VI Giornate Pediatriche “A. Laurinsich”
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FAILURE TO THRIVE: L'ALIMENTAZIONE PER PREVENIRE O CURARE IL RITARDO DI CRESCITA? FOCUS SUI FATTORI DI CRESCITA

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OSPEDALE dei BAMBINI

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Failure to thrive

Arch Pediatr 1908

Definizione

Non è una malattia, né una diagnosi

piuttosto

la descrizione di un problema pediatrico abbastanza comune che comprende un ritardo di crescita specie ponderale che avviene nei primi anni di vita nei paesi sviluppati

Table 1. Prenatal Causes of Failure to Thrive.

Complications of premature birth
Maternal exposures, such as substantial alcohol use
Maternal illness: rubella, cytomegalovirus, syphilis, toxoplasmosis, or herpes simplex virus
Maternal malnutrition
Chromosomal disorders
Single-gene disorders
Genetically associated short stature

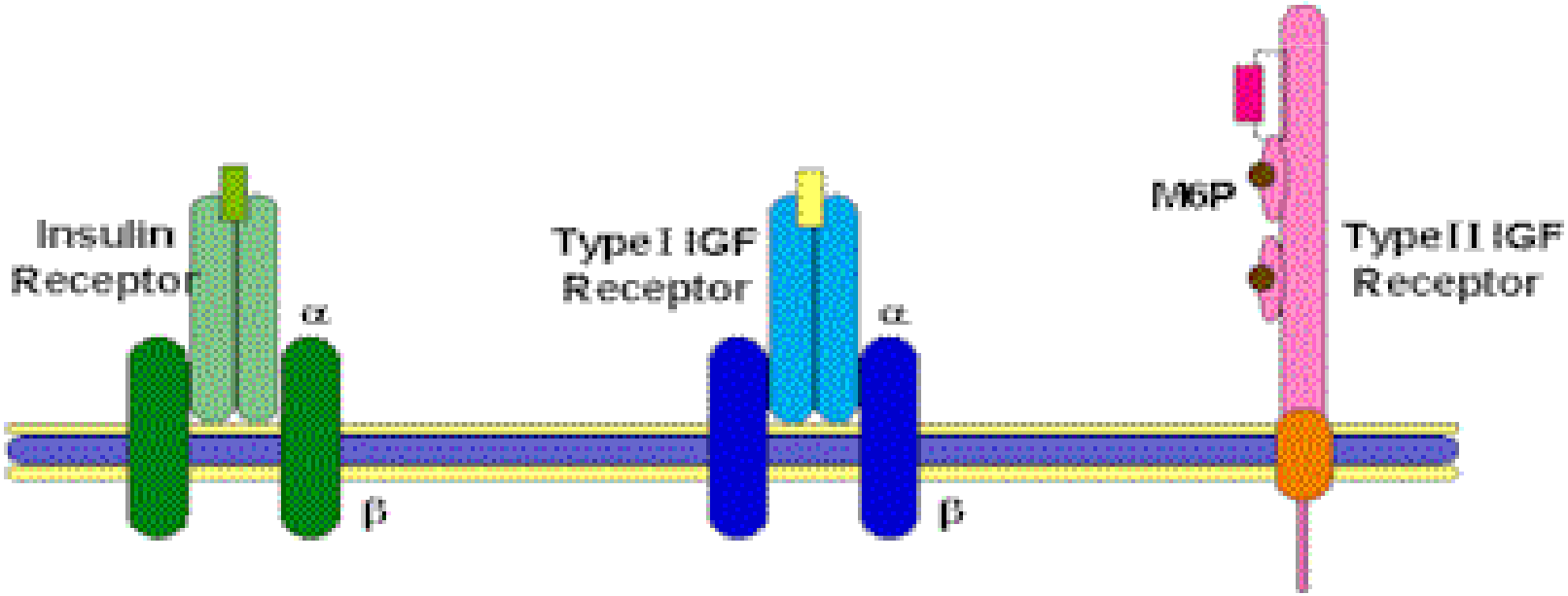
Table 2. Postnatal Causes of Failure to Thrive.

Mechanism	Underlying Cause	Example
Inadequate energy intake	Mechanical feeding problems	Cleft lip, cleft palate
	Breathing difficulties	Choanal atresia
	Poor suck and swallow reflex	Neuromuscular disorders
	Poor appetite	Anemia, chronic infections
	Easy fatigability	Congenital heart disease
	Chronic vomiting	Gastroesophageal reflux
Poor absorption or use of absorbed nutrients	Malabsorption syndromes with lack of pancreatic enzymes or inadequate substrate for absorption	Cystic fibrosis
		Short-gut syndrome
		Chronic liver or renal disease
		Chronic diarrhea
	Conditions with nutrient loss	
Increased metabolic demands	Conditions that have increased energy requirements	Congenital heart disease
		Bronchopulmonary dysplasia
		Hyperthyroidism
		Renal failure
		Neoplasms
		Infectious or inflammatory processes

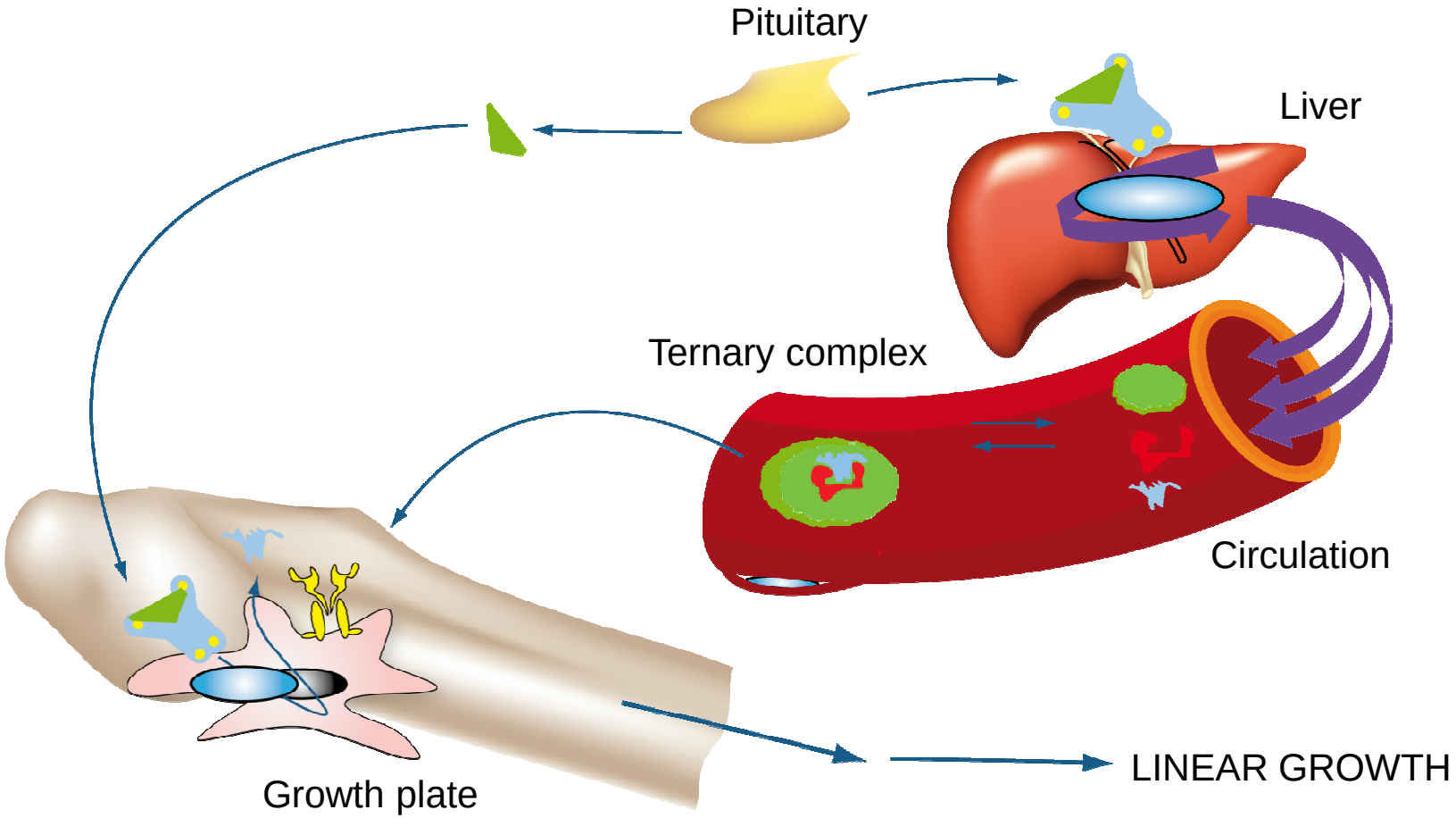
Outline della presentazione

- **Il SISTEMA IGF**
- **IL RITARDO DI CRESCITA INTRA-UTERINO**
- **LE MICI E LA CELIACHIA**
- **LA FIBROSI CISTICA**

The IGFs, their receptors, and their binding proteins



Circulating versus local tissue IGF-I expression and action[1–3]



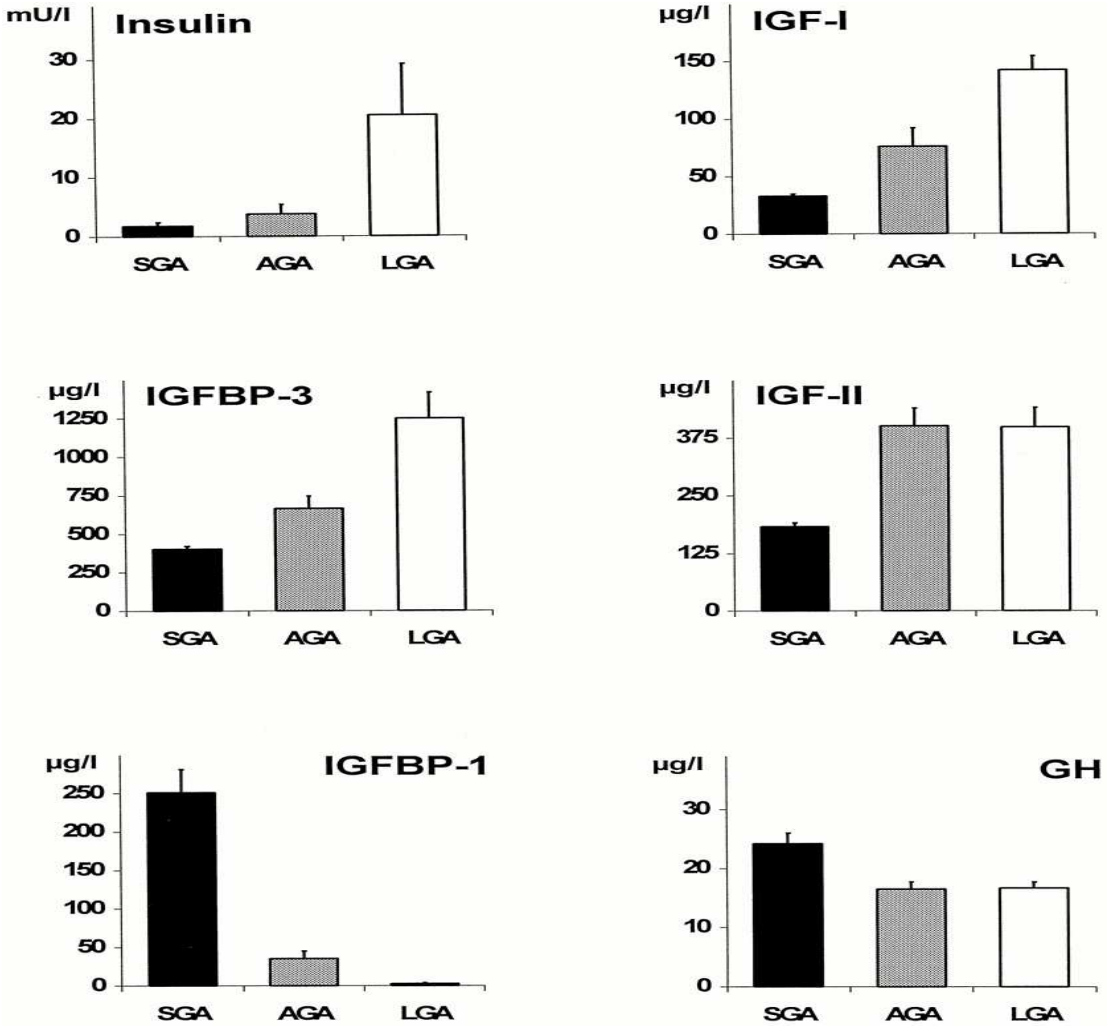
1. Bang P *et al. Horm Res* 2001:55(Suppl 2):84–93;
2. Isaksson OG *et al. Endocr Rev* 1987;8:426–38;
3. LeRoith D. *Pediatr Endocrinol Rev* 2008;5(Suppl 2):739–43

STAT5b, signal transducer and activator of transcription 5b

MODULATORS OF THE IGF SYSTEM

- Nutrional status;
- Inflammation;

INSULIN AND IGF SYSTEM : COMMON FEATURES REPORTED IN SGA CHILDREN- ALL POST-NATAL STUDIES



Zegher, F. d. et al. J Clin Endocrinol Metab 1997;82:2021-2026

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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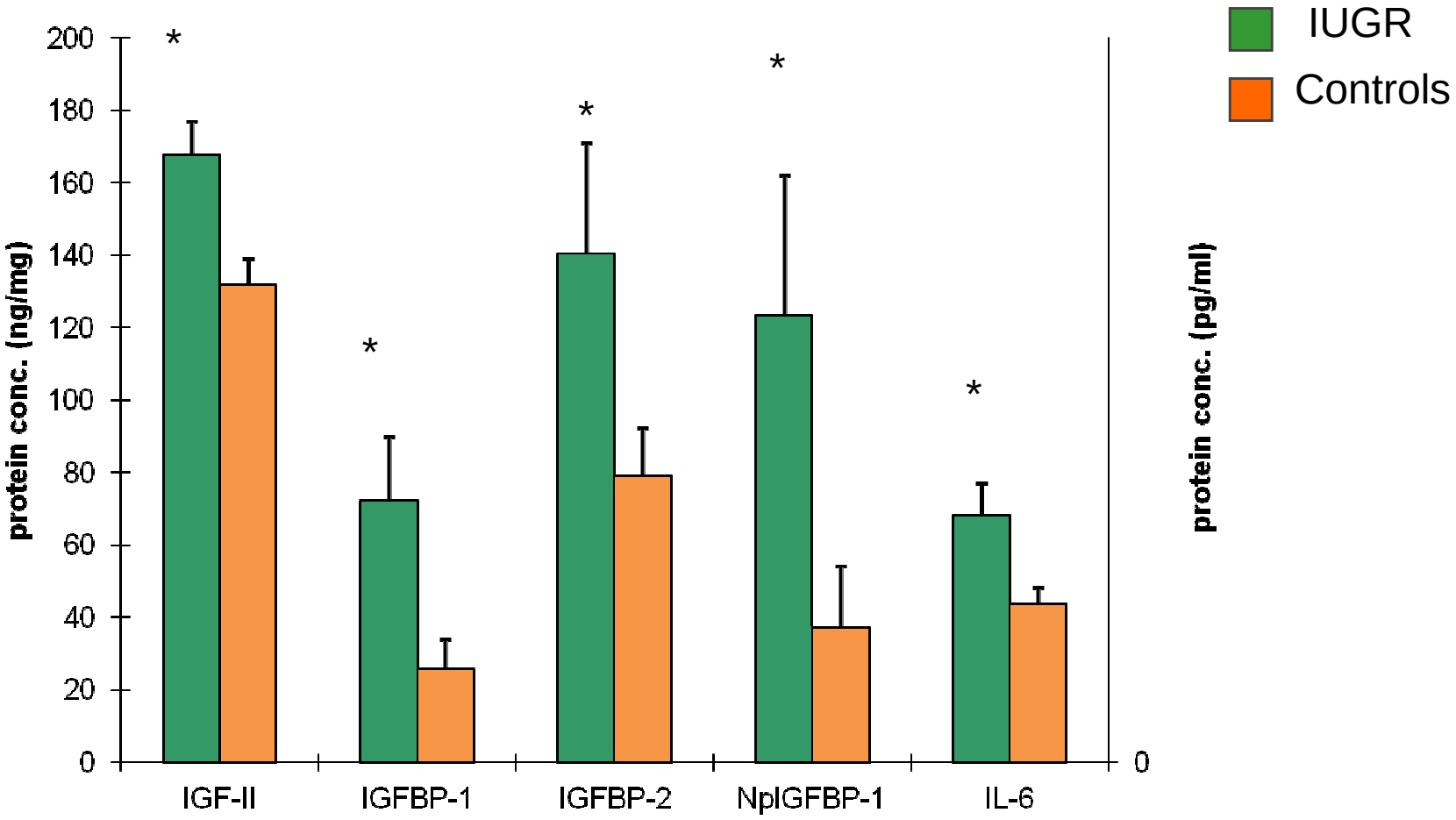
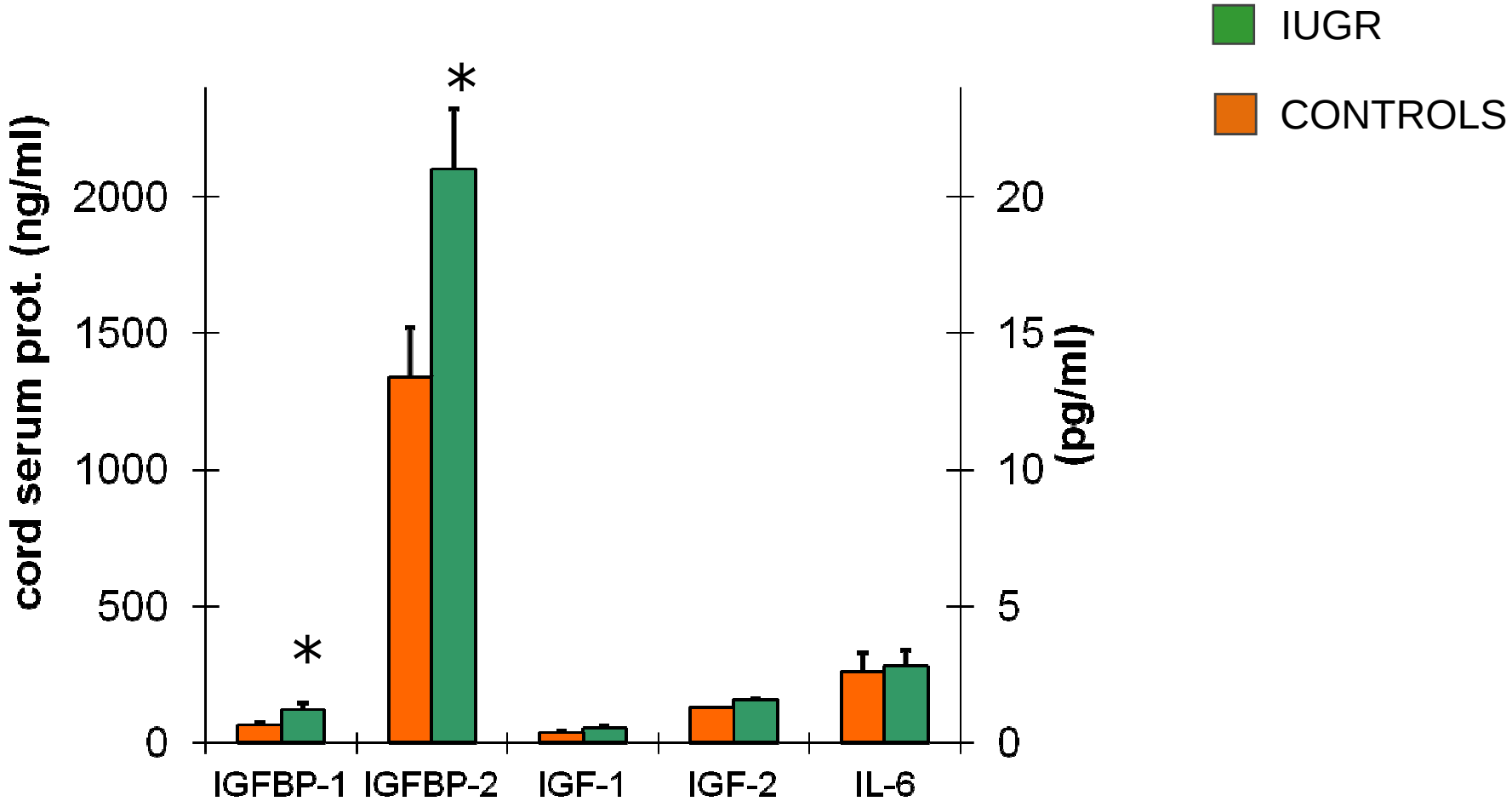
COMPARISON OF PLACENTA PROTEINS IN CONTROLS AND IUGR BORN > 32 weeks



Street et al. *Eur J Endocrinol* 2006; 155: 567-574.

COMPARISON OF CORD SERUM PROTEIN CONCENTRATIONS IN CONTROLS AND IUGR BORN > 32 WEEKS G.A.



Street et al. Eur J Endocrinol 2006

Clinical Endocrinology (2009) 71, 394–399 doi: 10.1111/j.1365-22

ORIGINAL ARTICLE

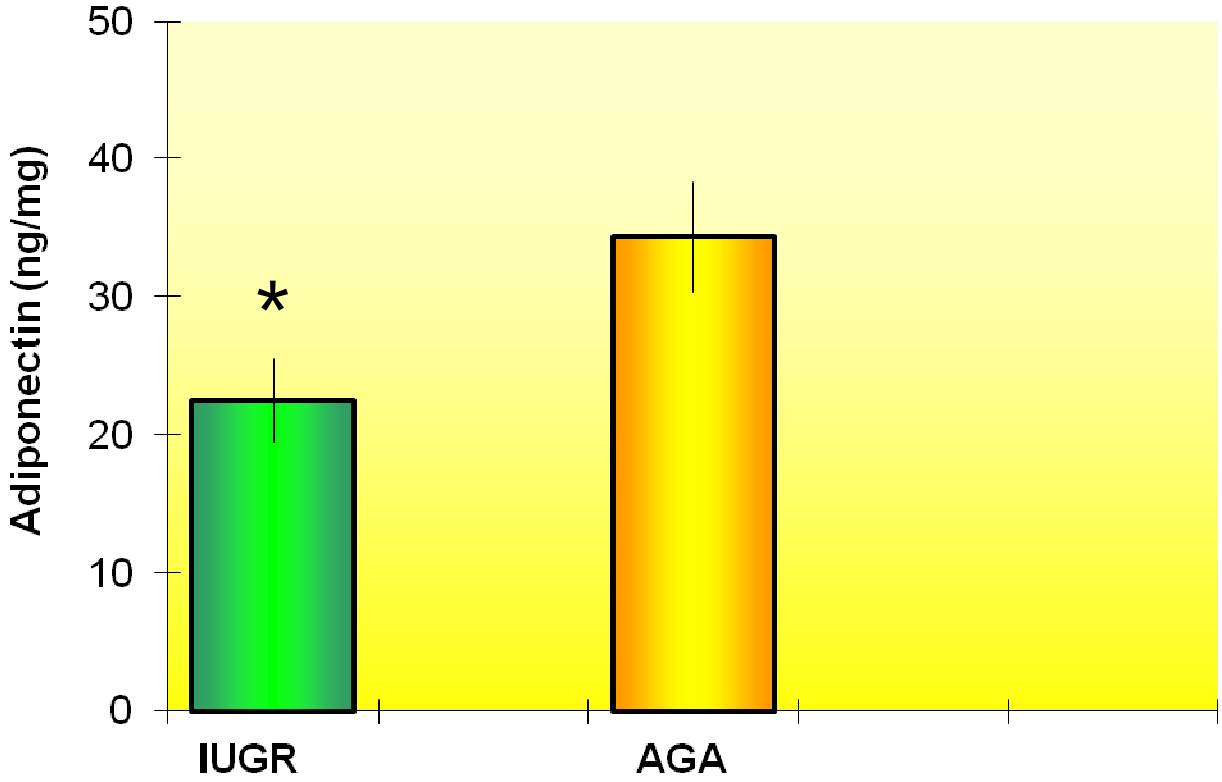
Markers of insulin sensitivity in placentas and cord serum of intrauterine growth-restricted newborns

Maria E. Street, Cecilia Volta, Maria A. Ziveri, Isabella Viani and Sergio Bernasconi

Department of Paediatrics, University Hospital, Parma, Italy

This study aimed to evaluate cortisol, insulin, total insulin receptor, resistin and adiponectin, as markers of insulin sensitivity, in placental lysates of IUGR and appropriate for gestational age (AGA) newborns, to establish relationships among these, with placental IL-6 concentrations and with growth parameters at birth. Cord serum concentrations of cortisol, insulin and resistin were also assessed.

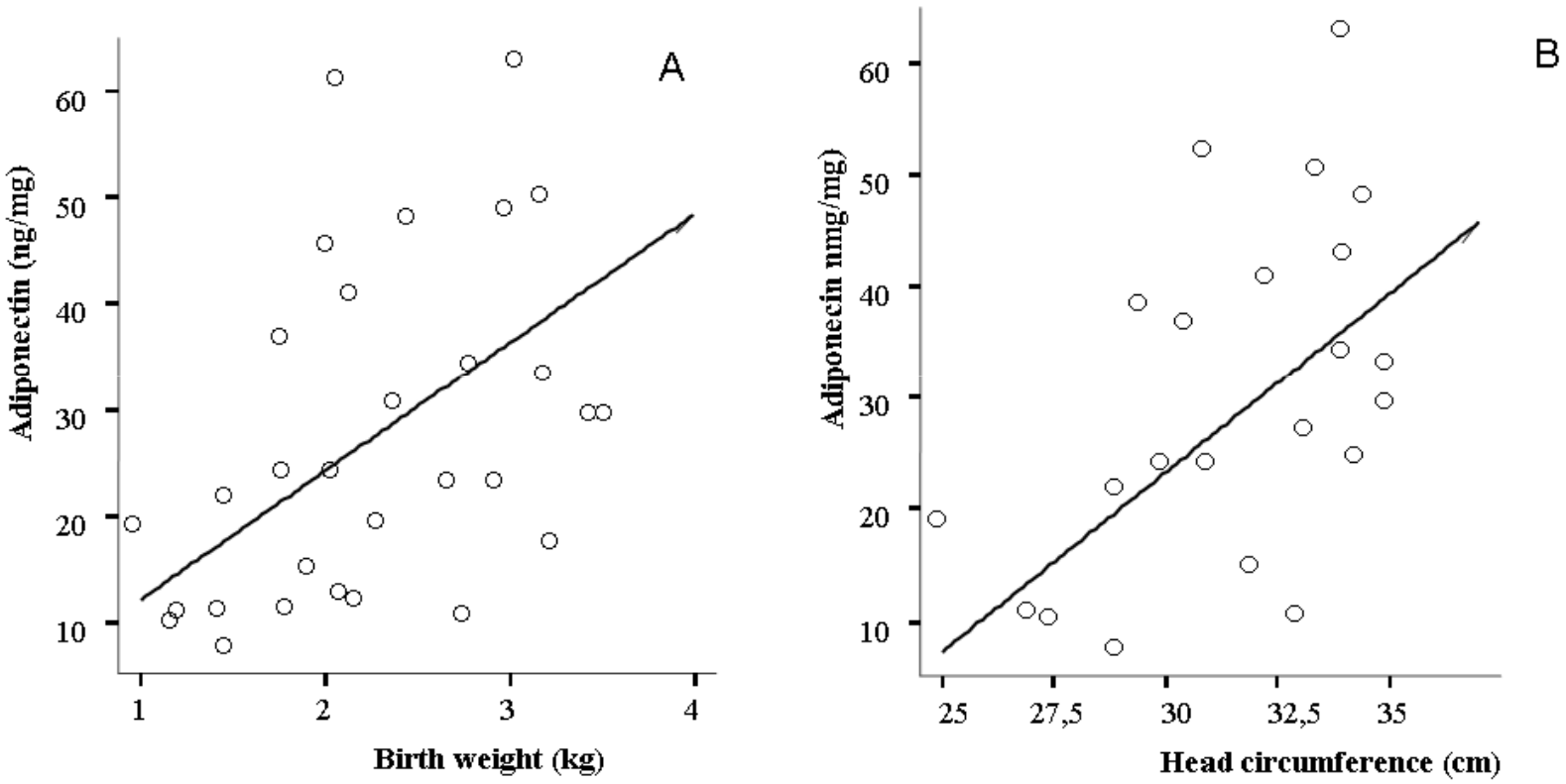
ADIPONECTIN IN PLACENTA



Data are mean ± SEM. Adiponectin concentrations were adjusted per mg of total protein in placental lysates in both groups (* p<0.05 vs AGA).

Street et al *Clinical Endocrinology* 2009

Correlations between placental adiponectin content and growth parameters at birth

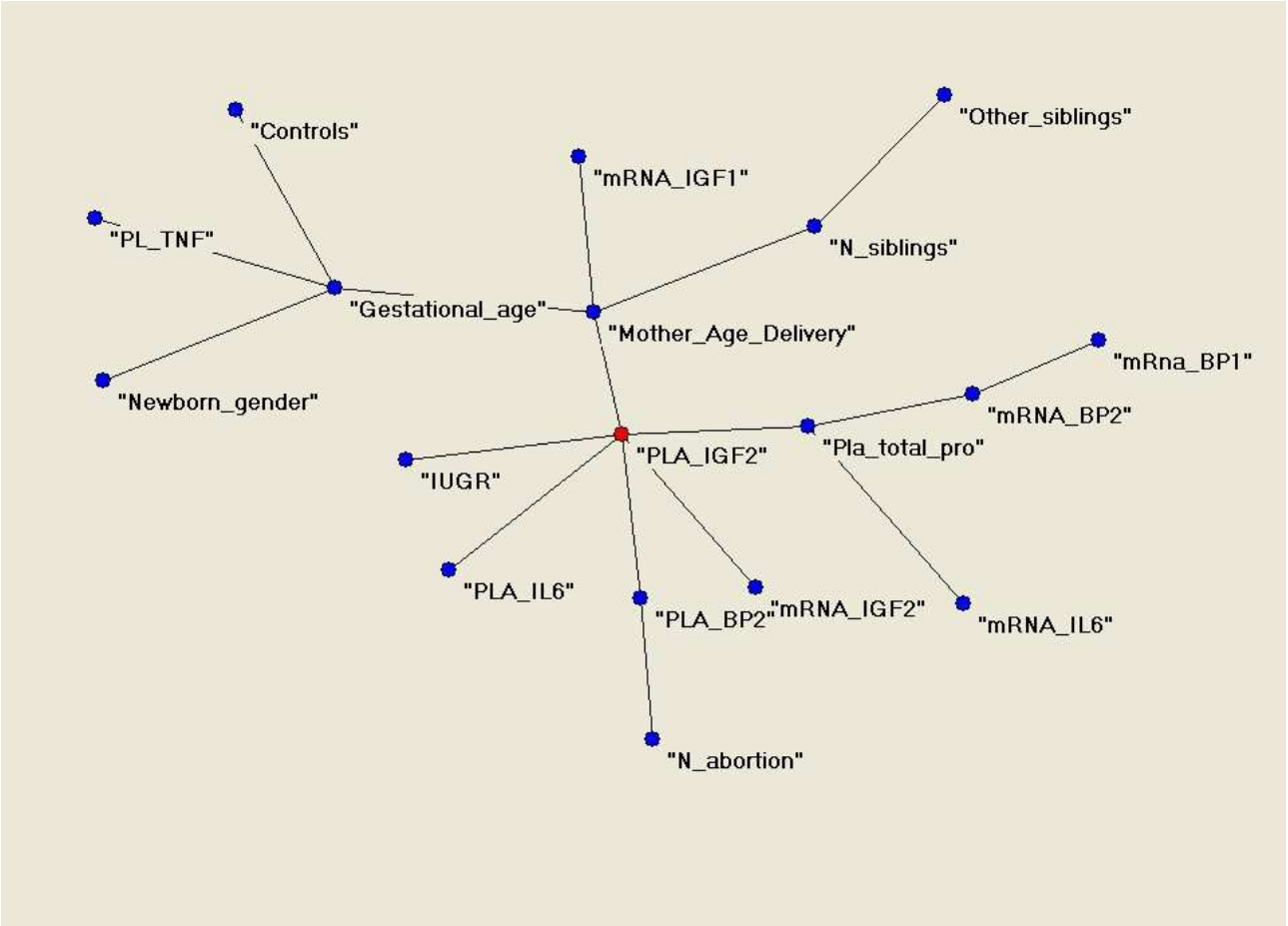


Street et al, *Clin. Endocrinol* 2009

BMC Pediatrics
Research article **Open Access**

Placental determinants of fetal growth: identification of key factors in the insulin-like growth factor and cytokine systems using artificial neural networks

Maria E Street*1, Enzo Grossi2, Cecilia Volta1, Elena Faleschini3 and Sergio Bernasconi1- 2008



Clinical features at birth of AGA and IUGR subjects re-evaluated at age 5 yr.

	IUGR (n=20: 10 M, 10 F)	AGA (n=15: 8 M, 7 F)	P value
Gestational age (yr)	35,1 ± 0,7	36,7 ± 0,4	n.s.
Mother's chronological age (yr)	32,12 ± 0,8	33,8 ± 0,6	n.s.
Mother's BMI at beginning of pregnancy (kg/m2)	22,4 ± 0,7	22,7 ± 0,5	n.s.
Mother's birth weight (kg)	3,2 ± 0,1	3,1 ± 0,1	n.s.
Father's birth weight (kg)	3,2 ± 0,2	3,3 ± 0,1	n.s.
Target Ht SDS	-0,2 ± 0,3	0,15 ± 0,2	n.s.
Placental weight (g)	345 ± 31,4	615 ± 21,5	0.0001
Birth weight (kg)	1,82 ± 0,3	2,89 ± 0,1	0.005
Birth length (cm)	40,6 ± 1,02	49,9 ± 0,6	0.0001
Birth head circumference (cm)	29,1 ± 0,7	34,6 ± 0,4	0.0001
Age at re-evaluation (yr)	5,2 ± 0,2	5,1 ± 0,1	n.s.

We recorded lengths and weights of all subjects at 3, 6, 12 , 24 months and measured the children at 5 yr of age;

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Initially we investigated, using a multiple linear regression model the effect of clusters of peptides on birth weight and length:

- cortisol
- IL-6
- insulin
- Total and activated insulin receptor content

In PLACENTA

- cortisol
- IL-6
- insulin
- IGF-II
- IGFBP-2

In CORD SERUM

The major effect on birth length and weight was given by cortisol and insulin concentrations in placenta

Length	B	Partial Correlation	p VALUE
Insulin	-1.338	-0.071	n.s.
Total insulin receptor	0.115	0.135	n.s.
Activated insulin receptor	-0.009	-0.004	n.s.
Cortisol	-2.114	-0.574	0.010
IL6	-0.496	-0.308	0.072

Weight	B	Partial Correlation	p VALUE
Insulin	1.8	0.385	0.058
Total insulin receptor	-0.015	0.59	n.s.
Activated insulin receptor	0.068	0.093	n.s.
Cortisol	-0.385	-0.615	0.0001
IL6	-0.054	-0.241	n.s.

Smerieri A,…Street ME. **. J BIOL REGUL & HOMEOST. AGENTS ACCEPTED 2012**

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The major effect on birth length and weight was given by IGF-II and IGFBP-2 in cord serum

Length

	B	Partial Correlation	p VALUE
Insulin	0.126	0.190	n.s.
IGF-II	0.523	0.546	0.001
IGFBP2	-0.321	-0.372	0.030
IL6	-0.195	-0.282	n.s.
Cortisol	0.066	0.580	n.s.

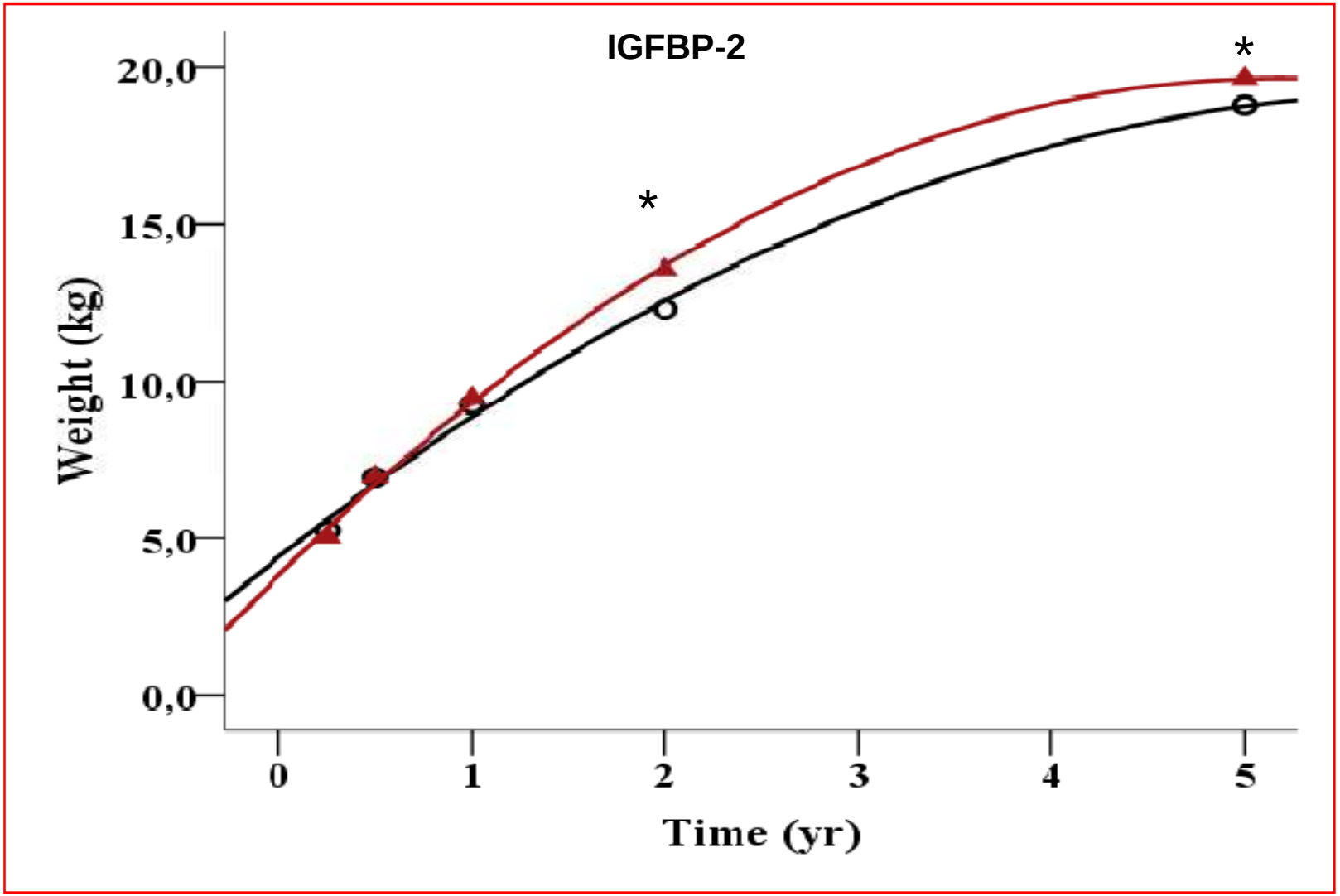
Weight

	B	Partial Correlation	p VALUE
Insulin	0.171	0.230	n.s.
IGF-II	0.679	0.679	0.0001
IGFBP2	0.307	-0.342	0.050
IL6	-0.210	-0.286	n.s.
cortisol	0.021	0.029	n.s.

OSPEDALE DEI BAMBINI

Smerieri A,…Street ME. PLoS One 2011; 6: e29562

EFFECT OF CORD SERUM PEPTIDES ON WEIGHT GAIN



Whereas, no significant effect of IGF-II

Street ME et al . **J BIOL REGUL HOMEOST. AGENTS ACCEPTED 2012**

Hypothesis

Hypoxia
Nutrient deficiency

High IL-6

High IGFBP-2

Impaired IR signal transduction

Reduced IGF-II Bioactivity

IUGR

Influence on post-natal growth

Chronic Diseases

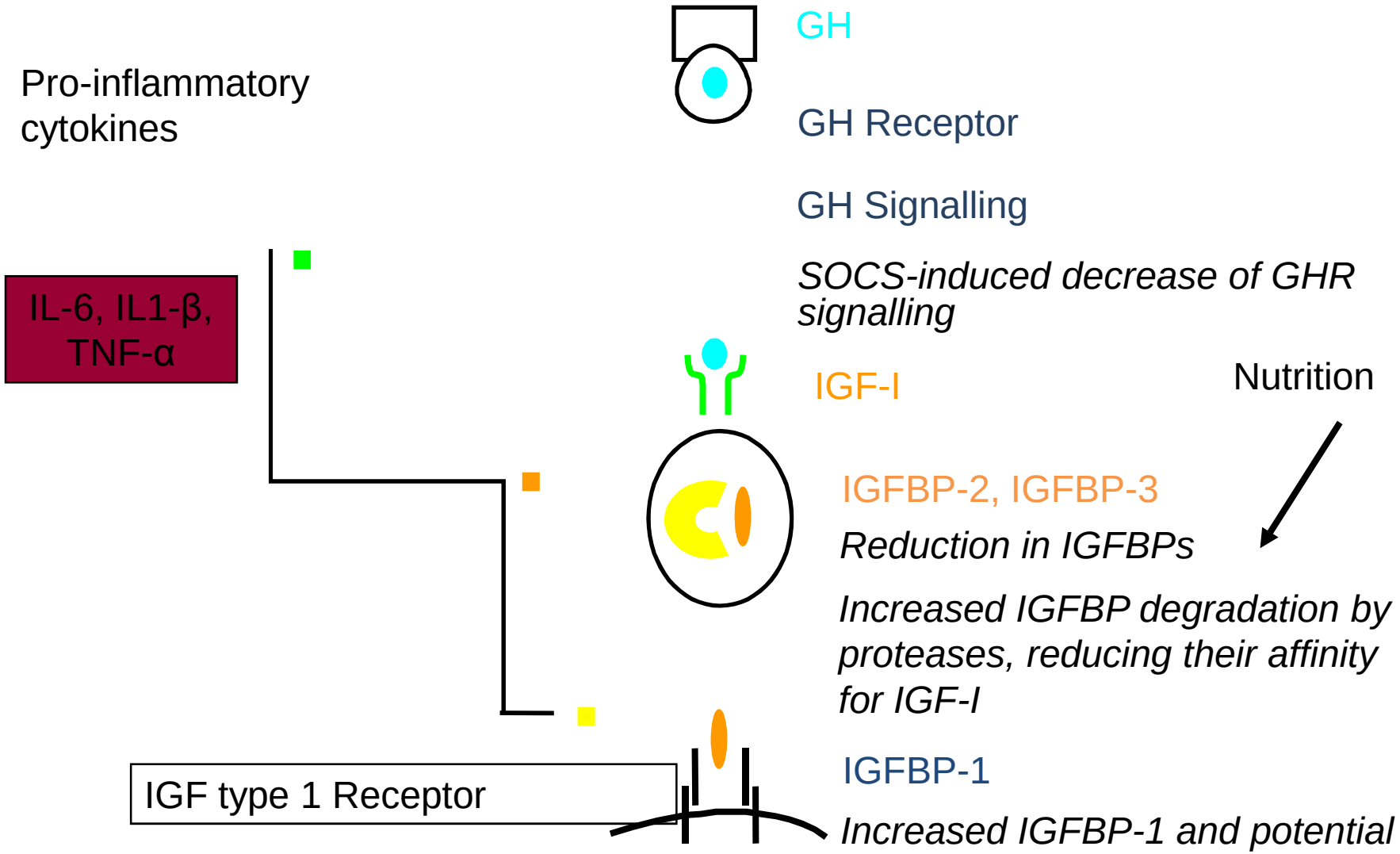
- Coeliac Disease
- Crohn's disease
- Cystic fibrosis
- Juvenile chronic arthritis

Endocrinology, Growth and Body Composition

Chronic diseases with growth failure

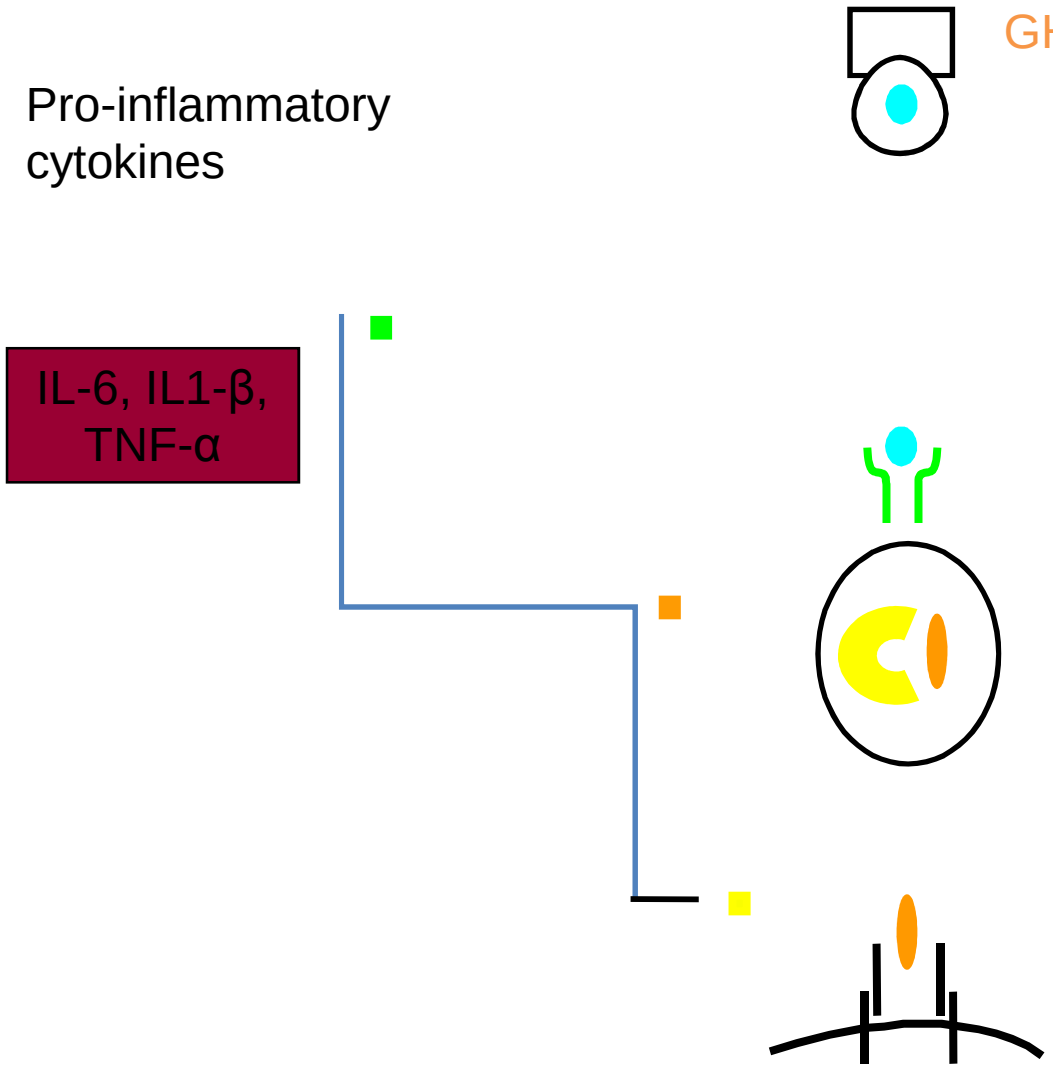
Disease	Pathogenetic mechanism
Coeliac disease	Nutrition, inflammation
Crohn’s disease	Nutrition, inflammation
Protein-losing enteropathy	Nutrition
Cyanotic congenital heart disease	Increased energy expenditure (IEE)
Cystic fibrosis	Nutrition, IEE, Inflammation
Chronic juvenile arthritis	Inflammation, nutrition
Alagille syndrome	Liver dysfunction

Potential disturbance of the GH-IGF axis



From J-P Thissen Horm Res 2007

Potential disturbance of the GH-IGF axis



GH *Alteration of GH secretion*

GH Receptor

Decreased liver GH receptor numbers

GH Signalling

Impaired STAT 5b phosphorylation and IGF-I gene transcription

IGF-I

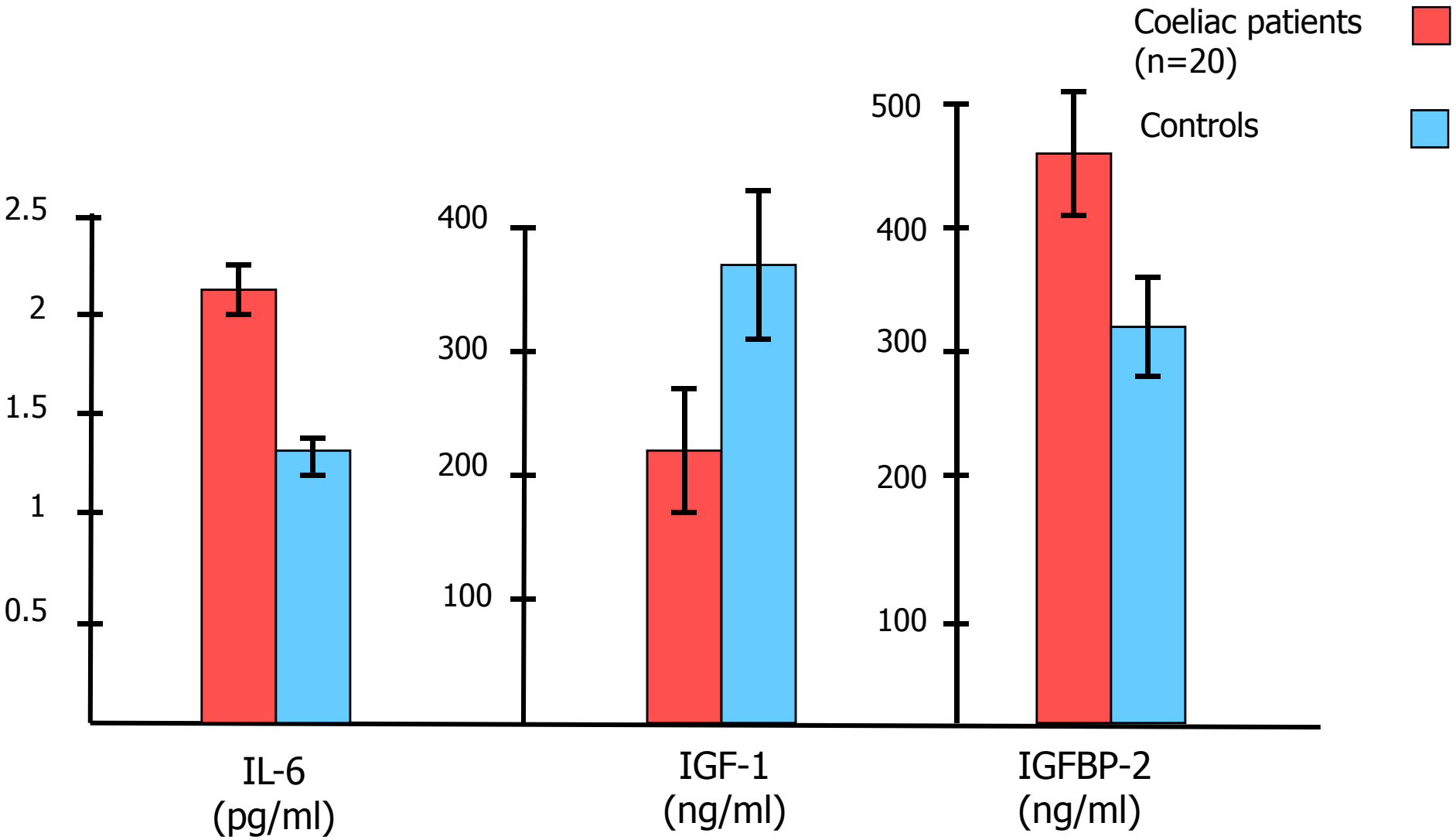
IGFBP-1
IGFBP-2
IGFBP-3

Nutrition

IGF type 1 Receptor

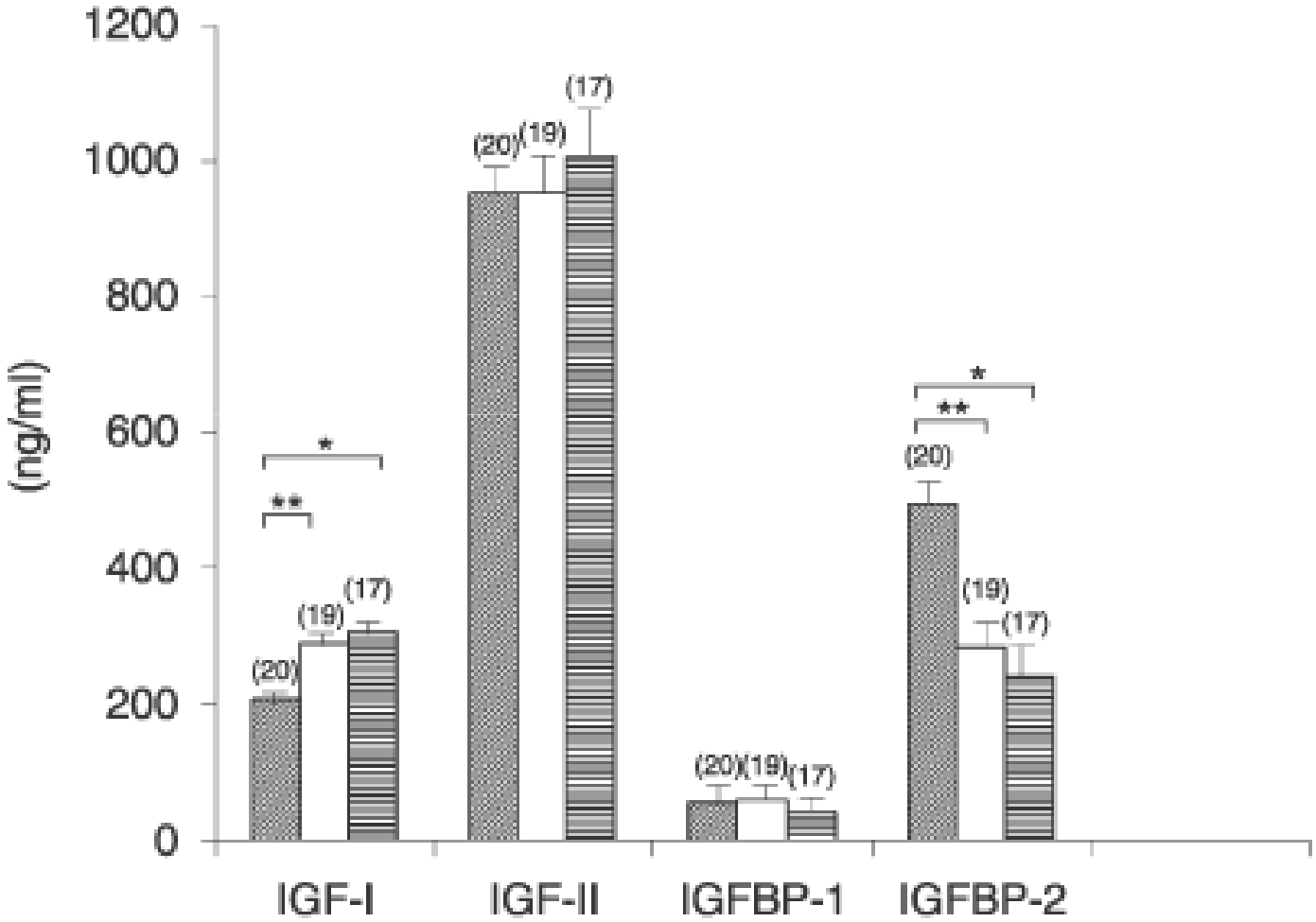
From J-P Thissen Horm Res 2007

Serum IL-6, IGF-I and IGFBP-2 at Diagnosis in Children with Coeliac Disease



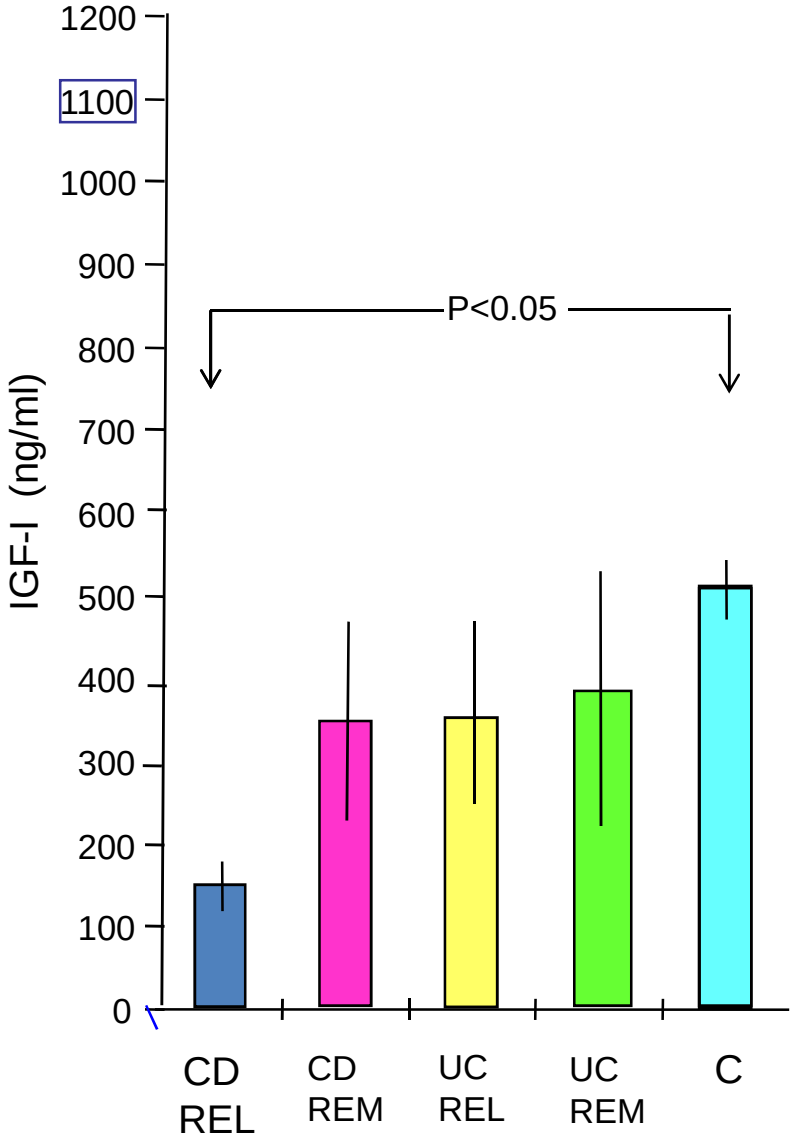
Street et al. Clin Endocrinol 2008

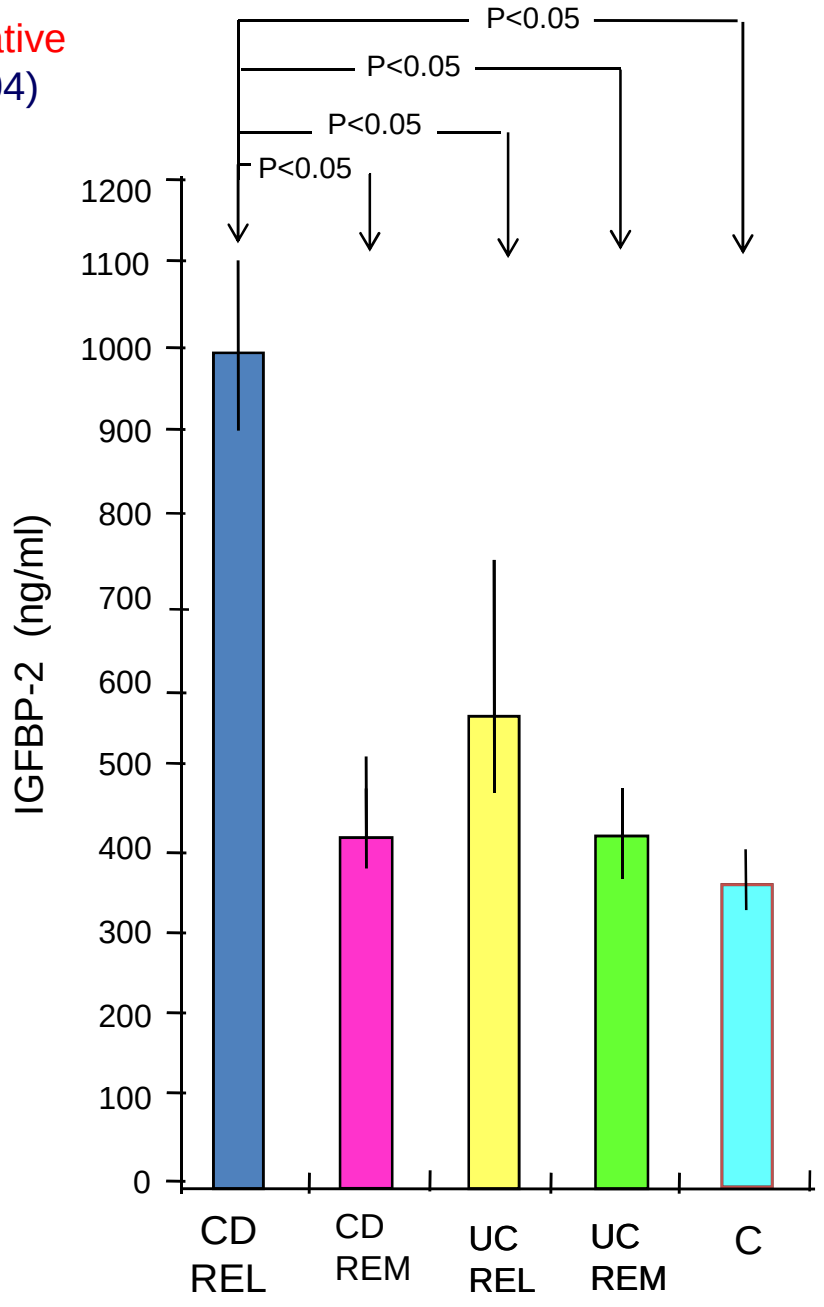
Changes and relationships of IGFS and IGFBPS and cytokines in coeliac disease at diagnosis and on gluten-free diet



Street et al . Clinical Endocrinology
Volume 68, Issue 1, pages 22-28, 11 JUL 2007 DOI: 10.1111/j.1365-2265.2007.02992.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2007.02992.x/full#f2

Serum IGF-I, IGFBP-2 in Crohn's disease, Ulcerative Colitis and Control subjects (Street et al. 2004)





PER L' AZIONE DI IGF-I E GLP-2 È IMPORTANTE LA PRESENZA DI IGFBP-3 ED IGFBP-5 NELLA MUCOSA INTESTINALE

Am J Physiol Gastrointest Liver Physiol 302: G794–G804, 2012.

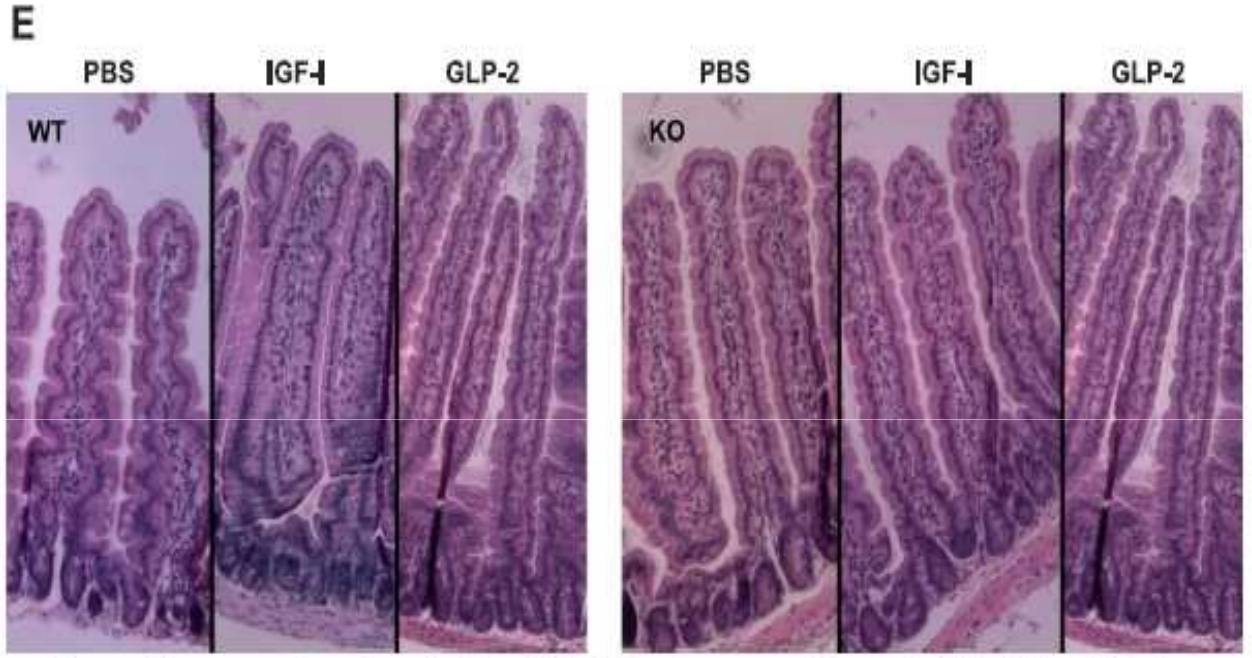
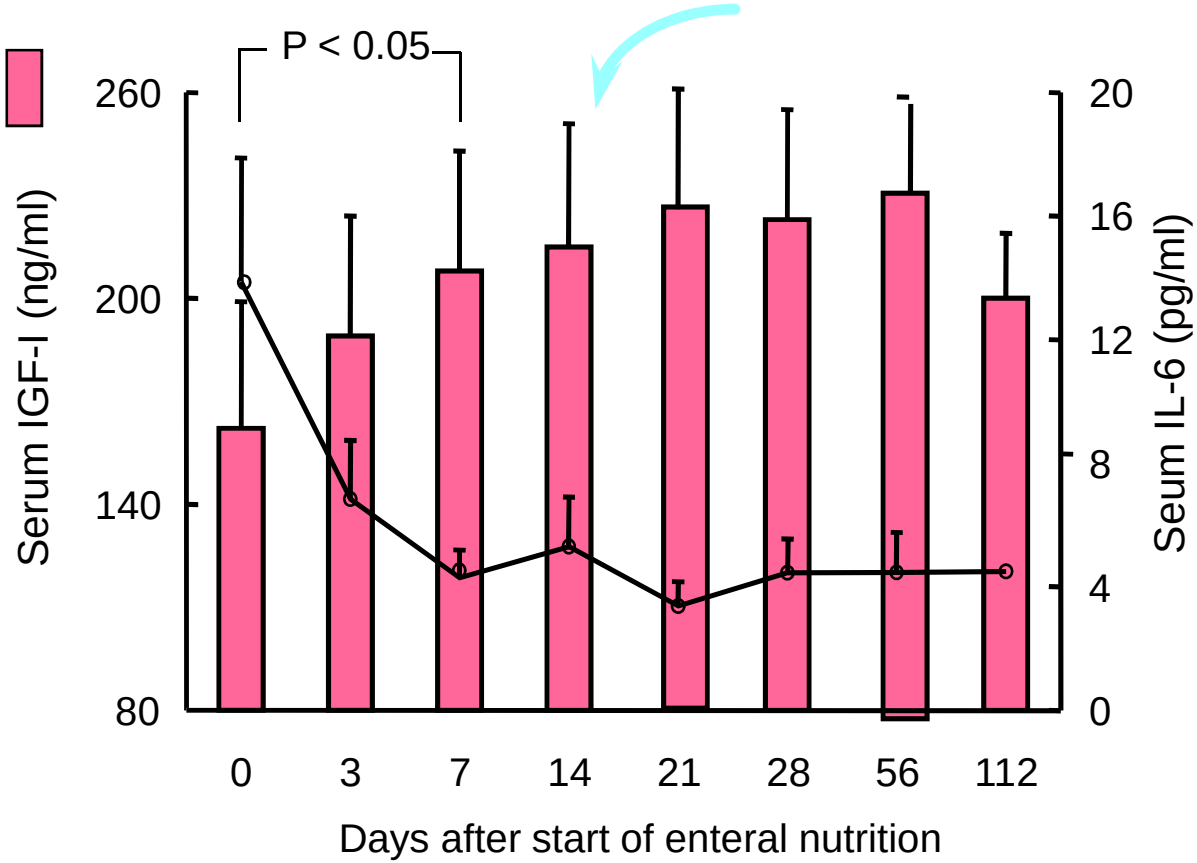


Fig. 5. Jejunal mucosa dry mass (*A*), concentrations of protein (*B*) and DNA (*C*), and sucrase specific activity (*D*) in WT and KO mice treated with PBS, IGF-I, or GLP-2 for 7 days. Values are means + SE; means with different superscripts (a-c) are significantly different ($P < 0.05$). There was a significant main effect for GLP-2 to decrease sucrase specific activity compared with PBS and IGF-I without interaction due to genotype (PBS = 0.15 ± 0.02^{a}; IGF-I = 0.14 ± 0.02^{a}; GLP-2 = 0.09 ± 0.01^{b}; in μmol/min/mg protein; GLP-2 treatment main effect, $P = 0.01$). Representative jejunal histology from WT and KO mice treated with PBS, IGF-I, or GLP-2 is shown in *E*; magnification is 100×.

Enteral Nutrition in Crohn's Disease (N=12)

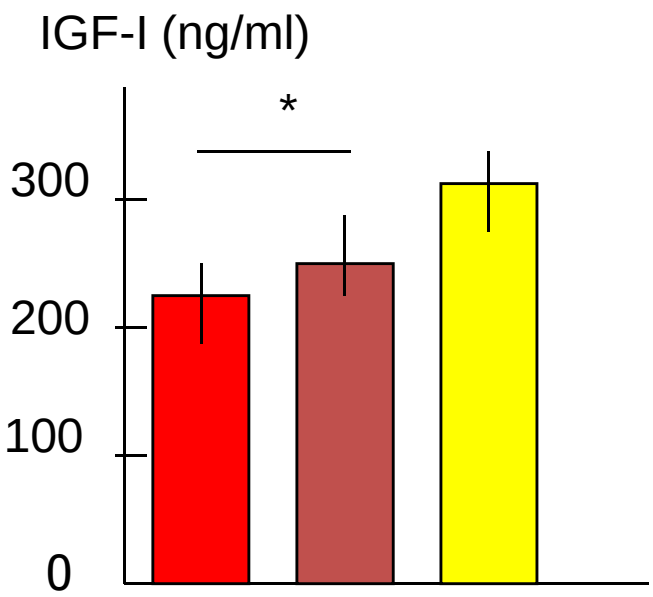
Increase in IGF-I pre-dates nutritional changes

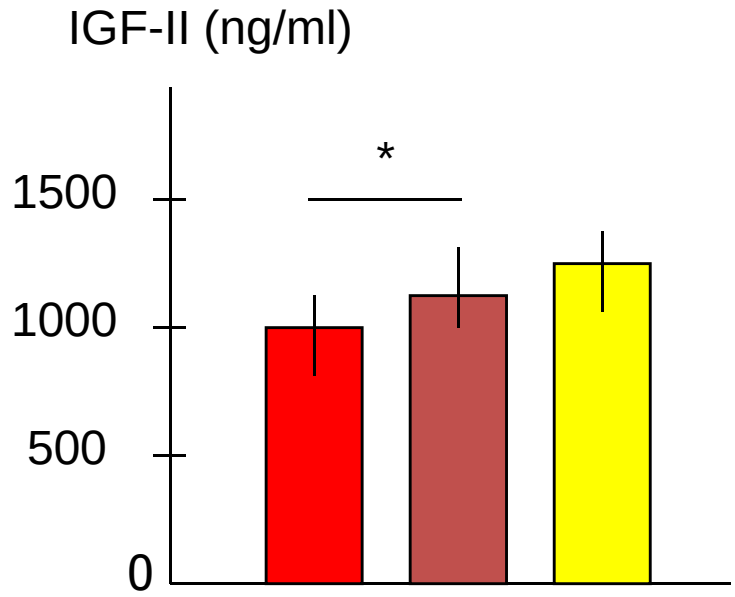


Banerjee K al. J Ped Gastr Nutr, 2004

IGF-I and IGF-II in Cystic Fibrosis

= CF CRP>2 = CF CRP <2 = Controls

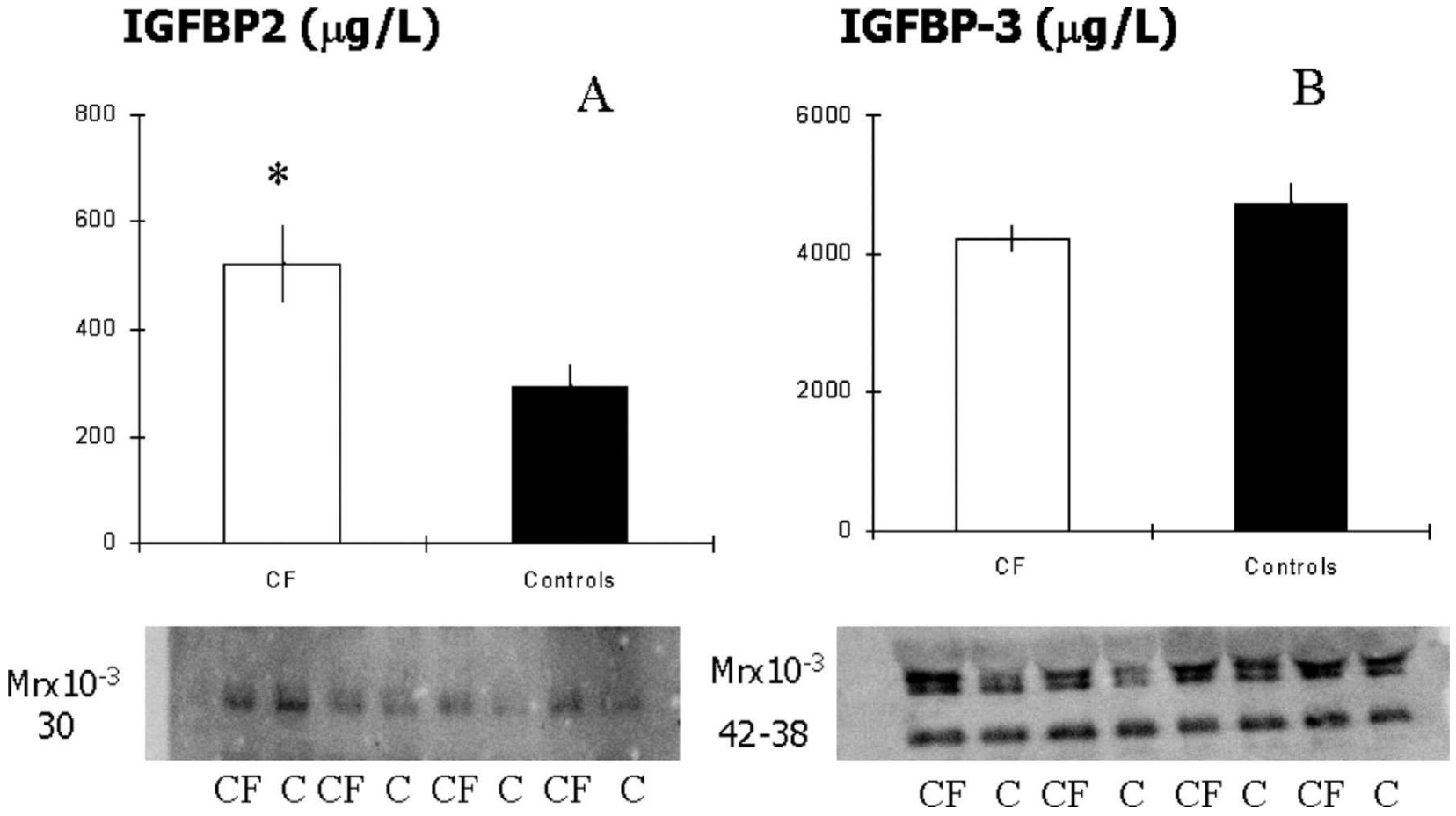




*p<0,05 vs controls

Street et al. 2006

Figure 2 Serum IGFBP-2 (A) and IGFBP-3 (B) levels in cystic fibrosis patients and in controls.



Street M E et al. Eur J Endocrinol 2006;154:47-52

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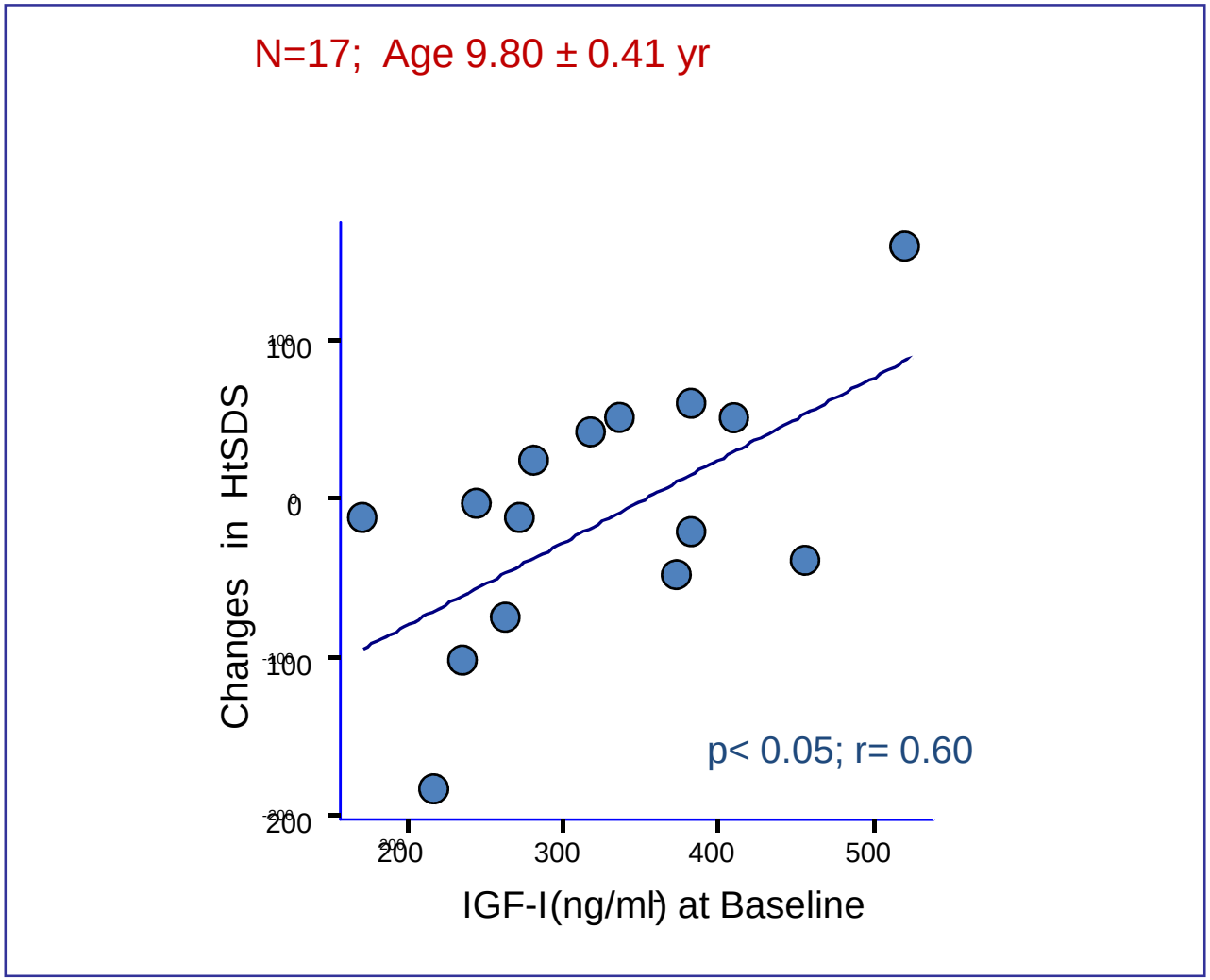


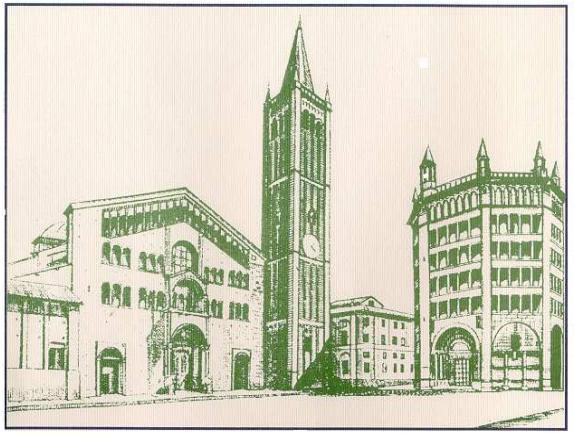
Street ME et al. Clin Endocrinol 2008

COME TRATTARE IL SISTEMA IGF

SPECIFIC CORRECT TREATMENT OF DISEASES

rhGH or rhIGF-I secondo indicazioni AIFA

Thank You for your attention



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