Insulin-like factor 5- a novel orexigenic hormone is dysregulated in obesity

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Background:

Insulin-like peptide 5 (INSL5) is a gut hormone produced by L-cells in the colorectal epithelium. The biological role of INSL5 is poorly investigated and current knowledge about this hormone is limited by the fact that it is involved in the regulation of appetite, control of β-cell development and fertility in mice. Nothing is known about the function of this gut hormone in humans. In this study we have explored associations between serum levels of INSL5 and multiple metabolic and hormonal variables in lean and obese men and women as well as effects of external interventions (e.g. food consumption, glucose loading test and bariatric surgery) on circulating levels of this newly discovered hormone.

Subjects and Methods:

INSL5 levels were measured in serum samples by ELISA. 25 lean and obese females and 23 lean and obese males were included in the study. All cohorts were fully characterized with anthropometric, metabolic and hormonal parameters and correlations between INSL5 concentrations and those parameters were evaluated. Furthermore we measured INSL5 levels in 10 lean and obese individuals after an overnight fasting, after a meal and during an oral glucose tolerance test (OGTT). In addition 15 morbidly obese patients were tested before and six months after they underwent weight loss intervention (bariatric surgery).

Results:

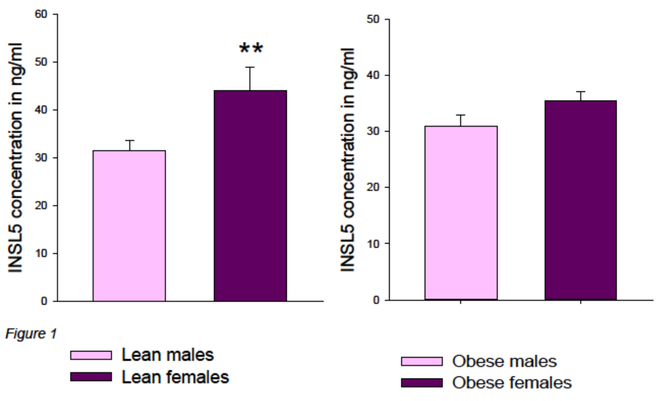

Figure 1

We found gender specific differences in basal INSL5 serum levels in a cohort of healthy lean humans (n=48; males n=23, females n=25). In contrast no significant gender specific differences in basal serum INSL5 levels in a cohort of obese humans (n=48; males n=23, females n=25) were observed (Figure 1).

Cohort Characteristics	Lean females (n = 23)	Obese females (n = 23)		Lean males (n = 25)	Obese males (n = 25)	
	(mean ± SE)	(mean ± SE)		(mean ± SE)	(mean ± SE)	
Age (years)	39.02 ± 3.33	35.16 ± 2.05		39.63 ± 3.55	35.72 ± 2.15	
Weight (kg)	66.19 ± 1.8	140.87 ± 4.26	0.001	77.00 ± 2.15	156.60 ± 5.18	0.001
Body mass index (kg/m2)	23.77 ± 0.46	51.00 ± 1.33	0.001	23.86 ± 0.43	51.40 ± 1.20	0.001
Glucose (mmol/l)	5.02 ± 0.09	5.67± 0.27	0.016	5.06 ± 0.16	5.84 ± 0.21	0.001
Insulin (pmol/l)	123.39 ± 16.34	154.31± 27.49	0.014	40.86 ± 4.02	288.80 ± 46.01	0.001
Total cholesterol (mmol/l)	5.62 ± 0.26	4.98± 0.22	0.075	4.67 ± 0.21	5.01 ± 0.17	0.217
Triglycerides (mmol/l)	1.59 ± 0.25	2.38 ± 0.48	0.941	1.18± 0.09	2.07 ± 0.20	0.001
LDL cholesterol (mmol/l)	3.34 ± 0.18	2.97 ± 0.20	0.183	2.96± 0.17	3.19 ± 0.14	0.315
HDL cholesterol (mmol/l)	1.50 ± 0.08	1.36 ± 0.02	0.134	1.30 ± 0.07	1.02 ± 0.04	0.001
Hemoglobin A1c (%)	5.47 ± 0.11	5.53 ± 0.14	0.644	5.40 ± 0.09	5.53± 0.09	0.349
C-reactive protein (mg/l)	2.92 ± 0.78	6.75 ± 1.36	0.006	1.74 ± 0.49	11.82± 2.39	0.001
Estradiol (pg/ml)	235.09± 60.21	395.50 ± 71.61	0.308	87.87 ± 13.58	146.14± 12.88	0.001
Cortisol (nmol/l)	314.38 ± 39.64	295.18 ± 23.48	0.661	406.19 ± 34.24	379.61 ± 27.98	0.547
Testosterone (ng/ml)				5.0 ± 0.92	2.47 ± 0.15	0.001

Table 1

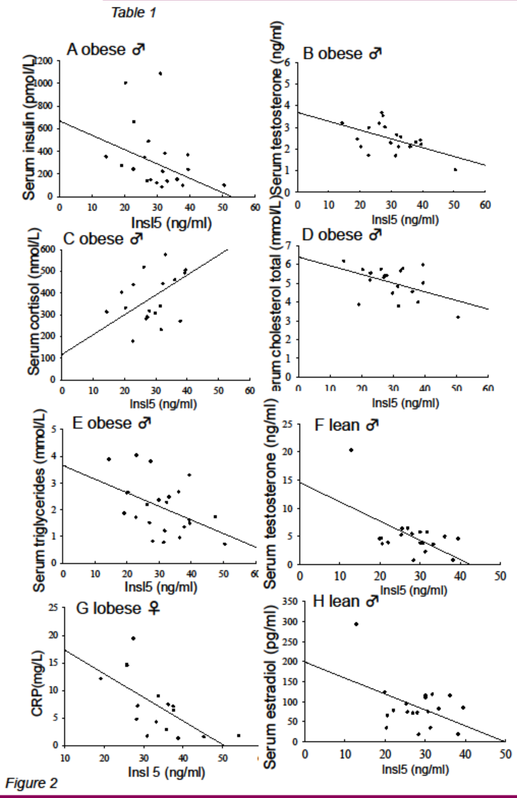

Figure 2

Anthropometric data, metabolic, hormonal and inflammatory markers from lean and obese females and males are depicted in table 1. Data are means ± SEM from cohort 1 and 2 (n=46). $p<0.05$ is significant*, $p<0.01$ highly significant **, ns is not significant (Table 1).

We found negative correlations between INSL5 and insulin, testosterone, total cholesterol and triglycerides in obese men (A;B;D;E) and a positive correlation with cortisol (C). Negative correlations between INSL5 and sex steroids in lean men (F;H) and CRP in obese women (G) were also observed.

	before interv. +SE	after intervent. +SE	Delta Change %	signific.
Age (years)	44.71 ± 2.62	46.14 ± 2.53	3.19	
Body weight (Kg)	176.25 ± 8.05	130.60 ± 6.06	-25.89	<0.001
BMI (kg/m2)	54.4 ± 2.23	40.54 ± 2.12	-25.47	<0.001
Fat mass (kg)	73.49 ± 4.61	38.56 ± 2.92	-47.52	<0.001
Body fat (%)	41.3 ± 1.13	31.15 ± 1.51	-24.85	<0.001
Glucose (mmol/l)	7.09 ± 0.61	5.33 ± 0.25	-24.72	0.002
Insulin (pmol/l)	168.28 ± 23.11	63.95 ±11.25	-61.99	0.001
HbA1C (%)	6.55 ± 0.29	5.28 ± 0.18	-19.31	0.001
C-Peptid (nmol/l)	1.68 ± 0.20	1.02 ± 0.11	-39.21	0.010
Proinsulin (pmol/l)	13.93 ± 1.52	4.24 ± 0.64	-69.50	0.060
Leucocytes(exp9/l)	9.0 ± 0.49	8.20 ± 0.54	-8.88	0.040
CRP (mg/l)	9.03 ± 1.47	6.49 ± 1.93	-28.19	0.136
Triglycerides (mmol/l)	2.09 ± 0.32	1.27 ± 0.16	-39.23	0.002
Cholesterol (mmol/l)	5.04 ± 0.22	4.10 ± 0.23	-18.62	0.01
LDL-Cholest. (mmol/l)	3.13 ± 0.15	2.46 ± 0.19	-21.33	0.013
HDL-Cholest. (mmol/l)	1.14 ± 0.07	1.13 ± 0.08	-0.19	0.749
Testosterone (ng/ml)	8.31 ± 0.91	16.33 ± 1.81	+96.43	0.005
Estradiol (pmol/l)	134.02 ± 8.86	119.45 ± 16.67	-10.86	0.272
Cortisol (nmol/l)	368.43 ± 44.75	334.16 ± 49.60	-9.03	0.424

Table 2

Anthropometric, metabolic, inflammatory and hormonal parameters were measured before and sixth months after bariatric surgery. All parameters improved dramatically six months after the intervention (Table 2).

We found significant lower INSL5 levels after weight loss which was induced by bariatric surgery. Furthermore we observed significant lower INSL5 levels between patients that were obese with and without T2DM before and after the intervention (Figure 3).

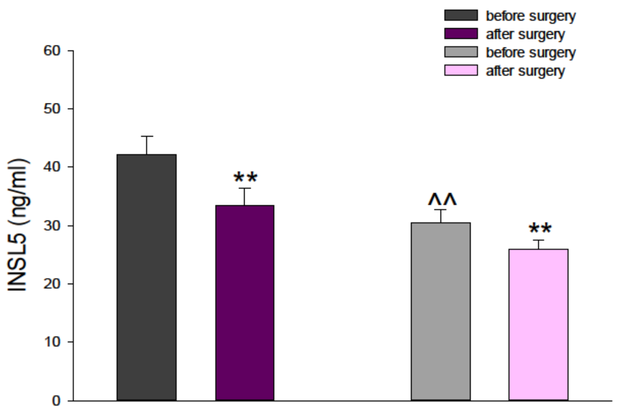

Figure 3

Influence of nutrition and glucose on INSL5 levels: A) INSL5 serum levels were measured before and 30, 60, 90 and 120 minutes after a meal. There were no significant acute changes of INSL5 after a meal. B) INSL5 serum levels were measured before the glucose load and 30, 60, 90 and 120 minutes after. INSL5 levels tend to decrease in obese males and females at 90 and 30 min, respectively (Figure 4).

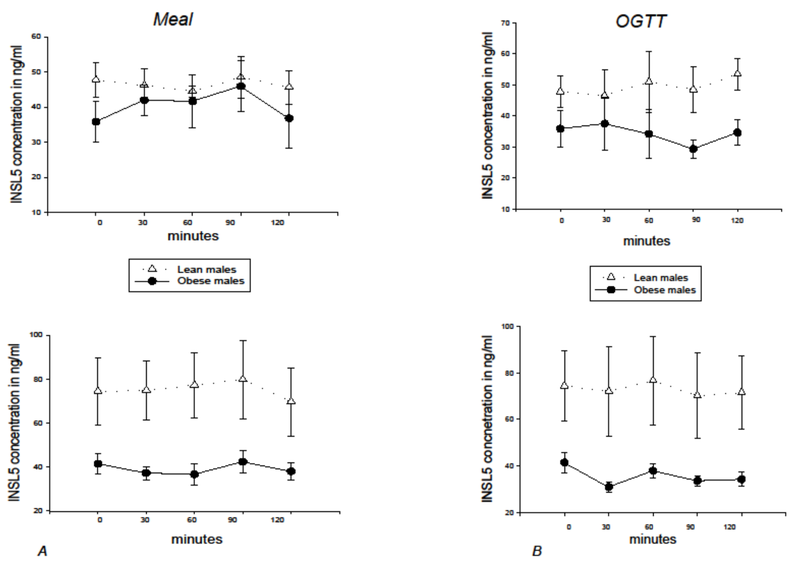

Figure 4

Summary and Conclusion:

We found gender-specific differences in INSL5 levels in lean individuals. Negative influence of insulin resistance and T2DM on INSL5 in obese individuals may indicate a link between β-cell function and INSL5 regulation. INSL5 levels decreased after weight loss which might be due to an effect of adipose tissue on the biosynthesis of INSL5 or changes in the metabolic and inflammatory profile after weight loss. Therefore, INSL5 may become an interesting target for the development of new therapeutic agents to treat metabolic disorders.

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