 9–12.5 years, 14 males: 10–13 years and G3 (Tanner IV and V): 18 females: 11.1–17 years, 14 males: 12–17.1 years. Measurements of urinary 6-sulfatoxymelatonin (6-SM) were performed (radioimmunoassay, Stockgrand Ltd, Guildford, UK) in nocturnal (6-SMn: 6 PM to 8 AM) and diurnal (6-SMd: 8 AM to 6 PM) samples. Levels of 6-SM were expressed as μg excreted by time interval and delta 6-SM as the nighttime-daytime difference. Leptin was measured by radioimmunoassay (DIAsource ImmunoAssay SA, Belgium). The Spearman test was used to evaluate correlations between 6-SM and leptin.

Results: No associations were found between melatonin excretion and leptin secretion in any of the subgroups of both genders.

Discussion and Conclusions: Various neuroendocrine mechanisms are involved in the onset and progression of puberty in humans. In addition, the role of adipose tissue during this physiological process is controversial. Melatonin plays an important role in the integration of peripheral signals and energy metabolism. It potentiates insulin-induced leptin synthesis and release via MT1 receptors in human adipocytes. The absence of correlation between melatonin and leptin secretion in obese patients, found under the conditions of this study, would not rule out the possibility that both hormones might play an essential role through different circuits in the central nervous system and peripheral tissues. This relationship might vary under different physiological and pathological conditions; therefore it should be evaluated in other experimental models with and without obesity. Our findings would contribute to a better understanding of the circadian rhythm and of the central and peripheral mechanisms related to energy homeostasis throughout normal pubertal development and in certain pathophysiological models such as obesity.

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Bone Mineral Density and Body Composition in 2 Year Old Infants, Born with Very Low Birth Weight (VLBW)

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Background: In small for gestational age (SGA) infants born at term, early (<1 yr) catch up (CUG) is linked to altered body composition which is associated to an adverse metabolic profile. In preterm infants born with VLBW differences by birth weight SDS and early CUG have not been consistently found at this age.

Subjects and Methods: VLBW preterm infants recruited in a longitudinal fashion had body composition determined by a Dual X ray absorptiometry (DEXA) scan (DXA; Lunar DPX-L, Madison, WI; software 1.3), in the fast scan mode at age 2 yrs (corrected age) at the Radiology department, Medicine Faculty of the Catholic University of Chile. Bone mineral density (BMD), Bone mineral content (BMC), total fat mass and fat mass at trunk and limbs and total lean mass, were evaluated.

Results: 39 healthy infants followed prospectively (16 SGA, 10 F; 23 AGA, 14 F) were included in this analysis. At birth, gestational age (mean and SDS) was 29.6 ± 2.2 weeks, birth weight 1132 ± 264 g and at evaluation: age was 2.4 ± 0.14 yr, weight -0.55 ± 1.2 SDS (SGA -0.66 ± 1.36 ; AGA -0.47 ± 1.17 , ns), height (SGA -0.23 ± 1.0 ; AGA -0.10 ± 0.25 , ns). Results of body composition are shown in the table, all data is presented as SDS. Statistics were applied to raw data and next adjusted by height SDS. Z scores are those of a population of 30 (15 F) Chilean healthy infants of 2 yrs born at term used to build normative data. Comparisons were made for each subjects group (SGA and AGA) by student t test or Mann Whitney test according to the data distribution. All statistics were run on STATA 10.0 for Windows.

Conclusions: At 2 yrs of corrected age no differences in BMD nor BMC in those infants born VLBW compared to infants born at term, however they had more fat mass and less lean mass. In addition within VLBW infants those born AGA had more fat mass

Table 1. (for Abstract 29)

	BMD	BMC	% of fat mass	Trunk fat mass	Limb fat mass	Lean mass
AGA n = 23	0.14±0.14	-0.66±1.40	1.13±3.10	2.67±5.09	1.90±2.87	-2.04±1.40
SGA n = 16	0.08±0.12	-1.22±1.90	0.87±2.90	0.50±2.01	-0.23±2.75	-2.52±0.96
p = non adjusted	0.07	ns	ns	0.04	0.02	ns
p = adjusted	ns	ns	ns	0.09	0.03	ns

in limbs and trunk than those born SGA. This latter difference was lost when adjusted by height SDS. Follow-up of these patients will allow to determine whether these differences ameliorate or increase at older ages.

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Short Stature Caused by Novel Nonsense IGFIR Mutation

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Background: IGF-I is essential for human growth *in utero* and postnatally, mediates its effects through the IGF-I receptor (IGFIR), a widely expressed, cell surface tyrosine kinase receptor. IGFIR is synthesized as a single polypeptide precursor, the mature functional receptor is a tetramer ($\alpha_2\beta_2$), with the extracellular dimeric α -subunits involved in ligand binding, whereas intrinsic tyrosine kinase activity is located within the β -subunits. The aim of this study was the analysis of the *IGFIR* gene and signaling pathway

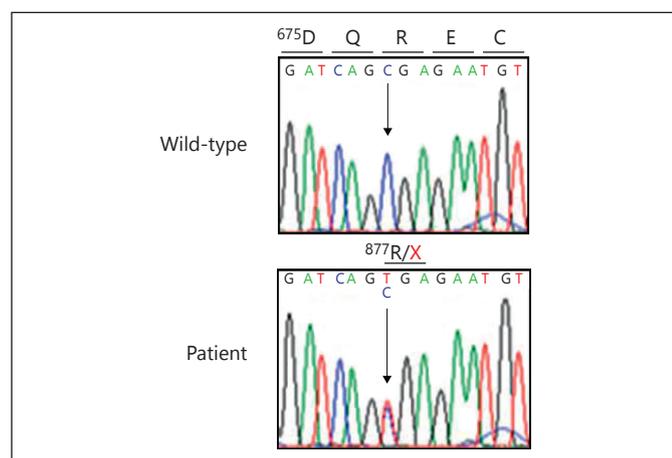


Fig. 1. (for Abstract 30).

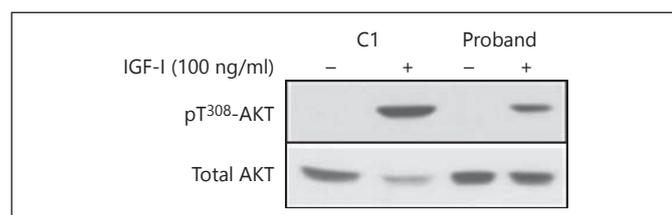


Fig. 2. (for Abstract 30).

in a patient with pre and postnatal growth retardation, and in his family members.

Subjects and Methodology:

Clinical presentation: The female patient, born at 35 wk gestation to nonrelated parents, had a birth weight of 2.1 kg [SD score (SDS) -1.02] and birth length of 42 cm (SDS -1.8). At age 8.3 yr, she had a height of 116 cm (SDS -2.1) a body weight of 21.7 (SDS -1.1), a head circumference of 51 cm, and a body mass index (BMI) of 16.3 (+0.25). Her father also had short stature (163 cm, SDS -1.81), but her mother and older brother had normal height.

Hormonal profile: GH, basal 1.1 ng/mL; peak GH after stimulation with clonidine 11.2 ng/mL; serum IGF-I, 380 and 488 ng/mL; and IGFBP3, 4.2 ng/mL.

Molecular studies: Fibroblast cell cultures were established from skin biopsies obtained from the 4 family members. From total cell extracts, phospho- and total AKT (IGF-I signaling mediator) were analyzed by Western blots after 20 min of IGF-I stimulation (100 ng/mL).

Results: The clinical picture and hormonal profile of the patient was suggestive of a defect in the IGF-I/IGFIR signaling pathway. Sequencing of the *IGFIR* gene from genomic DNA obtained from either whole blood or cultured fibroblasts revealed that the patient carries a novel compound heterozygous nonsense mutation: in exon 13 resulting in the change of codon R877 (CGA) into X877 (TGA) (figure 1). Analysis of the genomic DNA from the other family members revealed that the father was heterozygous for R877X, thus confirming the paternal origin of the R877X mutation. This heterozygous mutation generates a truncation before the disulfide bond formation, between α and β subunits of the IGFIR. Fibroblast cell culture from the patient showed reduced AKT phosphorylation on threonine 308 when stimulated with IGF-I (figure 2).

Discussion and Conclusion: This novel heterozygous mutation which causes short stature is located before the disulfide bond formation between α and β subunits of the IGFIR. The presence of the mutation results in a diminished IGF-I induced activation of the IGFIR pathway in skin fibroblast cells.

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Aortic Dilation in a Large Cohorte of Pediatrics Patients with Turner Syndrome. Implication of Chronological Age as a Variable to be Included in the Analysis

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Background: Aortic dilation (AD) occurs in Turner Syndrome (TS) increasing the risk of aortic dissection at all ages. It has been published by Matura et al (2007) an aortic size index (ASI), taking into account the ratio between ascending aorta (cm) (AA) and body surface (m²), setting a value >2 cm/m² for the diagnosis of AD in young adults TS patients. However, its usefulness in pediatric TS patients has not been validated. Another tool described in normal children, is the ratio (AVI) between AA and the diameter of the thoracic vertebra (TV).

Aim: To evaluate in pediatric TS patients the usefulness of ASI and AVI to assess AD.

Methods: Study subjects included 87 patients with TS, chronological age (CA): range 3.2–25.7 years (y) and 49 control girls, CA: range 0.7–19.2 y. For the analysis of results, data were divided according to CA in 3 groups (Gr). Gr1: 0.1–7.9 y (n: 10), Gr2: 8–15.9 y (n: 43) and Gr3: ≥ 16 y (n: 34). AA and TV diameters were measured by chest Computed Tomography. AD was defined according to the mean +2 SD of control group (ASiC and AViC) and were compared to ASI value (>2 cm/m²).

Results: In total TS patients, AD was found in 39.1, 17.2 and 13.3% according to ASI, ASiC and AViC respectively. ASI vs ASiC ($p < 0.01$). ASiC vs AVI (p : ns). AD by ASI vs ASiC were significantly higher in Gr1 80 vs 20% ($p < 0.02$) and Gr2 46 vs 16% ($p < 0.01$) respectively. In Gr3 ASI vs ASiC were not significantly different, 17.6 vs 17.6% (p : ns) respectively. A significantly negative correlation was found between ASiC and CA. Severe AD was detected by ASI, ASiC and AViC.

Conclusions: ASI overestimate AD during childhood and young adolescent TS patients (Gr1 and 2). In pediatric population the evaluation of AD required to be normalized by body surface and CA. In addition, AVI seems to be another useful tool to be used. Additional follow up is necessary to evaluate the long time consequences of these findings.

Objective: To determine urinary Cys-C in DM-1 children and adolescents, compared it with a control group and evaluate its correlation with clinical and biochemical parameters of renal function and metabolic control.

Methods: We studied 18 children and adolescents with DM-1 and 15 controls. Age, sex, anthropometry, time since diagnosis, Hb A1c, ACR, creatinine and Glomerular filtration rate by Schwartz was consigned. A 10 ml urine sample was centrifuged (12000 g x 10 min) and then ultracentrifuged (38000 gx1 hr, 4 ° C) to obtain supernatant(S) and exosomal (E) fractions. Cys-C abundance was determined in 100 ug S and E by Western blot. Flotillin was used to normalize Cys-C values.

Results: 18 DM-1 and 15 controls. Table 1 show results in DM-1 and control groups.

Correlation was found only between Cys-C/Flot and microalbuminuria (p 0.008) but not for the other renal function parameters measured.

Conclusions: Urinary Cyst-C/Flotillin and Cys-C E/S is significantly more abundant in DM-1 than control children. Cyst-C/Flot correlates with microalbuminuria but not to other classical parameters of Diabetic Nephropathy.

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Cystatin C in Children and Adolescents with Type 1 Diabetes Mellitus. A New Precocious Biomarker of Diabetic Nephropathy?

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Introduction: Cystatin C (Cys-C) had been identified as an early biomarker of acute and chronic renal damage, and useful in diagnosis of Diabetic Nephropathy.

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Androgen Insensitivity Syndrome: A Risk of Germ Cell Tumor Development Before Puberty

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Introduction: Certain disorders of sex development (DSD), as androgen insensitivity syndrome (AIS), are prone to develop germ cell cancer (GCC). This risk is related to the expression of OCT3/4, and other markers of GC as TSPY [1]. In AIS, high risk is associated with the onset of puberty and it is worst in parcial (PAIS) than in complete (CAIS) [2]. OCT 3/4 is expressed in embryonal gonocytes [3].

Table 1. General data and Cyst-C in DM-1 and control group (for Abstract 32)

Group	DM1 (n = 18)	Control (n = 15)	p
Age (years)	13.3±2.8	11.8±3.4	NS
Male/Female	9/9	5/10	NS
Time from diagnosis (years)	5.7±4.5		
HbA1c (%)	9.3±2.2		
ACR (mg/g)	4.9±5.2		
Cys-C (S) UA	47,637.5+70,860	28,740.1+18,840.8	NS
Cys-C (E) UA	552,000+130,267.6	12,187+12,725	NS
Cys-C/Flotilina	2.06±2.35	0.6±0.7	0.001
Cys-C E/S	1.96+2.26	0.57+0.42	0.03

Aim: To study the incidence of GCC risk in a pediatric/young adult population of AIS patients.

Material and Methods: We studied 19 gonads of 11 patients belonging to 9 families: 13 were prepubertal (PP): median of age 4.4, range 1.25–10.3 years-old (y) (CAIS n = 7; PAIS n = 6), and 6 were pubertal-young adult (PU), median of age 19.0, range 16.2–23.0 y (CAIS n = 6). The size of the gonad and the value of serum testosterone were used as criteria to define a PU. Five/6 PAIS gonads had an inguinal location and 1 had a labioscrotal location. Seven/13 CAIS gonads had an inguinal location and 6 had an abdominal location. Diagnosis of AIS was based on phenotypic features, hormonal studies, and AR gene loss-of-function mutations were performed in all cases. Histological description, as well as immunoexpression of OCT3/4 and TSPY were done. An ultra-structural study was carried out in 2 PP CAIS gonads. Nineteen testes of 19 patients without endocrine or metabolic disorders were used as controls (C).

Results: Signs of testicular dysgenesis, such as cords forming rings, microlithiasis, very fibrous interstitium and huge multinucleated and vacuolated GC, were found in the 19 AIS testes. High nuclear OCT3/4 expression was found in 4 of 7 inguinal PP CAIS testes and in 2 of 6 abdominal PU CAIS testes. Abundant gonocytes close to the basal membrane was assessed by electron microscopy in 2 PP CAIS testes. Gonocyte and OCT 3/4 positive expression are not normal at this age. No signs of dysgenesis or expression of OCT3/4 was found in C group. TSPY expression in GC was found not only in AIS but also in C testes.

Conclusions: Presence of dysgenetic signs, expression of a GCC risk marker, and abnormally immature GCs in testes of PP and PU patients with CAIS were found, suggesting that a careful follow-up of these patients should be recommended. The usefulness of premalignant markers in AIS testis to predict risk of germ cell tumor remains largely unclear. The concept that PP is a period of life with lesser risk of GCC development must be reconsidered.

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Sertoli Cell Function Was Not Affected by Chemotherapy in Boys with Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

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Introduction: Testicular germ cells are highly sensitive to chemotherapy, while precursors of Leydig cells in prepubertal boys would be less affected. However, it is not known yet if chemotherapy affects Sertoli cells, whose function is essential for normal pubertal and adult spermatogenesis. The objective of this work was to evaluate the function of the Sertoli cell in children and adolescent survivors of Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LL) who received polichemotherapy.

Study Design and Methods: We performed a retrospective cross-sectional study in male survivors of ALL or LL treated with polichemotherapy at hematology Unit of R. Gutiérrez Children's Hospital between 2004 and 2012. Exclusion: patients with incomplete laboratory results or ALL relapse. Patients were classified into 3 risk groups according to hematologic characteristics at diagnosis: High, Intermediate or Standard risk. Treatment was adapted to each risk group. The main outcome measure was serum Anti-Müllerian Hormone (AMH). Results were expressed as median and range of SDS according to published reference values [1]. Secondly, FSH values were analyzed as an indirect Sertoli cell marker.

Results: Out of 55 children (LLA: 52 and LL: 3), 18 had standard risk, 30 intermediate risk and 7 high risk. Median age at start of chemotherapy was 6.7 years (range 1.8 to 16.7). Treatment duration was 2.2 years (range 0.8 to 3.3). 31 patients completed treatment before the age of 10 years and 24 after the age of 10 years. Last hormonal evaluation was 3.0 years (range 1.1 to 12.1) after treatment.

Within the first year after termination of chemotherapy, 29 patients were evaluated; AMH concentration was at -0.09 SDS (-1.31 to 4.92). Between the 2nd and 6th year, 30 patients were evaluated; AMH was at -0.36 SDS (-1.07 to 1.66). In 13 patients evaluated 6 to 12 years after chemotherapy completion AMH was at -0.56 SDS (-1.24 to -1.45). Differences between the three time periods of evaluation were not significant, and no patient had a concentration of AMH <2 SDS (Kruskal-Wallis p : 0.38).

We did not find differences in AMH according to baseline risk, while n of patients at high risk was only 7.

7% of patients were evaluated within 1 year after chemotherapy completion and 16% of those evaluated after 1 year had an FSH $>97^{\text{th}}$ centile. All patients with high FSH were older than 11 years of age. AMH level in these patients was at -0.48 SDS (-1.24 to 1.45).

Conclusion: Sertoli cell function by means of their ability to secrete AMH was not damaged in children with ALL or LL who received polichemotherapy. This result provides insight for con-

servation of germ cells in boys submitted to chemotherapy, since the procedure requires a Sertoli cell population with appropriate function for normal spermatogenesis to be reestablished.

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Thyroid Function Follow-Up of Children with TSH Cutoff Between 5 and 10 mIU/L in Neonatal Screening

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Objective: The aim of this study was to evaluate late thyroid function evolution of children with dry bloodspot TSH (s-TSH) between 5 and 10 mIU/L in congenital hypothyroidism screening.

Methods: Retrospective study of thyroid function on a group of children born from 2003 to 2010 with T_{SH} between 5 and 10 mIU/L and who were put on L-thyroxin (L-T4) treatment in the first two years of life due to serum TSH (s-TSH) increased over 10 mIU/L. Exclusion criteria: premature birth (32), Down syndrome (13), severe neonatal anoxia (2), maternal hyperthyroidism (1), follow up lost or no late thyroid evaluation (42).

At the age of 2 or 3, after discontinue L-T4 for at least 1 month, serum levels of TSH and free T4 were determined to distinguish between permanent and transient congenital hypothyroidism. Permanent hypothyroidism was considered when, after the thyroid function reevaluation, L-T4 was reintroduced due to steadily s-TSH ≥ 10 mIU/L. When it was possible thyroid [TC]-99m scintigraphy was done for etiologic investigation.

Results: From 380,741 live born screened, 3,713 (1.0%) had T_{SH} between 5 and 10 mIU/L; 339 (9.1%) of them had s-TSH ≥ 10 mIU/L and were treated.

249 children (146 males) were included in the study after L-T4 withdrawal and 78 had permanent thyroid dysfunction; 76 had thyroid scintigraphy evaluation that showed 4 thyroid dysgenesis (2 hemiagenesis, 1 lobe hypoplasia and 1 thyroid hypoplasia) and 72 *in situ* thyroids (66 normal volume being 10 with increased and 5 with reduced uptake, and 6 goitres).

Conclusion: The s-TSH screening-test cutoff value of 5 mIU/L joined to the clinical and laboratory follow-up allowed the early detection of 78 permanent hypothyroid children that would have been missed by using the current T_{SH} cutoff of 10 mIU/L.

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Blood Pressure Profiles, Cardiovascular Risk, and Renal Handling During an Oral Sodium Load Test in Adolescents and Young Adults with Congenital Adrenal Hyperplasia (CAH) due to 21-Hydroxylase Deficiency

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Introduction: Long term glucocorticoid and mineralocorticoid treatment in patients with congenital adrenal hyperplasia (CAH) might increase the risk of cardiovascular disease. However, whether these consequences occur early in adolescents and young adults remain controversial.

Aim: To assess cardiovascular risk and renal handling throughout an oral sodium load test in adolescents and young adults with salt wasting (SW) and simple virilizing (SV) CAH due to 21-hydroxylase deficiency.

Patients and Methods: Cohort study. Patients with CAH regularly followed, through an exhausted clinical (height, BMI) and biochemical assessment, (17OHP, Androstenedione, total testosterone, plasma renin activity (PRA), glucose, insulin) from 2010 to 2013 and a healthy control group were enrolled (Tanner stage 5, age ≤ 28 years). CAH patients received mean equivalent hydrocortisone doses of 14.5 ± 2.4 mg/m² and 9 α -fludrocortisone doses for patients with SW-CAH was 0.09 ± 0.02 mg/d. Cardiovascular evaluation included ambulatory blood pressure measurement (ABPM), color Doppler echocardiography and intima media thickness (IMT) measurements by carotid Doppler ultrasonography before a 3-day oral sodium load test (NaCl 10 gr/d). Physiological nocturnal dip in blood pressure was defined as $\geq 10\%$ difference between day-time and night-time BP. Subjects suffering from renal or cardiac disorders and history of hypertension were excluded (n = 2). One CAH patient with poor hormonal control was excluded from the salt load test. Fisher exact test, t-test and ANCOVA using BMI as covariate were used as appropriate.

Results: 19 CAH patients (15 SW, 4SV) (5 males) aged 14.6–28.0 yr and 11 controls (6 males) aged 17.1–26 yr were included. Height SDS was significantly lower in CAH patients than controls (-0.83 ± 0.28 SDS vs 0.60 ± 0.21 SDS; p = 0.001) while a higher BMI SDS (1.04 ± 0.19 vs 0.43 ± 0.13 , P = 0.03), fasting insulin levels (17.5 ± 2.1 vs 6.6 ± 0.55 , P = 0.0006) and HOMA-IR (3.4 ± 0.3 vs 1.4 ± 0.1 , P = 0.002) was observed in CAH group as compared to controls. Day-time (systolic 120.4 ± 3.3 vs 121.1 ± 1.9 , diastolic 71.6 ± 1.5 vs 70.5 ± 1.8 mm Hg) and night-time (systolic 108.0 ± 1.3 vs 108.8 ± 1.1 , diastolic 59.8 ± 1.7 vs 58.4 ± 1.5 mm Hg) BP were not significantly different between patients and controls. The proportion of absent physiological nocturnal dip in BP was significantly higher in the CAH group than in controls (68% vs 32%, respectively); Fisher's exact Test P < 0.0001. Doppler echocar-

diography showed normal ventricular function and absence of left ventricular hypertrophy (LVH) in both groups. Doppler ultrasonography showed increased IMT (0.8 mm) at different sites of the left and right carotid artery in 2/18 CAH patients and in 1/11 controls. No significant difference in total sodium excretion was found between the CAH and control groups throughout the study period (B: 161.8±20.7 vs 148.5±22.6 mEq/d; Post: 269.0±21.6 vs 254.6±25.6 mEq/day). Baseline and post PRA was significantly higher in CAH patients (B: 9.9±1.9 vs 3.6±0.8 ng/ml/h, P = 0.009; Post 6.4±1.2 vs 0.70±0.1 ng/ml/h, P = 0.0004) compared to controls.

Conclusions: Adolescents and young adults with CAH have higher insulin and HOMA-IR levels than controls in spite of BMI correction. CAH cohort did not show overt signs of high BP and early cardiovascular disease, however, a high significant proportion of patients in this group had a non-dipping pattern and also a persistence of high PRA after a salt loading test compared to controls. These findings might be additional risk factors for cardiovascular morbidity. Therefore, we suggest including these cardiovascular markers in the regular management of CAH patients.

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Determination of Biochemical Markers Predictors of Metabolic Bone Disease in Newborns

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Introduction: The incidence of metabolic bone disease of the newborn estimate is 23% of newborns weighting <1500 g and 55–60% <1000 g. Premature babies are highly predisposed, being inversely proportional to the weeks of gestation and birth weight, gender (male), maternal age, prolonged use of parenteral nutrition and medications. Most clinical manifestations are detectable between the sixth to twelfth week of life. Considered for diagnosis: the clinical, radiological images and biochemical markers of bone resorption, characterized by increased alkaline phosphatase (ALP) >900 UI/L, and hypophosphatemia with normocalcemia; this detection method being used more common. Recent studies suggest the use of iPTH levels as a predictor of early metabolic bone disease.

Table 1. (for Abstract 37)

	Average
Days	21.67±9.14 (5–45)
Weeks of gestation	34.24±1.43 (31.6–36.1)
Birth weight (g)	1,841.50±394.76 (960–3,475)
Alkaline phosphatase (mg/dl)	175.22±34.06 (115–260)
Alkaline phosphatase control (mg/dl)	235.45±40.20 (125–795)
iPTH (pg/ml)	75.90±73.09 (9.3–461)
iPTH control (pg/ml)	78.10±28.18 (10.5–182)

Objective: Identify a predictive biochemical marker of early metabolic bone disease.

Methods: Longitudinal study analytical descriptive. We analyze new born preterm with risk factors staying in the UCIN of a private hospital in Mexico in period of 6 months. Measuring serum levels of iPTH, calcium, phosphorus, magnesium, albumin and alkaline phosphatase by chemiluminescence; and radiographs of long bones assessed by specialist. All parameters analyzed at baseline at 72 hours of life and at intervals of 2–3 weeks.

Results: The sample collected was 40 patients, predominantly female (60%).

15% only was low birth weight <1500 g. The levels of calcium, phosphorus, magnesium and FA were kept in normal parameters. 37.5% showed elevated basal iPTH, and 10% iPTH levels high weeks later. As for the initial radiographic findings until 40% had some degree of bone demineralization. At 4 weeks, only 4% continued with the same degree of demineralization. None of the patients analyzed were reported with significant data osteopenia or fracture.

Discussion: The analysis of iPTH as potential predictive marker of metabolic disease. In the reported cases with elevated iPTH and/or presentation of bone demineralization imaging showed no biochemical abnormalities of bone metabolism. In general, changes in iPTH not reach more than 2 SD above the mean. No correlation between elevated levels of iPTH and radiological findings according to Pearson correlation R = –0.173. Likewise, the relationship between the radiological findings and the presence of low birth weight was assessed, there also no correlation R = –0.027.

Conclusions: At the moment we can not conclude that the determination of iPTH may be a predictive marker of metabolic disease of the newborn in the early stages. The limitations of the study were the sample size. It is suggested to continue studying the possible biochemical markers for early detection and effective treatment.

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Vitamin D Deficiency: Risk Factor of Preterm Birth in Adolescents

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Background: Low serum 25-hydroxyvitamin D [25(OH)D] concentrations during pregnancy have been associated with adverse pregnancy outcomes such as premature birth.

Objectives: To evaluate the association of maternal serum 25-hydroxyvitamin D [25(OH)D] status with premature birth in adolescence.

Design: 615 adolescents with singleton pregnancies who were attending first-trimester screening in Campina Grande, Paraíba-Brazil were sampled. Serum 25(OH)D levels were measured. Outcomes of the delivery and newborn were collected. Multivariate logistic regression was conducted to examine the association between low 25(OH)D concentrations and preterm birth.

Results: The prevalence of preterm birth delivery in adolescents was 23% and vitamin D deficiency (25[OH]D <20 ng/mL) was observed in 59% of the cohort. With a 25(OH)D concentration less than 20 ng/mL, the odds ratios were 3.31 for premature birth (95% confidence interval, 1.52–7.19; $P < 0.002$). A 25(OH)D concentration of 20 ng/mL had 80% sensitivity and 45% specificity for premature birth. The cutoffs with the best combination of sensitivity and specificity were 14 ng/mL for premature birth (66.7% sensitivity and 71.0% specificity). The addition of 25(OH)D information to maternal and clinical risk factors improve the ability to predict premature birth in 8%.

Conclusion: Lower 25(OH)D levels are associated with preterm birth in adolescents.

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Hypoparathyroidism with Normocalciuria Understanding the Course of Treatment

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Autosomal dominant hypocalcemia (ADH) results from gain-of-function mutations of the calcium-sensing receptor (CaSR) coding gene, which is expressed in the parathyroid and in kidney tubules. The activation of CaSR inhibits PTH secretion and reduces calcium reabsorption in the kidney, resulting in hypocalcemia, low or normal levels of PTH and hypercalciuria. Seldom ADH can present with normal urinary calcium (relative hypercalciuria).

Objective: To present a patient with hypocalcemia and normal urinary calcium in who lack of response to treatment suggested diagnosis of ADH.

Results: A 13-yr-old girl was referred due to hypocalcemia which was discovered due family history of hypocalcemia. The girl was born at term after an uneventful pregnancy. Parents were not related. She had normal weight and length at birth. Learning difficulties were noted. She didn't referred dysesthesia, muscle cramps, or seizures. Family history: Her mother had calcification in the basal ganglia discovered in a brain CT scan performed during a severe headache. Subsequent hypocalcemia was found. Physical examination of the girl revealed: height on 50thpc, BMI 17.2 (pc25). No dysmorphic features were present. Breast development Tanner IV. No clinical evidence of rickets. She had positive Trousseau's sign at the first minute and positive Chvostek's sign.

Laboratory test results Ca T 6.8 mg/dl (8.5–10.5), plasma ionized calcium: 0.8 mmol/l (1.14–1.3) P 7.4 mg/dl (2.7–4.5) Mg 1.5 mg/dl (1.3–2.1) Albumin 4.4 gr/dl (3.5–5.0) PTH 9 pg/ml (12–72). Urinary Ca/creatinine ratio: 0.11 (NV<0.2), 25(OH)D: 25.8 ng/ml (NV:30–60) Bicarbonate 25.9 mEq/l (22–26), Na 138 mEq/l (132–145), K:4.25 mEq/l (3.5–5.1). She had normal kidney function and US. To rule out autoimmune polyendocrinop-

athy type 1 syndrome type the following determinations were made: ACTH16 pg/ml (0–46), Cortisol:9.7 ug/dl (7–24), TSH: 2.6 mUI/ml (0.3–5.0), T3:113.5 ng/dl (80–200) T4:6.21 ug/dl (4.5–13), freeT4:1.08 ng/dl (0.8–2.1). Celiac disease was ruled out. She had not radiologic evidence of rickets. DEXA scan at lumbar spine showed BMD: 1234 gr/cm² (Z score + 1.1), and total body BMD: 1152 gr/cm² (Z score +0.9). Echocardiogram was normal, ruling out congenital heart disease. Primary hypoparathyroidism was diagnosed. Treatment with intravenous calcium transiently normalized serum calcium, but thereafter under oral supplementation with 5.5 gr/day of Ca²⁺ and calcitriol (2 ug/day) serum calcium was:7.0 mg/dl. The 24-hrs- urinary calcium:120 mg (60–240). Mother laboratories: Ca T 6.26 mg/dl (8.5–10.5) plasma ionized calcium: 0.68 mmol/l (1.12–1.32), P:3.5 mg/dl (2.7–4.5), Mg:1.9 mg/dl (1.3–2.1), PTH:27.4 pg/ml (15–68) Urine Ca/Cr ratio: 0.02, 25-OH Vitamin D: 40.5 ng/ml (8.9–46.7). The lack of normalization of calcium suggested that the patient may had ADH. Genetic studies showed in the daughter: 2 mutations in compose heterozygous state: p.T151R and p.H429Y on CASR gene. Both of them have been described as cause of ADH. Her mother has only the mutation p.T151R in heterozygous state. DNA from the father was not available to perform the study.

Conclusions: Persistent hypocalcemia under calcium supplementation and relative hypercalciuria suggested ADH despite the lack of absolute hypercalciuria. The genetic test was an important tool allowing the correct diagnosis, avoiding unnecessary excessive calcium load and lowering the risks of hypercalciuria.

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Endocrine Alterations in Mexican Patients with 22Q11.2 Deletion Syndrome. Three Years Follow-Up After Diagnosis

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Introduction: The 22q11.2 deletion is one of the most common genetic syndromes, the prevalence is estimated at 1 in 2,000 to 4,000 live births in the general population. The associated endocrine alterations are growth hormone deficiency, hypocalcemia by aplasia or hypoplasia of the parathyroid gland and disorders of the thyroid gland, usually go unnoticed at birth.

Objective: Describe the incidence of endocrine alterations in patients with 22q11.2 deletion syndrome over the time.

Methods: Case series. Descriptive, longitudinal, prospective study. All the patients with 22q11.2 deletion syndrome were confirmed by FISH method from the endocrinology and genetics division at the Children's Hospital of Mexico, Federico Gomez. After Informed consent, blood samples were obtained to study the karyotype with GTG banding technique, a resolution of 450 bands and FISH analysis with TUPLE1 probe (Vysis r) reviewed 25 to 50 metaphases and 50 metaphase nuclei. The bone metabolism (calcium, phosphorus, magnesium, albumin, and iPTH), thyroid

Table 1. (for Abstract 40)

	Baseline	1 year	2 years	3 years
T3	173 (107–260) ± 39	158 (85–255) ± 44	145 (34–269) ± 54	135 (98–174) ± 28
T4	9.8 (6.9–16.6) ± 2.3	9.3 (2.2–16.5) ± 3.3	8.7 (0.0–11.1) ± 2.5	7.4 (0.0–11) ± 3.2
FT4	1.35 (1.01–1.77) ± 0.20	1.27 (0.44–1.66) ± 0.26	1.37 (1.1–1.87) ± 0.186	1.19 (0.72–1.50) ± 0.27
TSH	3.6 (0.16–10.3) ± 2.3	12.9 (1.01–96) ± 25	3.4 (0.73–9.1) ± 2.2	3.2 (0.65–7.1) ± 2.2
IGF1	132 (25–505) ± 128	124 (25–387) ± 105	156 (137–178) ± 20	104 (25–158) ± 57
IGFBP3		21 (1.46–48) ± 20.7	14.7 (1.17–14.7) ± 16	26.3 (0.12–76) ± 43
iPTH	43 (14.6–121) ± 27	27 (6.8–62) ± 14.4	31.8 (8.5–100) ± 25	26 (9.2–38) ± 9.6
Calcium	8.6 (4.6–9.9) ± 1.24	8.9 (5.2–10.6) ± 0.98	8.9 (7.9–9.8) ± 0.54	8.4 (4.9–10.2) ± 1.56

Table 1. (for Abstract 41)

	Referent TG/HDL-C ratio ≥2.32			Referent HOMA-IR >3.1		
	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV
Children <10 years						
AAP	64.4	81.5	84.4	55.8	61.1	53.3
IDF	45.7	92.1	90.0	32.6	70.4	46.7
Children ≥10 years						
AAP	50.0	83.3	89.7	41.2	57.7	71.8
IDF	37.1	83.3	86.6	29.4	61.5	66.7

function (TSH, T3, T4, FT4) and growth factors (IGF1 and IGF-BP3) were analyzed by chemiluminescence. Growth rate was evaluated in a period of 1 year.

Results: From 2010 to 2013, forty seven patients were included and clinical evaluated. Subclinical primary hypothyroidism was reported in 10.52% in the second year of follow-up, compared to 3.44% at diagnosis. About the bone metabolism, it was determined that 20% of patients had hypoparathyroidism in the second year, increasing to 30% by the third year of follow-up. Hypocalcemia was reported up to 25% by the third year of follow-up. At the third year, 10% of cases had hyperthyroidism. Regarding to growth rate, a decrease was observed in 12.5% of patients in the first year, maintaining a slow rate of only 6.2% in the following years.

Conclusion: The endocrine alterations in patients with 22q11.2 deletion syndrome may occur at any stage of life, from childhood to adulthood. An appropriate monitoring is important for an early and accurate diagnosis and treatment.

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Comparison of Criteria of the American Academy of Pediatrics (AAP) and the International Diabetes Federation (IDF) for the Diagnosis of Metabolic Syndrome and Its Relationship with HOMA-IR and Triglycerides/HDL-Cholesterol Ratio in Obese Children 4 to 14 Years Old

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Introduction: Metabolic syndrome (MS) can identify a common phenotype of cardiometabolic risk. Many studies have reported strong association between obesity, insulin resistance and MS. Despite the high prevalence of obesity in children, there is no consensus for the diagnosis of MS in children under 10 years. Our aim was to compare the criteria of the AAP and the IDF for the diagnosis of MS and its relation to the Insulin resistance index (HOMA-IR) and triglycerides/high density lipoprotein cholesterol (TG/HDL-C) ratio.

Methods: We included 191 obese children aged 4–14 yrs, 113 M/78 F, divided into two age groups (<10 yrs and ≥10 yrs). Anthropometric measurements, blood pressure (BP), glucose, in-

sulin, triglycerides, HDL-cholesterol, HOMA-IR and TG/HDL-C ratio were evaluated. The prevalence of MS was compared according to the criteria of the AAP and IDF. Sensitivity and specificity of both criteria considered as relating TG/HDL-C ≥ 2.32 and HOMA-IR > 3.1 was determined. Were used and inferential statistics and bivariate, tests of concordance.

Results: For children < 10 yrs, the prevalence of MS was 46.4% (95% CI: 36.2–56.8) AAP criteria and 30.9% (95% CI: 21.9–41.1) according to IDF, with significant difference ($p < 0.001$) between both criteria. For children ≥ 10 yrs was 41.5% prevalence (95% CI: 31.4–52.1) and 31.9% according to AAP (95% CI: 22.7–42.3) according to IDF, with significant difference ($p < 0.0039$). Agreement between AAP and IDF was good ($\kappa = 68.2\%$ in < 10 yrs, $\kappa = 79.6\%$ in ≥ 10 yrs). Agreement of both criteria was better with TG/HDL-C ratio was higher ($\kappa = 43\%$) compared with HOMA-IR. AAP criteria showed the highest sensitivity for the diagnosis of MS in both age groups. Specificity was higher with IDF for children < 10 yrs and unchanged in children ≥ 10 yrs.

Discussion: The lower prevalence of MS by IDF would be related to higher cutting points of BP and triglycerides, compared to the AAP values adjusting for age and sex. The lower detection MS using the IDF criteria may underestimate the increased cardio-metabolic risk in children and delayed intensification prevention measures.

Conclusions: High prevalence of MS in obese children and the AAP criteria were more sensitive for diagnosis was found. Both criteria agreed better with the TG/HDL-C ratio.

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Adrenocortical Cancer: Experience of a Pediatric Reference Center in Southern Brazil

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Introduction: Adrenocortical cancer is rare, but the incidence in Southern Brazil is 10 to 15 times higher than worldwide. The reason for the increased incidence is not yet fully understood, but the presence of a germ line mutation in the tumor suppressor gene p53, found in most of the affected children, appears to be associated with a higher risk.

Objective: To evaluate the clinical and epidemiological profile, treatment and the presence of p53 gene mutation of children with adrenal cortical cancer at a pediatric reference center in Southern Brazil.

Patients and Methods: Descriptive, retrospective study of 56 children with adrenal cortical cancer treated at Hospital Infantil Joana de Gusmão, Florianópolis, Santa Catarina, Brazil from January 1980 to December 2013. The data analyzed were age at diagnosis, sex, clinical presentation, the presence of p53 gene mutation, staging and treatment performed.

Results: The mean age at diagnosis was 3 years and 3 months. Of the 56 cases, 58.9% were girls. The most frequent manifestation

was isolated virilization, in 64.3% of the patients, followed by virilization with Cushing in 25% of the cases. Stage I was found in 32.1% of cases, stage IV in 21.4% and in 21.4% staging was not specified. Isolated surgical treatment was performed in 55.3% of patients, surgery with chemotherapy in 37.5%. Three patients did not undergo surgery because of unresectable tumor. Fourteen patients (25%) died and of these, 71.4% were stage IV at diagnosis. None were stage I. The mutation of the p53 gene was found in 80% of the 20 patients in whom it was performed.

Conclusion: Adrenocortical cancer occurred mostly in very young children and its main clinical presentation was virilization. Girls were slightly more affected than boys. It's a highly aggressive type of tumor, with a poor prognosis in advanced stages. The p53 gene mutation is very frequent in our patients.

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Association Between Sleep Disorders and Metabolic Syndrome in Obese Adolescents

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Introduction: A parallel increase of obesity and chronic partial sleep loss prevalence has been observed in modern societies. The proportion of adolescents that sleep < 7 h per night has increased from 15.6–37.1% in the last twenty years. Chronic partial sleep can be equated with an allostatic load situation contributing the development of the metabolic syndrome (MS).

Objectives: To determine the association between sleep disorders and the presence of metabolic syndrome in obese adolescents in a pediatric hospital.

Methods: Cross-sectional study; sample were 52 adolescents ages from 12–18 years. A group of obese adolescents with BMI $> 95^{\text{th}}$ percentile according to CDC, to present MS according to the IDF criteria teen vs a group of obese adolescents without MS were compared. Adolescents were assessed by pediatric services, nutrition, endocrinology and mental health. Subjects were performed anthropometric evaluation, glucose, HDL cholesterol, triglycerides. Pittsburgh Sleep Questionnaire Scale and severity of insomnia was applied.

Results: Men age was $14.48 \text{ years} \pm 1.72$, 63% girls and 37% boys. Higher frequency of poor sleepers ($p = 0.006$), decreased sleep latency ($p = 0.049$), sleep disturbances (.008), initial insomnia (P.005) and daytime sleepiness ($p = 0.002$) was found in obese adolescents with MS also had higher plasma cholesterol levels ($p = 0.039$), HDL ($p = 0.000$) and greater waist circumference ($p = -0.45$) compared to obese without MS. Not so in the subjective quality of sleep ($p = 0.165$), sleep efficiency ($p = 0.105$), and daytime dysfunction ($p = 0.726$). Positive correlation between glucose levels and poor sleepers $r = 0.696$ ($p = 0.001$) and between weight and poor sleepers $r = 0.712$ ($p = 0.05$) and positive correlation between the number of MS components and poor sleepers $r = 0.442$ ($p = 0.005$).

Conclusions: According to results, the sleep disorders can play a role in the etiology of metabolic syndrome, that's why is very im-

portant that we can make interventions that increase the amount and improve the quality of sleep as a primary preventative measures for metabolic disorders.

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Polymorphism rs9939609 of the FTO Gene and Its Association with Metabolic Syndrome in Families from Tamaulipas Mexico

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Introduction: The metabolic syndrome is commonly defined by the following components: central obesity, hypertriglyceridemia, low HDL cholesterol levels, hypertension and hyperglycemia. It is the result of environmental and genetic factors. In the side of the genetic factors genes associated to previously mentioned phenotypes such as TCFL2, WES1, IGFBP2 y FTO (Fat Mass and Obesity associated gene) have been studied, in FTO there have been reported important punctual variations which are related with the genesis of obesity, specifically, the Single Nucleotide Polymorphism (SNP) rs9939609 (T/A) that is associated in the increase of Body Mass Index (BMI) and the unchaining of complications such as DM2 and cardiovascular diseases among others.

Objective: To identify the SNP rs9939609 of the FTO gene, to determine the allelic and genotypic frequencies and their association with the components of metabolic syndrome in families from Tamaulipas, Mexico.

Materials and Methods: By invitation and previous signed written consent we studied 135 related subjects (parents, sons-siblings), 70 females y 65 males, with an average age of 28.2 years old ±15.6 years. All of them were measured in height using a SECA stadiometer and the body composition was measured by bioelectric impedance with a Tanita analyzer TBF300, a blood sample was

taken from them in order to obtain the leukocyte pellet and the serum to quantify glucose, insulin, HDL and LDL cholesterol and total triglycerides. The DNA was extracted from peripheral blood cells by the phenol-chloroform method, the amount of DNA was determined with a NanoDrop 2000 device and its integrity was assessed by electrophoresis in agarose gel, for the determination of the polymorphism we used the Real Time PCR system ILLUMINA ECO. The genetic analysis was performed in the Eco Real-Time PCR system software v4.1 which groups the samples according to its genotype: mutant homozygote, heterozygote or wild-type homozygote. The Hardy-Weinberg equilibrium was determined in the population using the χ^2 test with a significance level of 0.01%. The statistical analysis was conducted in the STATA v11.0 software.

Results: The 100% of the subjects were genotyped, 97 were found with the wild-type homozygote T/T (72.39%), 29 with the genotype heterozygote A/T (21.64%) and 8 with the mutant homozygote A/A (5.97%), all were found in Hardy-Weinberg's equilibrium. In the following table it is showed the Odds Ratio between the 3 genotypes and the metabolic syndrome components, and also the total high cholesterol and LDL high cholesterol.

Differences with the fat percentage and fat mass could not be found.

Conclusions: The genotyping frequencies are similar to the ones found in Asiatic populations and like other authors suggest, the possible associations found were not statistically significant. It is necessary to analyze more subjects and to utilize other experimental designs in order to probe our findings.

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Laparoscopic Sleeve Gastrectomy in Severely Obese Adolescents. Baseline Conditions and Midterm Outcomes

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Introduction: The prevalence of obesity and obesity-related disease among adolescents continues to increase worldwide. Bariatric surgery in adolescents is a controversial subject, Laparoscopic Sleeve Gastrectomy (LSG) is achieving credibility as a simple and efficient bariatric procedure with low surgical risk in obese adult population. Thus, LSG could be considered as an option in this young group of age.

Table 1. (for Abstract 44)

	Overweight	High Triglycerides	Low HDL-C	Prediab	DM	Total high cholesterol	High LDL-C
OR	2.56	0.91	1.06	1.02	0.81	1.38	1.67
CI 95%	0.3–121	0.3–2.1	0.4–2.7	0.2–3.5	0.1–3.6	0.5–3.6	0.5–5.2
P	0.37	0.82	0.87	0.97	0.77	0.47	0.32

Objectives: Analyze age, gender, comorbidities, effectiveness of treatment and possible complications in the adolescent patients undergoing LSG surgery with BMI >35 kg/m².

Methods: Descriptive, non-randomized, prospective study, adolescent patients with body mass index >35 kg/m² BMI, and comorbidities with one year of medical treatment and failure in weight loss, underwent LSG between September 2009 and September 2013. For data tabulation and statistical analysis we used Excel.

Results: 40 adolescents, 14 male (35%), 26 female (65%), mean age 17.28 years (15–19), mean BMI 39.9 (35–53.5). 24 class II obese patients (60%), 16 female (66.7%), 8 male (33.3%), mean age 17.58 years. 16 class III obese patients (40%), 10 female (62.5%), 6 male (37.5%), mean age 16.81 years. Comorbidities: Insulin resistance: 32 patients (80%), Non-alcoholic fatty liver disease: 14 (35%), hypertriglyceridemia: 8 (20%). Complications: 1 patient had an abscess treated with antibiotics, 1 trocar related bleeding. No mortality. Mean Percentage excess weight loss at 6 months: 78.28%, at 12 months: 92.27%, at 24 months: 85.66%.

Conclusion: Laparoscopic Sleeve Gastrectomy is a safe and effective procedure for severely obese adolescents. It could be advantageous for this age group, with efficient weight loss and with rare complications. Further studies are required to evaluate the long-term results.

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Deptor a Novel Endogenous Regulator of mTOR Activity in Human Term Placenta. Differences According to Birth Weight

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Introduction: We previously reported a higher mRNA expression and protein content of IGF-I and IGF-IR in placentas from small (SGA) compared with large (LGA) for gestational age newborns. IGF-I through IGF-IR activates the IRS-1/AKT/mTOR/S6K signal transduction pathway through IGF-IR. DEPTOR is a regulatory protein containing mTOR, which was recently reported to be associated with both mTORC1 and mTORC2, and inhibit their activities in myocytes and adipose tissue.

Aim: To study the protein content of IRS-1, AKT, mTOR, S6K_{1/2} and DEPTOR and the effect of IGF-I on the phosphorylation of S6K_{1/2} in human full term SGA, AGA and LGA placentas.

Methods: We collected placentas from 25 SGA (birth weight (BW) = -1.66±0.07 SDS), 21 AGA (BW = -0.02±0.16 SDS) and 17 LGA (BW = +2.17±0.26 SDS) newborns (gestational age: 38.9±0.2 weeks) and we studied the protein content, and the effect of IGF-I in the chorionic (CP) and basal (BP) plates of the placentas by Western Blot. Results are shown as mean ± SEM and the differences were studied by ANOVA.

We also observed an inverse correlation between DEPTOR with AUC S6K1 in CP (r = -0.378; p = 0.003) and in BP (r = -0.383; p = 0.003).

Table 1. (for Abstract 46)

		SGA	AGA	LGA
Total IRS-1 (AU)	CP	0.60±0.17	0.43±0.13	0.50±0.13
	BP	0.60±0.16	0.44±0.17	0.48±0.16
Total AKT (AU)	CP	0.46±0.07*	0.32±0.06	0.25±0.05
	BP	0.47±0.08	0.30±0.05	0.24±0.03
Total mTOR (AU)	CP	0.46±0.06*	0.31±0.07	0.63±0.25
	BP	0.49±0.08	0.36±0.09	0.30±0.07
Total S6K1 (AU)	CP	0.37±0.06	0.46±0.09	0.84±0.26
	BP	0.41±0.06	0.50±0.13	0.71±0.20
Total S6K2 (AU)	CP	0.17±0.02*	0.09±0.02	0.16±0.05
	BP	0.17±0.03	0.09±0.02	0.16±0.04
Total Deptor (AU)	CP	1.08±0.22*	0.60±0.18***	0.87±0.14
	BP	1.29±0.29*	0.63±0.18	0.95±0.26
Phospho S6K1 (AUC)	CP	40.9±1.5*	66.9±6.9***	21.0±0.3**
	BP	25.4±0.8*	84.7±10.2**	25.8±2.5
Phospho S6K2 (AUC)	CP	14.6±0.5*	43.7±4.1	61.5±5.3**
	BP	16.3±0.9*	41.9±9.4	51.4±7.7**

* p < 0.05 SGA vs AGA; ** p < 0.05 SGA vs LGA; *** p < 0.05 AGA vs LGA.

AU = Arbitrary units; AUC = area under curve.

Conclusion: The higher protein content of DEPTOR and the lower response to IGF-I of S6K1 and S6K2 in SGA compared to AGA placentas, suggest that the placental DEPTOR is a critical endogenous regulator of mTOR activity in the placenta and may be influencing the human fetal growth (FONDECYT 1110124).

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A New Mutation in *TRHB* in a Patient with a Giant, Multinodular Goiter Secondary to Antithyroid Medication

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Introduction: Resistance to thyroid hormone (RTH) is characterized by elevated T4, fT4, and T3 levels and normal or slightly increased TSH levels. The disease expression is highly variable. Goiter is the most common clinical manifestation.

The genetic alteration is caused by mutations in the genes encoding thyroid hormone receptors *THRA* (thyroid hormone receptor A) and *THRB* (thyroid hormone receptor B), located on chromosomes 3 and 17, respectively.

Objective: To describe the clinical features and laboratory findings of a patient with RTH due to a new mutation in the *THRB* gene.

Case Report: The patient was an 11-year-old boy who first consulted at 3.5 years of age because of goiter and mild clinical signs of hyperthyroidism. The initial laboratory tests showed: TSH 6.74 μ UI/ml (NR 0.97–4.32 mUI/ml), T4: 18.8 μ g/dl (NR 6.9–13.5 μ g/dl), fT4 3.11 ng/dl (NR 0.93–1.94 ng/dl), T3: 3.74 ng/ml (NR 1.04–2.18 ng/ml), and negative antithyroid antibodies. X-ray bone age (BA) was 3 years and thyroid ultrasonography revealed diffuse enlargement of the gland. In the boy's home town hyperthyroidism was diagnosed and treatment with methimazole was started. A moderate decrease of T4 (11–16 μ g/dl), increased TSH levels (45 mUI/ml), and progressive enlargement of the goiter were observed.

At 11 years of chronological age the patient was seen at our hospital. Weight and height were according to age and heart rate was normal (70/minute). The boy had a giant goiter deforming the neck, learning difficulties due to attention deficit, and serum levels of TSH 1.88 μ UI/ml, T4 17 μ g/dl, fT4 2.39 ng/dl, T3 3.64 ng/ml, negative anti-TPO and TgAb while receiving methimazole treatment of 10 mg/d. Bone age was 12 years and thyroid ultrasonography showed a globally enlarged thyroid gland with a heterogeneous echotexture, diffusely spread cystic nodules of different sizes, moderately increased intranodular vascularization, thickened isthmus with a similar echotexture, without regional adenomegalies. Right lobe: 124 cm³, left lobe: 85.5 cm³. As RTH was suspected, methimazole was withdrawn, and surgical resection of the goiter was indicated. The surgical specimen weighed 250 gr. Pathology showed nodular hyperplasia.

Molecular analysis of the *TRHB* gene revealed a new mutation: P452L. *In silico* assays (Polyphen, SIFT and Mutation taster) predict that this variant will affect receptor function and may be disease causing.

Conclusion: The diagnosis of RTH is based on clinical and laboratory findings (elevated thyroid hormones associated with normal or slightly increased TSH levels). Molecular study of the affected gene confirms the syndrome. One-third of patients with RTH are inappropriately treated with antithyroid drugs producing large goiters secondary to consistently high TSH levels.

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Haplotype Analysis Reveals a Possible Founder Effect of *SDHB* Gene Mutation C166_170delCCTCA in Argentine Patients

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Introduction: Paragangliomas are tumors arising from chromaffin extra-adrenal tissue. Familial paraganglioma associated with *SDHB* gene mutations (PGL 4) is an inherited syndrome with autosomal dominant inheritance, with incomplete penetrance and frequently malignant. Twenty four families with PGL 4 from different regions of Argentina were included in this study. Thirteen out of 24 families (55%) showed the C166_170delCCTCA deletion of *SDHB* gene. Have previously determined that the presence of this mutation in our population is significantly higher than in others ($p < 0.0001$). These findings prompted us to evaluate by haplotype analysis if this specific mutation was inherited from a common ancestor, showing a founder effect and ruling out the hypothesis of an independent origin (hot spot).

Patients: We studied 14 patients (9 unrelated) with C166_170delCCTCA deletion of *SDHB* gene with PGL4. Fourteen control individuals were also included in this study.

Aim: To determine by haplotype analysis the presence of a common ancestor in the inheritance of the recurrent mutation C166_170delCCTCA due to a founder effect in a population Argentina.

Methods: Haplotype analysis of the polymorphic regions that are in linkage disequilibrium in the locus of *SDHB* (intron 2 to 6) was performed. The polymorphic regions studied were: rs 2235930, rs 2746467, rs 7550829, rs 10887990, rs 4920653. These five 'tag SNP' were selected using Haploview Tagger software tool. Two additional microsatellites GATA29A05 and D1S2697 were included in the analysis. Genotype of the five Tag-SNP were determined through PCR and automatic sequencing or digestion with restriction enzymes. Microsatellites were amplified by PCR with one primer labeled with the fluorophore 6 -FAM. These labeled PCR products were separated by capillary electrophoresis according to their size, which was determined in each case using the Peak Scanner software. The PHASE program was used to calculate the frequency of haplotypes in the patients and in the control population.

Results: Haplotype distribution revealed the same haplotype 267 ACGTC 202 in all the SDHB c166_170delCCTCA mutation carriers and was not present in the control population of this study. These results are consistent with the low calculated theoretical frequency in CEU population (2.28%) as well as the low frequency observed in the Spanish population (1.05%).

Conclusion: The presence of this rare haplotype 267 ACGTC 202 in all PGL4 patients analyzed with C166_170delCCTCA deletion of the SDHB gene support the hypothesis of the existence of a common ancestor for this mutation in our population, suggesting a founder effect.

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Novel *IGSF1* Mutation in Three Brothers with Central Hypothyroidism and Macroorchidism

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Introduction: *IGSF1* Deficiency Syndrome is an X-linked syndrome caused by loss-of-function mutations or deletions in Ig superfamily member 1 (*IGSF1*, OMIM 300888). The main clinical characteristics are congenital hypothyroidism of central origin (C-CH) and macroorchidism from late adolescence. Other features are prolactin deficiency, transient GH deficiency, delayed growth spurt and pubarche, and increased body mass index (BMI).

Subjects and Methods: A family composed by 3 young adults, born to non-consanguineous parents, referred in adolescence for growth retardation and delayed puberty. Mother's menarche 14.5 yrs. Mid-parental Height 0.4 SDS. **Case 1.** At 13.4 yrs: height -0.8 SDS, BMI 1.6 SDS, Tanner stage G1, testicular volume (TV) 2/2 ml, bone age (BA) 11 yrs, TSH 5.1 mU/L, T4 4.2 ng/dl, FT4 0.55 ug/dl, Prolactin 1.8 ng/ml. Pubertal onset occurred at 14.5 yrs. GH test (at TV of 12 ml, Tanner P2, and serum testosterone (T) 230 ng/dl): GHmax 5.4 ng/ml (Normal reference >10 ng/ml). rhGH treatment started at 15.7 yr for 2.7 yrs. **Case 2.** At 14.0 yrs: height -1.2 SDS, BMI 2.1 SDS, Tanner stage G1, TV 3/3 ml, BA 12.5 yrs, TSH 1.6 mU/L, T4 5.4 ng/dl, T3 94 ng/dl, Prolactin <0.5 ng/ml. Pubertal onset at 14.5 yrs. At 18 yrs, TV was 30 ml, TSH 2.8 mU/L, T4 3.8 ug/dl, FT4 0.7 ng/dl, LH 0.6 IU/L, FSH 1.6 IU/L, T 110 ng/dl and L-thyroxine substitution was started. **Case 3.** At 13.1 yrs: height -1.2 SDS, BMI 0.8 SDS, Tanner stage I, TV 2/2 ml, BA 11 yrs, TSH 1.9 mU/L, T4 4.6 ng/dl, T3 152 ng/dl, Prolactin <0.5 ng/ml. Pubertal onset at 13.7 yrs. GH testing with priming: GH max 5.6 ng/dl. He was treated with depot testosterone for 1 yr. At 16 yrs TV was 20 ml, TSH 2.6 mU/L, T4 5.7 ug/dl, FT4 0.85 ng/dl, T3 128 ng/dl, T 137 ng/dl, and L-thyroxine was started.

All developed macroorchidism, and none continued L-thyroxine treatment after 20 yrs of age.

Results: Updated clinical examination and hormonal evaluation in adulthood are shown in table 1.

No signs of cognitive impairment were observed and all attained University degree.

Sequence analysis of *IGSF1* (ref.seq: NM_001170961.1) showed a novel frameshift mutation located in exon 14, in all 3 patients (hemizygous) and their mother (heterozygous): c.2422dupC, p.His808Profs*14. The mRNA produced might be targeted for nonsense mediated decay.

Conclusion: This new family with an *IGSF1* mutation shows most of the typical clinical and laboratory features of *IGSF1* deficiency syndrome: C-CH, probable macroorchidism (awaiting ultrasound studies), delayed puberty, transient GH deficiency, and prolactin deficiency. In spite of mild hypothyroidism, normal mental development was attained. Genetic testing for *IGSF1* is indicated in patients with C-CH, especially when associated with delayed puberty and post-pubertal macroorchidism.

Table 1. (for Abstract 49)

	Case 1	Case 2	Case 3	Mother	Father	Reference
Age (years)	27.9	29	30.4	57	59	
Height (SDS)/BMI (SDS)	1.43/1.19	0.47/3.0	-0.26/1.26	-1.09	1.64	
Testicular volume (ml)	>25/25	>25/25	>25/25			25±4
TSH mU/L	4.68	2.49	1.6	1.56	1.17	0.5-6.5
T4 (ug/ml)/FT4(ng/ml)	4.1/0.67	4.5/0.78	5.0/0.73	5.7/1.01	6.3/1.25	4.5-12.5/0.8-2.0
T3 (ng/ml)/FT3 (pg/ml)	92/2.5	95/2.8	92/2.5	97	106	80-220/1.4-4.4
Thyroglobulin (ng/ml)	16.5	11.0	6.9			6.0-40.0
Prolactin (ng/ml)	1.5	1.8	0.5			3.0-20.0
LH/FSH (IU/L)	1.7/7.44	1.55/3.83	1.36/3.44			1.4-9.2/1.0-7.9
Testosterone (ng/dl)	313	526	307			220-900
IGF-I (ng/ml)/IGFBP-3 (ug/ml)	361/5.3	356/5.8	436/6.6			127-424/2.9-7.2
AMH (pmol/L)	63	47	78			25-140

Congenital Adrenal Hyperplasia Screening in Buenos Aires Province, Argentina. Changes Since It Became Obligatory

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Introduction: Screening for classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is carried out with 17 α -hydroxyprogesterone (17 OHP) assay on filter paper-dried. In Buenos Aires province not obligatory screening (NOS) started in 1999, through Fundación Bioquímica Argentina (FBA), becoming obligatory (OS) in July 2010. Disease Confirmation Center is Hospital 'Sor María Ludovica' of La Plata, Buenos Aires, Argentina.

Objectives: 1) To study in OS stage: a) incidence of the disease, b) positive predictive value (PPV) of the screening method, c) median chronological age (CA) when screening sample was obtained in referred patients for confirmation, and median CA at diagnosis in confirmed cases (CC), d) mean 17 OHP level in screening sample and mean extracted 17 OHP level in CC, e) the distribution between classic and non classic CAH (CCAH and NCCAH), f) mutations found and its relation with clinical forms, g) relation between 17 OHP screening value with gestational age (GA) and birth weight (BW) in referred cases divided in CC and not confirmed cases (NCC). 2) To compare the incidence and PPV with previous stage (NOS).

Material and Method: Between July 2010 and December 2013, 591351 newborns (NB) were evaluated, 212 showed positive results. Diagnosis confirmation was made with a extracted 17 OHP value >5.8 ng/ml in full-term NB, and in preterm NB extracted 17 OHP values were adjusted according GA. At moment, molecular CYP21A2 gen study was made in only 15 children at Hospital 'JP Garrahan'. Statistical analysis: Spearman correlation test was used to analyze the relation between screening 17 OHP level with BW and GA.

Results: 27 cases of CAH (M:14, F:13) were confirmed. The incidence was 1: 21901 NB (1: 7094 NB in NOS). The PPV was 12.7% (46% in NOS). Median CA at screening sample was 4.0 (1–30) days, and median CA at diagnosis in CC was 14.0 (1–44) days. In CC mean 17 OHP level in screening sample was 292.62 \pm 169.49 nmol/ml and mean extracted 17 OHP level was 31.93 \pm 16.37 ng/ml. CCAH was diagnosed in 92% of patients (salt wasting form in 78% and simple virilising form in 22%). NCCAH was found in 8%. Most frequent mutation found in CCAH was In2/In2. In 2 patients with NCCAH the mutation found was V281L/I172N. In 2 patients no mutations were found, in one of them cystic fibrosis was detected by screening. In NCC negative correlation was observed between screening 17 OHP level with BW and GA ($p < 0.001$), but not in CC.

Discussion: 1) Current data, compared with previous stage of not obligatory screening, more accurately reflect the true incidence of the disease. 2) Screening PPV is low perhaps due to the high

number of children with low BW and GA referred for confirmation in which the disease is ruled out. 3) Although median CA when screening sample was obtained and median CA at diagnosis are within recommended, in some cases are still late, so that should be improved. 4) Molecular biology studies allow to relate clinical forms with the described mutations.

Conclusion: Screening allows early diagnosis of salt wasting forms avoiding metabolic disturbances and incorrect sex assignment and provides early detection of patients with less severe forms.

Adolescent Girls with Polycystic Ovary Syndrome (PCOS): Risk for Subclinical Vascular Disease?

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Introduction: Adult women with PCOS exhibit multiple cardiovascular disease (CVD) risk factors [1, 2, 3] and have been reported to have impaired endothelial function, an early feature of atherosclerosis. Adolescents with PCOS are more insulin resistant than similarly obese girls without PCOS (4). Insulin resistance may play an early role in the development of endothelial damage. We hypothesized that 1) girls with PCOS have worse endothelial function than non-PCOS girls of similar body composition; 2) this is related to higher insulin resistance in girls with PCOS.

Materials and Methods: Participants, 14 with PCOS and 7 non-PCOS according to NIH criteria underwent evaluation of: endothelial function by peripheral arterial tonometry (PAT) with determination of reactive hyperemia index (RHI) and monocyte function studies; insulin sensitivity (hyperinsulinemic-euglycemic clamp) with determination of glucose disposal rate (Rd); oral glucose tolerance test; fasting lipids, high sensitivity C-reactive protein (hs-CRP), and body composition (anthropometric measurements, and dual energy X-ray absorptiometry). They were all nonsmokers and were not on any pharmacotherapy. Results are Mean \pm SEM.

Results: Girls with and without PCOS had similar age, tanner stage, race, BMI (34.0 \pm 1.1 in PCOS vs. 30.3 \pm 1.5 kg/m² non PCOS, $p = 0.07$), % body fat (38.1 \pm 1.1 in PCOS vs 38.4 \pm 4.4% non PCOS, $p = 0.88$) and waist circumference (99.9 \pm 2.8 vs. 90.3 \pm 3.5 cm, $p = 0.06$). Girls with had higher free testosterone levels (9.8 \pm 2.3 vs. 3.7 \pm 1.2 pg/mL, $p = 0.02$) and were more insulin resistant (Rd: 6.7 \pm 1.1 vs. 12.7 \pm 1.3 mg/min/kg fat-free mass per μ mL $p = 0.004$) compared with non PCOS adolescents. The 2 groups did not differ with respect to HbA1c, lipids, liver enzymes or inflammatory marker (hs-CRP). There was no significant difference in reactive hyperemia index (RHI) (1.60 \pm 0.08 vs. 1.64 \pm 0.2, $p = 0.8$) or in inflammatory CD14+CD16+ monocytes (8.3 \pm 1.32 vs. 8.8 \pm 1.27%, $p = 0.7$) in girls with vs. without PCOS. RHI was not related to HbA1c, androgens or insulin sensitivity.

Conclusions: Despite higher insulin resistance in obese adolescent with PCOS, endothelial function is not significantly lower in these girls compared with controls of similar total body and abdominal adiposity. The CVD risk in PCOS may evolve over time in these girls.

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Childhood Obesity as Part of the 'Reward Deficient Syndrome': Association with SNP TaqIA C32806T of the DRD2 Gene

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Introduction: The worldwide prevalence of obesity has increased at an alarming rate in all age groups. While some rare obesity syndromes are caused by mutations in single genes, the highest proportion of obesity results from an interaction between variants in several genes (susceptible genotype) and a favorable environment. The Reward Deficiency Syndrome (RDS) is a hypo-dopaminergic state that predisposes to obsessive-compulsive and impulsive behaviors. Obesity is part of RDS since the individual eats compulsively to compensate the defect in dopamine levels. The polymorphism TaqIA C32806T in the Dopamine D2 receptor gene (DRD2) is associated with reduction up to 40% of DRD2 levels, and is associated with higher BMI in adults. There are few studies in the literature involving children, with conflicting results. The present study was designed to investigate the relation between the SNP TaqIA C32806T of the DRD2 gene and obesity and altered lipid profile in children.

Material and Methods: This is a case control study involving 105 children (55 obese/50 eutrophic). We accessed the nutritional state based on the OMS' definition (Z score of BMI). Peripheral blood samples were taken to determine the lipid profile and for analysis of DRD2 polymorphism through RFLP-PCR.

Results: We found A1 and A2 alleles, resulting in A1A1 (12.4%), A1A2 (33.3%) and A2A2 (54.3%) genotypes. The frequency of the A1 allele in obese and controls was 34.5% and 23% respectively, showing a statistically significant association of the A1 allele with childhood obesity, with a relative risk of 1.3. As we assessed the children into groups according to the presence (risk genotype) or absence (NOT risk genotype) of the A1 allele: we observed statistically significant differences: higher mothers' BMI

and minor levels of triglycerides (TG). The evaluation of each genotype separately showed significant differences in Z-BMI, fathers' BMI and TG levels. Allelic distribution was performed by separating the children into groups according to the reference values of metabolic variables. A significant difference in allelic distribution was observed in children with total cholesterol (TC) <170 mg/dl or TC ≥170 mg/dl.

Discussion: Until the present moment only 5 studies have evaluated the allele A frequency in obese children, ranging from 17% to 51%. The increase in CT levels is explained by feeding behavior itself assigned to A1 allele carriers as a way to compensate for the DRS. It was hypothesized that children with the presence of the A1 allele have the lower TG levels due to increased physical exercise practice, since the A1 allele is associated with certain behavioral traits (impulsiveness, extravagance, disorganization, persistence and gregarious attitude) that can lead to increased physical activity.

Conclusions: The A1 allele (T) of the DRD2 gene TaqIA polymorphism was associated with an increase in childhood obesity and higher BMI of the parents, corroborating some literature data. Our results show for the first time that the A1 allele is associated with TC ≥170 mg/dl and lower TG levels. Understanding how genetic variations affect the tendency to become or remain obese is an important step in understanding the mechanisms that lead to obesity.

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Association Study of the SNP TaqIA C32806T of The DRD2 Gene and Alterations in Glucose Metabolism in Obese and Normal-Weight Children

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Introduction: Obesity is associated with an increased risk for several chronic diseases, including diabetes and metabolic syndrome. About 60% of obese 5 to 10 year old children have at least one risk factor for cardiovascular disease (hypertension, dyslipidemia, hyperinsulinemia, abnormal glucose metabolism, prothrombotic factors) and 20% have two or more of these factors. The present study was designed to investigate the relationship between the SNP TaqIA C32806T of the dopamine receptor 2 gene (DRD2) and alterations in glucose metabolism in obese and normal-weight children.

Material and Methods: This is a case-control study involving 105 children (55 obese and 50 lean). The nutritional status followed the WHO definition in accordance with the standard deviation of the Z score of BMI (lean: ≥ Z -2 and < Z +1; Obese: ≥ Z +2). Peripheral blood samples were taken to determine glucose and insulin and to evaluate the polymorphism of DRD2 gene (TaqIα - C32806T) by PCR - RFLP. The Homeostatic Model Assessment (HOMA) was calculated to assess the insulin resistance (IR) and β cell secretion (β).

Results: We found A1 and A2 alleles, resulting in A1A1 (12.4%), A1A2 (33.3%) and A2A2 (54.3%) genotypes. HOMA IR showed no difference between groups. HOMA β was abnormal in 52.7% of obese and 10% of eutrophics. A1 allele was present in 38.2% of children with altered HOMA β and in 24.6% of normal HOMA β ($p = 0.037$; $RR = 1.5$). The children were divided into 4 groups according to HOMA β and BMI. The groups were: Obese with normal HOMA β (O β N), Obese with elevated HOMA β (O β ↑), Eutrophic with Normal HOMA β (E β N) and Eutrophic with elevated HOMA β (E β ↑). Subgroups with normal secretion of β cell (O β N and E β N) had genotype distribution and allele frequencies statistically different, with less presence of genotypes A1A1 and A1A2 and higher frequency of A2 allele. The comparative allelic distribution among the 4 subgroups showed statistically significant differences between the groups O β ↑ and E β N. Children from O β ↑ group showed higher frequency of A1 allele.

Discussion: Studies in diabetic adults and in animals show improved glycemic control with the use of bromocriptine, a dopamine agonist that acts via DRD2. The DRD2 are expressed in beta cells and modulate insulin secretion. Mice 'knockout' for the DRD2 gene have impaired insulin response to a glucose load, higher fasting glucose, glucose intolerance and reduction of beta cell mass, which shows that DRD2 is important for beta cell proliferation and for insulin secretion, and may be regarded as a growth factor essential for the control of glucose homeostasis. The presence of the A1 allele leads to reduction in the number of brain DRD2 and it is assumed that it also reduces the number of receptors in beta cells, explaining our clinical findings.

Conclusions: Our study found an unpublished result in the literature: the A1 allele was associated with HOMA $\beta \geq 175$, RR of 1.5. The A2 allele was associated with the normality of HOMA β in both obese and lean, implicating this allele as protective factor for pancreatic secretion. The recognition of predisposed individuals through determinations of risks polymorphisms can lead to new paths for treatment and prevention of obesity and alterations in insulin secretion. We believe that in the future children will be treated based on their genomes.

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Bone Mineral Density Evaluation in Children with Gaucher Disease

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Bone involvement is described as a relevant sign in patients suffering Gaucher Disease (GD).

Objective: To analyze the long-term effect of enzyme replacement therapy on bone mineral density, a retrospective observational study was conducted in a cohort of 34 GD pediatric patients (14 males, 20 females, median age 11.3 years).

Patients and Method: Lumbar spine (LS)(L2-L4, N: 34) and total body (TB)(N: 24) bone mineral density (BMD) (determined

by dual-energy X-ray absorptiometry (DXA)(GE Lunar), were performed and expressed as Z-scores. According to the International Society of Clinical Densitometry guidelines, a Z-score ≤ -2.0 was considered pathological. Results were expressed in $X \pm SD$. Patients received imiglucerase infusions (57.7 ± 17.4 IU/kg), during a period of 7.7 ± 4.5 years.

They were divided in two groups: pre pubertal (G1) and pubertal (G2), both for boys (B), (G1B-G2B) and girls (G), (G1G-G2G).

Results: Mean BMD were normal in the whole group: -0.26 ± 1.4 and 0.11 ± 1.3 in LS and TB respectively. Only two patients had LS BMD below -2.0 z-score, but none in TB BMD. BMD was: G1B: LS -0.6 ± 1.28 ; G2B: -0.15 ± 1.4 , TB -0.07 ± 1.4 and 0.58 ± 1.2 ; and G1G: LS: -0.23 ± 1.4 , G2G -0.56 ± 1.9 ; TB G1G -0.08 ± 0.9 , G2G 0.05 ± 1.9 respectively.

Conclusions: Patients with GD have normal BMD during therapy with imiglucerase. It seems that the pubertal groups are better than de pre pubertal, reflecting the action of sexual steroids on bone. A longitudinal study is needed to confirm this.

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Correlation Genotype and Phenotype in 8 Patients with Transient Neonatal Diabetes (TND) or Permanent Neonatal Diabetes (PND)

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Introduction: Neonatal diabetes (ND) is a rare entity with approximate incidence of one in 300000 to 400000 live births. It develops during the first days or weeks of life, and in half of children it disappears in the first years (transient neonatal diabetes or TND), while in the others it requires treatment for life (permanent neonatal diabetes or PND). Some patients with PND in remission can recur during puberty or pregnancy.

The mutations responsible for the disease identified to date are: In the ATP sensitive potassium channel (KCNJ11), associated with PND and gene ABCC, associated with TND in the proinsulin gene INS associated with both PND and TND. Also associated parental disomy of chromosome 6.

Materials and Methods: We report the correlation genotype-phenotype in patients with neonatal diabetes in whom genetic abnormalities were investigated.

Results: We studied eight patients, six females (75%) and two males (25%) diagnosed with neonatal diabetes at a mean age 23 days of life without ketoacidosis (KA) or hyperglycemia. Six patients with PND and two TND. We found mutations in six of our patients. Three siblings had the same mutation, one of them was diagnosed at age 7 with diabetes, we highly suspect a recurrence. Ketoacidosis was present in only one patient. The Six patients are insulin but sulfonylurea therapy is being started.

Conclusion: We conclude that genetic investigation in patients with ND allows for a correlation with the phenotype and modification of therapy such as the change from insulin to a sulfonylurea.

Table 1. Correlation between genotype and phenotype in patients with (TND) or (PND) (for Abstract 55)

Patient	Age (days)	Sex	KA	Type DM	Genes-Mutation
1	20	F	NO	TND	Uniparental Isodisomy chromosome 6
2*	60	F	NO	PND	ABCC8; L1147P Y KCNJ11: carrier G228D
3*	42	M	NO	PND	ABCC8(L1147P) y KCNJ11 carrier of G228D
4	30	F	NO	PND	ABCC8: L659L y KCNJ11: A190A, V337I
5	25	M	NO	PND	Heterocigote gen INS EXON Pc109Y .C326> A.Missense
6	10	F	NO	TND	no mutation found
7	60	F	YES	PND	no mutation found
8*	7 years	F	NO	PND	Diabetes (L1147P) and carrier of G228D

* Siblings.

56**Familial Hyperaldosteronism Type I, Early Diagnosis and Treatment: Avoiding Future Complications**

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Background: Familial hyperaldosteronism type I (FH-I, OMIM #103900) is often characterized by severe hypertension, variable hyperaldosteronism, low plasma renin activity (PRA) and normal or decreased serum potassium due to unequal crossing over of the genes that encode the steroid 11 β -hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) enzymes, which results in a chimeric *CYP11B1/CYP11B2* gene (CG) with aldosterone synthase activity regulated by plasma ACTH.

Clinical Case: A 3 months old boy was referred for evaluation because his mother, grandfather and uncle have FH-I confirmed by presence of chimeric *CYP11B1/CYP11B2* gene. He was born at 36 weeks of gestation, cesarean delivery due to intrauterine growth restriction, birth weight 2365 gr (<p10th), birth length 44 cm (<p10th), he was admitted to the hospital during one week with diagnosis of transient tachypnea; without electrolytes or blood pressure disturbances during hospitalization. At initial evaluation he was normotensive (75/54 mm Hg, reference <106/62 mm Hg) and his physical exam was unremarkable. Laboratory tests were consistent with hyperaldosteronism: elevated serum aldosterone (SA) (> 120 ng/dL, reference: 5–90 ng/dL), suppressed PRA (0.39 ng/ml/hr, reference: 2.35–37 ng/ml/hr), elevated aldosterone/renin ratio (ARR) (307, reference: 10 in childhood, not validated in new-born), genetic study was performed by XL-PCR and confirmed chimeric *CYP11B1/CYP11B2* gene.

The patient began treatment with cortisol (10 mg/m²/d) showing favorable response. After 8 months of therapy his laboratory tests have normalized: SA (77.8 ng/dL, n: 5–90 ng/dL), PRA (5.2 ng/ml/hr), ARR (14.9), normal echocardiography, normal fundoscopic exam and normal hs-CRP (0.35 mg/L, reference: <3 mg/L). He has remained normotensive and has shown catch-up growth without Cushingoid side effects.

Conclusion: patients with FH-I usually show a rapid response to the institution of glucocorticoid therapy. Clinical and experimental data suggests that aldosterone excess can induce adverse cardiovascular, cerebrovascular, metabolic and renal sequels independently of its effects on blood pressure, this put emphasis on high suspicion diagnosis, especially in patients with childhood onset arterial hypertension, confirmatory diagnosis is made by genetic test and early treatment should be introduced, not only to manage hypertension but also to avoid possible deleterious effects of aldosterone on endothelial dysfunction and cardiovascular diseases.

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57**Estimated Base Rate of Glucose and Its Relationship in Patients with Metabolic Syndrome Type 1 Diabetes**

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Introduction: Metabolic syndrome (MS) is a frequent clinical association with Type 2 Diabetes Mellitus (DM2). In some reviews its possible association with Type 1 Diabetes Mellitus (DM1) is enhanced along with the impact of insulin resistance (IR) in micro and macroangiopathic complications. Since IR cannot be measured in DM1 patients by conventional methods because patients are under insulin treatment, the estimated rate of glucose disposition (TeBG) which is based in clinical parameters whose values are inversely correlated with insulinorresistance degree has been recently validated.

General Objective: Measure TeBG as an estimation of insulin sensitivity and its relation with the presence of MS.

Material and Methods: We included 48 patients with DM1 in two groups. 24 patients with MS and 24 without MS. All patients included were above 10 years of age and had been under clinical control in the Diabetes clinic in the UMAE Pediatrics Hospital CMNO with more than one year of disease diagnosis.

Results: Average age was similar in both groups. Both sexes were also equally distributed (54.2% females). Obesity and DM2 were significantly more frequent in first degree relatives in the group of patients with MS. Acanthosis was found in 75% of patients with MS, and in 37.5% of DM1 patients without MS. The most frequent component of MS was hypertriglyceridemia followed by hipoalphalipoproteinemia. Glycated haemoglobin was higher in the group with MS ($p = 0.006$). TeBG was lower in patients with MS, ranging from 5 to 11.7, and an average of 8.32, as compared with those without MS ranging from 6.31 to 11.14, and an average of 9.82 ($p = 0.013$). A higher TeBG is found in patients with a good metabolic control ($p = 0.002$).

Conclusions: Obesity and DM2 in parents were the most important hereditary factors to predict the presence of MS. Acanthosis was the most significant clinical sign. Abdominal obesity was higher in patients with MS. Metabolic control was worse in patients with MS. A lower TeBG is related with the presence of MS.

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LH 3 Hours Post Depot Triptorelin for Monitoring Therapy in Central Precocious Puberty (CPP) Related to Suppression of Ovarian Steroidogenesis

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Depot GnRH-analogues (GnRHa) represent the first-line of therapy in central precocious puberty (CPP). Stimulated LH post GnRH or GnRHa has been proposed for monitoring treatment, however there is no consensus on the criteria of inhibition of gonadotropin axis. As the suppression of the estradiol ovarian synthesis is the main objective of the treatment to lead to the involution of pubertal signs and to arrest the accelerated bone maturation, a reliable test to assess the suppression of ovarian estradiol synthesis and to explore the inhibition of the gonadotropic axis suppression could be a useful tool in the management of these patients.

Objective: To evaluate the usefulness of stimulated gonadotropins and estradiol levels by using the free fraction of Triptorelin depot for monitoring treatment efficacy of the gonadotropin axis inhibition.

Table 1. (for Abstract 58)

	At first dose	3–6 Months	12–18–24 Months
n	11	29	49
LH-3 h (IU/L)	20.8±14.3	1.6±1	1.7±0.9
FSH-3 h (IU/L)	20.3±8.3	2.3±1	2.9±1.2
E ₂ -24 h (pg/mL)	232±130	10±0.1	10±0.7
LH-3 h 97 pc ((IU/L)		4.0	3.3
FSH-3 h 97 pc (IU/L)		4.5	6.0

Patients and Methods: A prospective and longitudinal study was performed including 37 girls >4 years of age naïve to or under Triptorelin depot 3.75 mg IM every 28 days for idiopathic CPP. Monitoring visits for clinical and auxological assessment and GnRHa-stimulation testing were performed at 3, 6, 12, 18 and 24 months. Serum LH and FSH were measured at baseline and 3 hours after the intramuscular injection of depot Triptorelin (LH-3 h, FSH-3 h) whereas serum estradiol at 24 hours (E₂-24 h) (ECLIA-Cobas e411, Roche) post injection. In order to evaluate the stimulatory effect of the free fraction of GnRHa the response of gonadotropins and estradiol after the first dose were assessed in 11/37 girls. Clinical/auxological criteria of adequate inhibition were: a decrease of the breast size and trophism and vulvar estrogenization at 3 and 6 months, together with deceleration of the growth rate and decrease of BA/CA from 12 months and beyond. Percentiles 97 (97 pc) of LH-3h and FSH-3h for 3–6 months and 12–18–24 months of treatment were calculated.

Results: The response of gonadotropins and estradiol obtained after the first dose of Triptorelin was pubertal (Table). In 78/81 monitoring visits adequate clinical pubertal inhibition was observed. Responses of gonadotropins and estradiol (mean ± SD) and 97 pc for 3–6 months and 12–18–24 months of treatment are summarized in the table. From 3 months GnRHa treatment, serum stimulated estradiol at 24 h was found close or equal to the limit of detection of the assay (10 pg/mL).

Three patients were clinically suspected of inadequate inhibition at 6 months of treatment. These patients showed LH-3 h and/or FSH-3 h levels over the 97pc observed in the group with adequate treatment and elevated stimulated E₂-24 h levels.

Conclusion: The first injection of depot Triptorelin due to its free fraction was able to stimulate gonadotropin and ovarian estradiol synthesis to pubertal levels. After successive doses of treatment the assessment of stimulated estradiol showed that GnRHa leads to a profound suppression of ovarian steroidogenesis. These findings allow us to suggest that levels of LH 3 hours post depot Triptorelin below 4.0 IU/L at 3–6 months of treatment, or below 3.3 IU/L after one year of treatment ensure an adequate inhibition of the pituitary-ovarian axis.

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Hepatic Steatosis as a Factor Associated with the Presence of Metabolic Risk in Obese Children and Adolescents

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Introduction: One of the complications associated with obesity is nonalcoholic fatty liver disease (HD), which is defined as an excessive accumulation of fat in hepatocytes, characterized by chronic elevation of aminotransferases and ultrasonographic abnormalities (increased echogenicity). In the United States is now the most common liver disease. Prevalence of around 15 to 25% in the general population, this increases to 57.5 obese people 75%. The aim of this study was to evaluate whether hepatic steatosis is a

factor associated with the presence of metabolic risk in children and obese adolescents.

Materials and Methods: Ambispective one cross-sectional study in the High Specialty Medical Unit No. 25 of the Mexican Social Security Institute in Monterrey, Nuevo Leon, Mexico, in which the clinical records of patients from age 5 to 15 years old, referred with a diagnosis of obesity were reviewed, in the period of January 1, 2012 to June 30, 2013. Children and adolescent patients diagnosed with obesity were included, we excluded patients with a history of acute and chronic viral hepatitis, and use of antiepileptic and hepatotoxic drugs. For descriptive analysis we used absolute frequencies, percentages, means and standard deviations. For inferential analysis we used chi-square test, Fisher exact test and Student T test to establish the association of HD with the studied variables. The odds ratio was measured, considering 95% and statistical significance $p < 0.05$.

Results: 160 children and adolescent patients were included with median age 11.23 ± 2.2 years, of which 85 (53.1%) were male gender, and 75 (46.9%) were female. All were obese, with BMI and abdominal circumference greater than the 95th percentile for age. In total, 131 (81.8%) patients had nonalcoholic fatty liver disease (HD) and 29 (18.2%) patients did not. HOMA index was increased by 3.9 ± 2.1 ($p < 0.05$) in patients with the HD group with a mean of 6.4 ± 4.9 in the group without HD. The cutoff point we found that insulin resistance associated with HD was 9. We found 4 subjects with high levels of LDL (>130), and none in the control group. Transaminase levels were significantly higher in the group of patients with nonalcoholic fatty liver disease, ALT greater than 40 U/L in 127 (96.94%) of patients with nonalcoholic fatty liver disease, with OR (95% CI) of 63.5 (18.5–217) and $p < 0.005$. LDL-C greater than 130 mg/dL occurred in 4 (3%) patients with nonalcoholic fatty liver disease, and in none of the patients without nonalcoholic fatty liver disease ($p < 0.0001$). Acanthosis nigricans was found in 128 (97.7%) patients with nonalcoholic fatty liver disease and in only one (3.4%) in the group without nonalcoholic fatty liver disease, OR 1194.7 (119.8–1191.5) with $p < 0.0001$.

Discussion: Our research shows that insulin levels are predictor factors for the development of hepatic steatosis when high both insulin and HOMA index levels. Transaminase levels are also of relevance in these patients. The clinical presence of acanthosis nigricans may be a clinical marker to determine which patients should intentionally sought this abnormality.

Conclusion: Obesity and insulin resistance are risk factors for the development of fatty liver in children and adolescents.

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Prevalence of Substance Abuse in Chilean Young Patients with Type 1 Diabetes

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Introduction: Adolescence is a vulnerable period where high risk behaviors have negative impact on health. In type 1 diabetes (T1D) alcohol, cigarette and illicit drugs may contribute to the development of acute and chronic complications and also have a negative effect on psychosocial well-being.

Objective: To determine the current prevalence of alcohol, cigarette and marijuana consumption in Chilean adolescents with T1D and compare it with the last national survey of alcohol and drugs consumption on school population (SENDA).

Subjects and Methods: The SENDA survey was applied to adolescents with T1D between 12 and 19 years whom attended to the summer camp organized by the Chilean Diabetes Foundation in February 2014.

Results: Total 74 adolescents, 47.3% women. Average age 14.9 years (12–19 yo). 60.7% from public schools. *Alcohol consumption:* 79.7% of adolescents reported having consumed alcohol at least once in their life, 43.2% have consumed during the last month vs 34.7% (SENDA). 10.8% reported heavy drinking (more than 5 drinks per night) vs 8.9% (SENDA), but only 37.9% reported having been drunk at least once in life vs 59.5% (SENDA). *Marijuana consumption:* 37.8% reported having used marijuana at some time in their life and 28.3% consumed during the last year vs 19.5% (SENDA). The average age of onset was 15.2 years and the most common source of obtaining was friends (39.1%). *Tobacco consumption:* 56.7% reported have consumed cigarette at least once in their life and 36.4% consumed during the last month vs 25.9% (SENDA). The average age of onset was 13.7 years (7–18), 12.1% of them recognizes a habitual consumption (more than 20 days in a month) vs 8.1% (SENDA).

It is noteworthy that 56.7% of adolescents considered to have easy access to marijuana vs 38.7% (SENDA) Only 51.3% of participants reported having received education on alcohol and drugs abuse at School in the last year and only 25% have never talked to their parents about this.

Conclusions: This study showed that substance abuse is a problem in adolescents with T1D. This is a population at risk, since they have a higher intake of alcohol, marijuana and cigarette compared with the national survey (SENDA). Therefore it is essential to implement education tools aimed to prevent and educate about consumption of these substances.

Quality of Life in Children and Adolescents with Type 1 Diabetes Mellitus

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The evaluation of quality of life related to health (HRQoL) of youths with type 1 diabetes mellitus (T1DM) has been widely studied and considered an assessment of treatment parameters that allow development of strategies to minimize the impact of T1DM.

Aims: To evaluate the HRQoL of children and adolescents with T1DM, followed in a reference service, and to identify related factors.

Methods: 59 patients (9–16 y, T1DM for over a year, without comorbidities that could interfere with HRQoL) responded the Quality of Life Instrument for Young People with Diabetes (IQVJD), composed of 50 items distributed in the areas: satisfaction, impact and concerns (lower score corresponds to better HRQoL) and sociodemographic and clinical data survey (SDCDS).

Results: 57.6% were female, mean age 13.6±1.5 y, median age at diagnosis was 7.16 y (0.66–13.58), median disease duration 6.5 y (1.33–14.5), 66.1% lived with both parents, 40.7% had already school failure and 91.5% were involved in physical activity (PA). Sixty-three presented diabetic ketoacidosis (DKA) on diagnosis, 29% during follow up, with an average of 1.5 hospitalizations (0–6) over the years. Mean HbA1c in the last evaluation was 10.2±2.6% and in the last year 10.0±1.6%. All patients used multiple dose regimen of insulin, with an average of 4.2 injections per day (3–6); 74.5% received analog basal and ultra fast (UF) insulin, 22% NPH and regular and 3.5% NPH plus UF. Insulin administration was done with pen in 67.8%, syringe in 18.6% and both, in 13.6%. Parents and patients were responsible for the administration of insulin in 45.7% and patients themselves 37.2%. Mean daily blood glucose measurements was 3.9 (2–10). (Results of) Mean IQVJD scores overall and in the domains of satisfaction, impact and concerns were within the cutoff limit of better QoL. Analysis of each domain separately and SDCDS, showed that patients with better QoL had higher height Z score ($p = 0.04$) and lower HbA1c (9.7% versus 11.3%, $p = 0.02$). Univariate regression analysis revealed that as higher HbA1c higher the probability of a poor satisfaction ($p = 0.03$). The practice of PA ($p = 0.01$) and the use of pen ($p = 0.04$) were associated with better QoL; use of syringe and more than one hospitalization increased 5 and 4.4 fold respectively, the chance of poor satisfaction. Absence of DKA on diagnosis contributed with 75% of chance of better satisfaction. In the domain of impact, the use of pen ($p = 0.04$), the practice of PA ($p = 0.04$), and less hospitalizations ($p = 0.007$), were indicative of better QoL. Chance of worst impact increased 7.5 fold with use of syringe, 6 fold with the presence of DKA at diagnosis 15 fold with the occurrence of DKA on follow up. In the domain of concerns, patients with better QoL showed higher height Z score ($p = 0.02$), lower HbA1c (9.7% versus 10.6%, $p = 0.03$) and lived in small cities of the state ($p = 0.04$).

Discussion and Conclusions: Although most of the patients come from families with low income, they have access to the recommended treatment with multiple doses of insulin, frequent self-monitoring and access to insulin analogs and appropriate devices, when prescribed. The rate of DKA on diagnosis was high and metabolic control was inadequate in most patients. QoL analysis showed that 71% of patients had scores compatible with better QoL. Parameters associated with better QoL were: to live in small cities, lower frequency of DKA on diagnosis and follow up, less hospitalizations, use of pens for insulin injection, practice of physical activity, higher height Z score and lower HbA1c.

Clinical and Biochemical Findings in a Prepubertal Boy with a Homozygous R192C Mutation in CYP19 (Aromatase) Gene

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Background: Aromatase deficiency is a rare autosomal recessive disorder produced by *CYP19* gene mutations. This enzyme is essential for the biosynthesis of estrogens from androgen precursors. DSD has been reported in 46,XX affected patients. In these girls, a resetting of central gonadotropin feedback resulting in moderate-high increases of serum FSH, and occasionally mild increments in serum LH has been reported. All 46,XY affected patients presented normal external genitalia except for one recently reported boy. In adult affected male patients, slight increment of basal serum FSH but normal LH, testosterone and inhibin levels were reported. There is scarce information about clinical and biochemical findings in affected boys during childhood.

Clinical Case: We report the clinical phenotype and hormonal studies of a 7.9-year-old 46,XY aromatase deficient boy. Molecular analysis revealed a novel homozygous mutation (R192C) in the *CYP19* gene, predicted to compromise enzyme function. This affected *CYP19* deficient patient was the oldest brother of a 46,XX affected sister carrying the same *CYP19* gene mutation. Maternal virilisation was present during both pregnancies. On physical exam, height was 134.2 cm (1.63 SDS), within target height, while weight and BMI were within the normal range; he presented normal male prepubertal external genitalia. Bone age was delayed 3 years. Laboratory tests showed normal prepubertal basal serum LH and FSH (including an adequate GnRH stimulation test), inhibin B, AMH, testosterone and androstendione levels. OGTT was normal, as well as bone mass, assessed by DEXA.

Conclusion: In males, aromatase deficiency may go unnoticed until late puberty, except when there is a family history of this entity. Although maternal virilization during pregnancy is not a universal finding in reported patients, the presence of this clinical sign should alert gynecologist/obstetricians to the possibility of this disorder. Early diagnosis of aromatase deficiency allows to: 1) improve our knowledge on the pathophysiology in the prepubertal

and pubertal period in affected males regarding testicular function and gonadotropin regulation, 2) optimize clinical management and the timing of estrogen replacement therapy, specially to protect bone mass, and lipid and carbohydrate metabolism, and 3) provide genetic counseling to the family.

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Optical Coherence Tomography (OCT): A Useful Tool for Evaluation of Idiopathic Intracranial Hypertension during GH Treatment

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Background: Headache is a common complaint, and its onset or worsening can occur during GH treatment, requiring differential diagnosis with idiopathic intracranial hypertension (IIH). Complete ophthalmologic examination, angiography, SNC-MRI and measurement of cerebrospinal fluid pressure is used to confirm IHH. The availability of third-generation equipment and reference values for children allowed the use of optical coherence tomography (OCT) as a tool to identify children at risk for IIH.

Aim: To measure the retinal nerve fiber layer (RNFL) thickness by OCT in patients under GH treatment.

Patients and Methods: we evaluated 103 patients with age between 5.7 and 19.7 years (46 F:57 M) receiving GH for 2.48 (0.25–10.9) years. The OCT was performed with the device TOPCON 3D OCT 1000, Japan. The results of nerve thickness were corrected according to the reference values for age, and expressed as SDS scores. Papilledema was investigated by direct ophthalmoscopy, and patients divide in 2 groups: Papilledema (+): 17/103 patients (7 F:10 M), and Papilledema (-).

Results: Direct ophthalmoscopy identified papilledema predominantly in the nasal quadrant. The comparison of patients with papilledema (+) versus papilledema (-) the nerve thickness was increased in all quadrants of cases with papilledema (+), more sig-

nificantly identified in the nasal quadrant (mean \pm SD: 1.3 \pm 1.1 vs. 0.4 \pm 1.2; Mann-Whitney test, $p = 0.02$). There was no correlation of RNFL thickness with BMI, height, GH dose, duration of GH therapy, GH peak or IGF1 values. Prospective studies comparing OCT values before and after GH therapy are essential to identify the amplitude of SDS increase that add relevant risk for clinical papilledema.

Conclusion: OCT is a noninvasive method useful to identify incipient papilledema in patients under GH therapy, allowing the selection of those who need close follow-up and eventual invasive CSF measurement.

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Differences in Folate Transporters Contents in Placentas from Small (SGA), Appropriate (AGA) and Large (LGA) for Gestational Age

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Introduction: Adequate nutrition during gestation is essential for normal development and growth. A positive correlation between folate intake during pregnancy and birth weight has been shown. However, a high supply of folates (through fortified foods and supplements) together with the observation that its excessive consumption in the third trimester of pregnancy has been associated to a lower birth weight. The folate is transported across the placenta mainly through the specific transporter FOLR1, HCP1 and RFC1.

Aim: To study the protein contents of FOLR1, HCP1 and RFC11 in human term placentas from SGA, AGA and LGA gestations.

Subjects and Methods: We selected 68 placentas, SGA = 21, AGA = 27 and LGA = 20; and we determined in the chorionic (CP) and basal plates (BP) of the placentas the protein content of folate

Table 1. (for Abstract 64)

	SGA	AGA	LGA
Gestational age (weeks)	38.7 \pm 0.2	39.4 \pm 0.2	39.4 \pm 0.3
Birth weight (SDS)	-1.63 \pm 0.07*	0.06 \pm 0.15	2.23 \pm 0.24**
Birth length (SDS)	-1.63 \pm 0.16*	-0.15 \pm 0.16	1.33 \pm 0.16**
Cord Blood Folate (ng/ml)	35.9 \pm 5.9 ^{&}	19.5 \pm 1.8	22.3 \pm 2.3
RFC1 (AU)	0.59 \pm 0.11	0.55 \pm 0.05	0.47 \pm 0.05
BP	0.46 \pm 0.06 ^{&}	0.65 \pm 0.07	0.41 \pm 0.05**
FOLR1 (AU)	0.26 \pm 0.05 ^{&}	0.43 \pm 0.07	0.25 \pm 0.07**
BP	0.42 \pm 0.11	0.31 \pm 0.05	0.25 \pm 0.05
HCP1 (AU)	0.30 \pm 0.06 ^{&}	0.39 \pm 0.04	0.62 \pm 0.13
BP	0.47 \pm 0.08	0.40 \pm 0.05	0.36 \pm 0.07

* $p < 0.05$ SGA vs AGA and LGA; ** $p < 0.05$ LGA vs AGA; [&] $p < 0.05$ SGA vs AGA.
AU = Arbitrary units.

transporters by western blot. We also measured the folate concentration in cord blood by electrochemiluminescence.

Results: Results are shown in table 1 as a mean \pm SEM. The differences were analyzed by Kruskal-Wallis.

We observed lower RCF1 placental content in the BP of SGA and LGA compared to the AGA condition and a lower placental content of FOLR1 in the CP of SGA compared to AGA. We also found an inverse correlation between FOLR1 content in BP with birth weight ($r = -0.235$; $p = 0.050$).

Conclusion: The higher folate cord blood concentrations and the lower content of the transporters observed in SGA placentas suggest that this system may influence fetal growth. Optimal concentrations of folates intake and the period of its supplementation during pregnancy should be reviewed for preventing foetal pathologies. Supported by Fondecyt # 1130188 and 1110240.

nents associated mainly with proliferation processes (IRS-1, ERK1 and ERK2).

Aim: To study the protein content of IGF-IR, IRS-1 and ERK_{1/2} and the effect of IGF-I on the phosphorylation of these proteins in human full term (37–41 weeks of gestation, WG) and preterm small (SGA) and appropriate (AGA) for gestational age placentas (32–36 WG).

Methods: We collected placentas from 26 T-SGA (birth weight (BW) = -1.65 ± 0.07 SDS), 22 T-AGA (BW = -0.12 ± 0.15 SDS), 14 PT-SGA (BW = -2.09 ± 0.24 SDS) and 15 PT-AGA (BW = -0.56 ± 0.23 SDS) newborns and we studied the protein content, and the effect of IGF-I by Western Blot in the chorionic (CP) and basal (BP) plates of the placentas by Western Blot. Results are shown as mean \pm SEM. The differences between groups (T and PT) placentas were studied by Mann-Whitney test.

Conclusion: The higher protein content of IGF-IR and IRS-1 and the higher response to IGF-I of ERK1 and ERK2 in T-SGA compared to T-AGA placentas, suggest that this signal transduction pathway may be a maturational compensatory process to enhance growth by the end of gestation. However, this difference was not found in the preterm group, perhaps due to that it is not ongoing at that gestational age. Nevertheless a higher response to IGF-I in ERK2 in PT-SGA compared to PT-AGA placentas suggest a role for this kinase in earlier period of gestation (FONDECYT 1110124).

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Differences in IGF-IR/IRS-1/ERK_{1/2} Protein Content and Their Response to IGF-I in Human Term (T) and Preterm (PT) Placentas

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Introduction: The human placenta expresses the mRNA and protein of IGF-I and IGF-IR and their intracellular signal compo-

Table 1. (for Abstract 65)

		T-SGA	T-AGA	PT-SGA	PT-AGA
Total IGF-IR (AU)	CP	0.60 \pm 0.09*	0.24 \pm 0.04****	0.39 \pm 0.08***	0.46 \pm 0.07
	BP	0.78 \pm 0.11*	0.23 \pm 0.04****	0.38 \pm 0.06***	0.55 \pm 0.10
Total IRS-1 (AU)	CP	0.69 \pm 0.37*	0.35 \pm 0.10****	0.80 \pm 0.06***	0.82 \pm 0.07
	BP	0.88 \pm 0.52	0.22 \pm 0.07****	0.75 \pm 0.08***	0.90 \pm 0.09
Total ERK1 (AU)	CP	0.89 \pm 0.15	1.01 \pm 0.11	1.01 \pm 0.29	1.37 \pm 0.25
	BP	0.99 \pm 0.15	0.90 \pm 0.10	1.07 \pm 0.31	1.80 \pm 0.23
Total ERK2 (AU)	CP	0.94 \pm 0.15	1.03 \pm 0.13	1.11 \pm 0.30	1.15 \pm 0.21
	BP	0.99 \pm 0.13	0.98 \pm 0.14	1.09 \pm 0.41	1.32 \pm 0.28
Phospho IGF-IR (AUC)	CP	18.2 \pm 1.5*	36.3 \pm 2.9****	26.2 \pm 1.1***	13.4 \pm 3.0**
	BP	102.0 \pm 22.8*	46.0 \pm 7.1****	80.3 \pm 3.0***	15.3 \pm 1.9**
Phospho IRS-1 (AUC)	CP	17.0 \pm 1.0*	9.6 \pm 1.6****	12.8 \pm 0.7***	5.4 \pm 1.0**
	BP	44.4 \pm 9.4	47.3 \pm 12.3****	20.0 \pm 1.5***	11.9 \pm 0.9**
Phospho ERK1 (AUC)	CP	14.8 \pm 1.5*	7.9 \pm 0.8****	10.7 \pm 0.5	9.9 \pm 0.7
	BP	20.8 \pm 1.4*	9.2 \pm 0.6****	13.9 \pm 0.5	13.7 \pm 1.2
Phospho ERK2 (AUC)	CP	18.1 \pm 0.6*	11.8 \pm 0.9	13.9 \pm 0.8***	11.4 \pm 0.8**
	BP	14.8 \pm 0.3*	11.3 \pm 0.5	19.2 \pm 0.9***	14.7 \pm 1.6**

* $p < 0.05$ T-SGA vs T-AGA; ** $p < 0.05$ PT-SGA vs PT-AGA; *** $p < 0.05$ T-SGA vs PT-SGA; **** T-AGA vs PT-AGA.

AU = Arbitrary units; AUC = area under the curve.

Adiponectin and Leptin Concentrations in Children with and without Metabolic Syndrome in a Third-Level Care Hospital

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Introduction: Knowledge of the role of adipose tissue as a bioactive endocrine organ, secretor of adipokines, supports the idea that fatty tissue is a determinant of systemic inflammation. Adiponectin is capable of increasing insulin sensitivity and hypoadiponectinemia correlates with hyperinsulinemia and insuline resistance (IR). Leptin is secreted by the adipocyte as a response to diet to suppress appetite through a hypothalamic action. The adipocytes of visceral fat produce less leptin than subcutaneous fat. High levels of leptin and low levels of adiponectin predict additional metabolic stress. The association of low adiponectin with IR appears to be mediated by adiposity. Obesity in infancy is considered the main risk factor for developing metabolic syndrome (MS) during adolescence and adult life. In prepubescent children, leptin and adiponectin allow the early detection of individuals at risk of presenting metabolic alterations of glucose.

Objective: To determine the concentrations of adiponectin and leptin in a sample of children with and without metabolic syndrome cared for in the doctor's office of a third-level care hospital.

Design: Analytical cross-sectional.

Material and Methods: Patients were included aged 6 to 12 years with a diagnosis of exogenous obesity. All patients underwent a physical exam to evaluate weight, height, waist circumference, blood pressure and to calculate body mass index. A fasting blood sample was taken to determine lipid profile, glucose, adiponectin and leptin. Metabolic syndrome was defined according to IDF criteria: waist circumference higher or equal to 90 percentile, plus two

of the following criteria: elevated plasma glucose ≥ 100 mg/dL or known type 2 diabetes, triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL and systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg.

Results: Of a total of 80 patients, 33 (41.2%) met the criteria for MS. Statistically significant differences were found between groups: in waist circumference, triglycerides, HDL cholesterol, LDL cholesterol and total cholesterol. Levels of leptin and adiponectin in patients diagnosed with MS were 20.7 ± 20.1 ng/ml (1.4–77.9) and 14.7 ± 8.2 μ g/ml (3.2–39.9) respectively; in subjects without metabolic syndrome they were 13.1 ± 6.1 ng/ml (1.44–29.96) and 16.9 ± 18.8 ng/ml (3.1–88.7) respectively, without statistically significant differences between the two groups. Statistically significant correlation was observed between adiponectin and diastolic blood pressure ($p = 0.006$) and between leptin and waist circumference ($p = 0.002$). In patients with MS a negative correlation was found between leptin and adiponectin ($r = 0.35$) with statistical significance ($p = 0.044$).

Discussion and Conclusions: 41.2% of the patients met the diagnosis of MS. Correlation was found between leptin values in patients with SM but not in those without MS.

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Metabolic Syndrome and Puberty

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Aims: To demonstrate if puberty development modifies the metabolic syndrome biochemical markers in normal and obese brothers and sisters.

Material and Method: Observational, cross-sectional, analytical, comparative and prospective study in 264 patients (116 males, 148 females) with obesity and 390 non obese brothers (196 males, 194 females), selected in public and private schools.

Table 1. (for Abstract 67)

	Tanner 1		Tanner 2		Tanner 3		Tanner 4		Tanner 5	
	O	N	O	N	O	N	O	N	O	N
Metabolic Syndrome	28	3	28	2	36	2	48	3	49	3
Glucose > 100 mg/dl	3	0	6	0	10	1	12	3	12	3
CH Intolerance	21	1	20	2	24	2	25	4	25	2
DM-2	1	0	2	0	4	0	5	0	6	1
HDL < 40 mg/dl	45	30	50	35	52	38	52	40	52	40
TG > 110 mg/dl	30	2	46	2	58	3	59	3	57	4
Acantosis	97	0	97	0	98	1	98	1	99	0
Waist $>$ percentile 90	100	0	100	0	100	0	100	0	100	0
AT $>$ percentile 90	25	0	28	0	40	0	42	2	49	1
Fattv liver by US	25	0	30	0	60	0	80	1	83	2
PCO by US	8	3	20	4	30	6	33	6	33	8

O = Obese child; N = not obese child (brother/sister).

Although not at the same time, all the patients were followed since 8.5 ± 4.0 years old until the end of growth, and every 6 months were collected oral glucose tolerance test, lipid profile, insulin, hepatic and ovarian ultrasound, arterial tension, waist circumference and the presence of acanthosis nigricans.

The patients with obesity remain with BMI higher than 90 percentile during all the study, and the brothers and sisters between 10 and 50 percentiles.

Inclusion criteria was: one patient with obesity (O) and one or more brother with normal BMI (N), gender match in every case, no chronic disease, no pharmacological treatment for more than 2 weeks/year, no use of oral or dermal steroids, no changes in more than 10% in BMI during the study.

Results: See table 1.

Analysis: During childhood obese children had significant more clinical and biochemical markers of metabolic syndrome, with exception of HDL cholesterol, which is increase both in obese and no obese males and females (Latin American phenotype?).

All the biochemical markers tend to increase from Tanner mammary (females) or genital (males) 3 to 4.

Conclusions: Puberty increase prevalence of metabolic syndrome biochemical markers in obese males and females, and consequently is a high risk period for the development of metabolic complications associated with obesity.

pineapple juice (Jumex®) which contains 26 g of carbohydrates per 200 ml, with a glucose equivalent of 1.75 g/kg (OGTT-2).

The total sample for this study was calculated as 50 patients (100 tests.) This report is preliminary, based on 26 patients (52 tests.) which represent 52% progress in the study. The results are analyzed using Student' t test, to compare the values between the two tests (with anhydrous glucose and quick-absorption food-stuff.) The value of $p \leq 0.05$ was assigned according to a confidence level of 95%.

Results: See table 1.

Discussion: We observed a similar value of glucose during the test at 30 and 60 minutes, however, at 120 minutes a p value has statistical significance. Although none patient showed diabetes or carbohydrate intolerance (glucose ≥ 200 mg/dl o 140 mg/dl, respectively) in any of the two OGTT, we found an abnormal postprandial glucose (>100 mg/dl) in 19 patients with OGTT-1, but only in 3 of them during OGTT-2.

The sensitivity for OGGT-2 abnormal postprandial glucose was 100% and specificity 28%.

Conclusion: As glucose and insulin 2 hours after intake, did not have the same elevated values after the test with fruit juice as they did with the test of anhydrous glucose, and these values (OGTT-2) are nearest to normality, we must answer if the result of a traditional OGTT really represents physiological or normal response.

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Traditional Oral Glucose Tolerance Test (OGTT) vs. Fruit Juice OGTT Based on Glucose Equivalent

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Aims: To compare the effects of glucose between a traditional OGTT (1.75 g/k with anhydrous glucose) and an OGTT with commercial juice (pineapple juice Jumex®) administering as equivalent of 1.75 g/kg in obese children with *acanthosis nigricans*.

Method: In 26 patients with obesity and *acanthosis nigricans* we performed two CTOG with difference of 72 ± 24 hours, first always with anhydrous glucose (OGTT-1) and second with commercial

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Neurological and Cognitive Development of a Cohort of Patients with Congenital Hypothyroidism

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Introduction: Congenital Hypothyroidism is currently the leading preventable cause of mental retardation and neurological damage through neonatal screening.

Table 1. (for Abstract 68)

	Time minutes	OGTT-1 Media (CI 95%)	OGTT-2 Media (CI 95%)	p
Glucose (mg/dL)	basal	91.3 (87.9–94.7)	87.4 (84.6–90.1)	0.026
	30	150.9 (141.2–160.7)	148.0 (138.5–157.5)	0.579
	60	128.8 (117.2–140.5)	107.8 (99.2–116.5)	0.001
	120	111.7 (104.7–118.7)	89.2 (85.6–92.9)	<0.001
Insulin (UI)	basal	16.6 (11.3–21.9)	16.9 (12.2–21.6)	0.911
	120	99.3 (63.4–135.1)	34.0 (25.2–42.8)	<0.001
HOMA	basal	3.8 (2.6–5.1)	3.9 (2.7–5.0)	0.800
	120	28.8 (17.6–40.0)	7.9 (5.9–10.0)	<0.001

The National Program of Hypothyroidism provides neurological and psychometric evaluation four times in the first year of life, and then once a year.

Objective: To evaluate the actual neurological and cognitive development of a cohort of 41 patients born between 1997 and 2013, actually in control and treatment in the Unit of Endocrinology of de E. González Cortés Hospital of Santiago.

Subjects and Methods: They are 41 patients (24 females and 17 males), with ages between 1.1 and 16 years. TSH at screening was between 12.5 and 623 uUI/ml. 26 have echography or cyntigraphy study diagnostic at birth: 9 ectopic thyroid gland, 6 agene-sics, 5 diffuse goiter, 2 hypoplasia, 3 with poor captation and 1 without captation. The age of beginning of the treatment was in average 16.8 days (21 until 15 days, 15 between 16 and 29 days, 4 at one month and 1 at one and a half month of life. Neurological and cognitive evaluation was done using WISC III.

Results: 5 patients were excluded: 3 Down Syndrome and 2 with mild mental retardation with chromosome defect Of the others 36 patients, 24 have normal IQ, 2 normal slow IQ, 1 borderline IQ with bad compliance to treatment and controls. There are 4 with deficit of attention and hyperactivity, and 5 with language delay.

Conclusion: Patients with congenital hypothyroidism have a normal neurological development or minor neurological pathology, except those with associated pathology. The neonatal screening was effective in prevent the intellectual damage in 97% of ours patients.

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Prevalence of Hyperglycemia in Obese Children and Adolescents Followed at a Tertiary Hospital

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Introduction: In recent years with the obesity epidemic there has been an increase in cases of type 2 diabetes in childhood and adolescence. There are clear regional and ethnic differences in prevalence of diabetes and glucose alterations though. The goal of our study was to evaluate changes in blood glucose through fasting glucose, oral glucose tolerance test (OGTT), glycated hemoglobin, insulin, glucose insulin ratio and HOMA index in obese children and adolescents and correlate glucose alterations with clinical variables such as index of body mass index (BMI), acanthosis nigricans, and pubertal stage and epidemiological data as family history of diabetes, birth weight, and time tracking.

Methods: Cross-sectional observational study conducted by records review, evaluating clinical data – age, sex, Tanner stage, weight, height, BMI, family history of type 2 diabetes, waist circumference, glycated hemoglobin, fasting glucose, insulin, HOMA index, G/I, abdominal ultrasound, medication use and follow up time.

Results: We evaluated the records of 156 consecutive patients seen in 2013 in the obesity clinic. The mean age was 11.9 ± 3.08 years, ranging from 3.08 to 17.6 years and 86 (55.1%) were female. The average follow-up time in the clinic was 49 months. 67.9% of the patients were in puberty, 3.2% demonstrated only pubarche. In relation to birth weight there were 25/156 (16%) large for gestational age and 9% small for gestational age, with mean birth weight of 3249 g. Family history of type 2 diabetes was positive in 58.3% and 59.7% of the patients presented with acanthosis nigricans. The average BMI z score was $+2.63 (\pm 0.91)$, with 26 $> +1$ SD, 84 $> +2$ SD AND 41 $> +3$ SD. Glycated hemoglobin was evaluated in 104 patients and was above 5.7 in 17 (16.3%) patients and above 6.5% in 5 patients (4.8%). Of these patients 2 presented also with a elevated fasting glucose, and 2 met criteria for diabetes. There were 5 patients with impaired fasting glucose and normal HbA1c. GTT was performed in only a small number of patients and could not be included for statistical analysis.

Discussion: A high prevalence of elevated A1c was found in our group of obese children and adolescents, with small correlation with fasting glucose. As this was a retrospective study and due to the small number of patients screened with GTT we were not capable to compare sensitivity between the exams. Family history of diabetes and acanthosis nigricans were risk factors commonly found in our population.

Conclusion: Obese children and adolescents, specially with family history of type 2 diabetes and positive finding of acanthosis nigricans are a high risk group for impaired glucose metabolism and type 2 diabetes. None of the existing measurements is sufficient to detect all cases. Screening should include different measurements of glucose metabolism and insulin resistance to increase sensitivity and prevent complications of diabetes by early treatment.

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Carotid Intima-Media Thickness Is Increased in Brazilian Adolescents with Type 1 Diabetes Mellitus

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Background: Cardiovascular disease is the leading cause of death in the diabetic population. Increased thickness of the intima-media layer of the carotid artery (CIMT), assessed by ultrasound has been reported in children and adolescents with chronic diseases as an independent predictor of atherosclerosis and future cardiovascular events.

Objective: To evaluate CIMT and identify associated metabolic parameters in adolescents with type 1 diabetes (DM1).

Methods: Cross-sectional study of 118 adolescents: 57 with DM1, followed up at the Pediatric Endocrinology Service at a University Hospital and 61 healthy individuals, recruited from a public school located in Belo Horizonte, Brazil. To be included, patients with diabetes should have at least 5 years of diagnosis and no chronic complications related to diabetes at the time of evaluation. No participant had a history of chronic or regular medication, ex-

cept for diabetes treatment. It was performed clinical, biochemical, and ultrasonographic evaluation, by a single, blinded radiologist. The high-resolution B-mode ultrasounds were performed according to the recommendations of the Consensus Statement of the American Society of Echocardiography Carotid Intima-Media Thickness Task Force, on Philips HD11XE equipment, with a high-resolution multi-frequency linear transducer adjusted to 12 MHz.

Results: Diabetic patients were 14.5 ± 2.6 years old, 66% female and had 9 ± 4 years of disease duration. Healthy adolescents were 14.3 ± 2.6 years old and 62.3% female. Of 118 teenagers 96.5% had normal weight for height; 2 diabetics were underweight (BMI percentile for age). All adolescents had normal systolic and diastolic blood pressure (BP), according to the percentile for age and height;

SBP in 66% of diabetics was equal to or greater than the 50th percentile. Glycemic control was inadequate in 75% of DM1 adolescents (ADA criteria). Increased CIMT was observed in diabetic patients compared to the control group (0.53 mm vs. 0.51 mm $p < 0.004$ on the right side, 0.55 mm versus 0.51 mm in the left side, $p < 0.001$). CIMT showed independent, positive and moderate association with disease duration ($r = 0.414$, $p < 0.001$), total cholesterol ($r = 0.397$, $p < 0.002$), LDL cholesterol ($r = 0.405$, $p < 0.002$) and SBP percentile ($r = 0.243$, $p < 0.072$).

Conclusion: The finding of increased CIMT in diabetic adolescents suggests its assessment could be useful to identify early cardiovascular risk in this population, and reinforces the need for monitoring and maintenance of strict metabolic control.

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