Published in final edited form as:

J Diabetes Complications. 2017 May ; 31(5): 850–853. doi:10.1016/j.jdiacomp.2017.02.019.

Leptin is associated with cardiopulmonary fitness independent of body-mass index and insulin sensitivity in adolescents with type 1 diabetes: a brief report from the EMERALD study

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Brief summary

Cardiopulmonary fitness is decreased in type 1 diabetes for reasons that are incompletely understood. In this study, leptin was associated with exercise capacity independent of insulin sensitivity (IS) and body mass index (BMI), suggesting that leptin may relate to cardiopulmonary fitness by mechanisms beyond IS and/or obesity.

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PB researched, wrote, formulated analytic plan, contributed to discussion and analytic plan, and reviewed/edited the manuscript; MCG contributed to discussion, and reviewed/edited the manuscript; AB contributed to discussion, and reviewed/edited the manuscript; GC contributed to discussion, and reviewed/edited the manuscript; YGR contributed to discussion, and reviewed/edited the manuscript; MS contributed to discussion, and reviewed/edited the manuscript; LP contributed to discussion, and reviewed/edited the manuscript; JGR contributed to discussion, and reviewed/edited the manuscript; JEBR contributed to discussion, and reviewed/edited the manuscript; KN researched, formulated analytic plan, contributed to the discussion and analytic plan, and reviewed/edited the manuscript.

None of the authors have any conflicts of interest to disclose.

Keywords

leptin; type 1 diabetes; cardiopulmonary fitness; adiposity; insulin sensitivity

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in type 1 diabetes (T1D) (1, 2) with abnormalities measurable in adolescence (3). In T1D youth we have reported an inverse relationship between insulin sensitivity (IS) and peak exercise capacity (VO_2peak) (4). Adipocyte dysfunction is linked to insulin resistance (5), which is an important factor in CVD and cardio-renal disease in T1D (6). Leptin, an adipocytokine, is increased in obesity, and induces metabolic and cardiovascular actions that may contribute to CVD. Leptin is also associated with IS (7) and we previously demonstrated that higher IS relates to better peak exercise capacity (VO_2peak) (8). Adiposopathy, as assessed by low plasma adiponectin/leptin ratio has also been proposed to contribute to cardiovascular disease (9). However, it is unknown whether leptin or adiponectin/leptin ratio are related to cardiopulmonary fitness itself, and whether this relationship is dependent or independent of adiposity and/or IS in youth with T1D. Accordingly, we tested the hypothesis that circulating leptin concentration is associated with VO_2peak independent of IS and BMI, in youth with T1D.

Methods

Participants

Forty-one pubertal adolescents ages 12 to 21 years were included from the **E**ffects of **ME**tformin on Cardiovascula**R** Function in **A**do**L**escents with Type 1 **D**iabetes (EMERALD) study. Participants were recruited from the Barbara Davis Center and private practices with advertisements. The study was approved by the University of Colorado Denver Institutional Review Board, with appropriate consent and assent obtained. Pubertal development was assessed by a single pediatric endocrinologist (KJN) as previously described (8, 10). After 5 minutes of supine rest, 3 blood pressure measurements were obtained and averaged using a DynaPulse 5200A (Pulse Metric, San Diego, California). Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer; weight was measured to the nearest 0.1 kg using a Detecto scale (Detecto, Webb City, Missouri).

Laboratory testing was performed after an inpatient 12-h fast with an overnight intravenous insulin infusion to normalize glycemia (8, 10). Leptin and adiponectin were measured via radioimmunoassay (Millipore, Billerica MA). Other fasting laboratory evaluations included: total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL-C) cholesterol, triglycerides, glucose and HbA1c (DCCT-calibrated); assays were performed by standard methods in the CTRC laboratory. Body composition was assessed dual-energy x-ray absorptiometry (Hologic, Waltham, MA) (11). IS (glucose infusion rate [GIR] in mg/kg/min and mg/lean kg/min) was calculated from a hyperinsulinemic euglycemic clamp (80 mU/m^2/min insulin) the morning following the inpatient stay (8, 10).

VO_2peak was assessed using a graded bicycle protocol to exhaustion as previously reported (8). Oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE) were measured breath-by-breath, at rest and during exercise. Respiratory exchange ratio (RER) was calculated as VCO_2/VO_2. To quantify the internal cardiac workload response, we calculated the Rate Pressure Product [(RPP) = Heart Rate (HR) * Systolic Blood Pressure (SBP)].

Analyses were performed in SAS (version 9.4; SAS Institute, Cary, NC). Variables were checked for the distributional assumption of normality. ANOVA was used to test the mean of the dependent variable across tertiles of leptin. Univariable and multivariable linear regression models were employed to examine the relationships between leptin, VO_2peak, unadjusted and adjusted for age, sex, BMI and IS. Linear regression results are presented as β estimate ± standard errors (SE). Significance is an α-level < 0.05.

Results

In youth with T1D we evaluated the relationships between leptin concentration, adiponectin and adiponectin/leptin ratio and VO_2peak. Stratifying data by tertiles of leptin, participants in the high leptin group had significantly lower IS and VO_2peak and higher blood pressure percentiles (Table 1). Leptin concentrations were significantly higher in females and individuals with elevated BMI (data not shown). After adjusting for sex and BMI or sex and IS, the relationship between leptin and VO_2peak remained (Figure 1). HbA1c and LDL-C did not differ by leptin tertiles. Leptin correlated negatively with VO2peak and positively with RPPwhich remained significant after adjusting for age, sex, BMI and IS (Table 2). Whereas adiponectin concentration was not associated with VO_2peak or RPP in univariable or multivariable models, adiponectin/leptin ratio was positively associated with cardiopulmonary fitness and inversely associated with RPR (Table 2).

Discussion

We found that in T1D, elevated leptin may relate to decreased cardiopulmonary fitness by mechanisms other than IS and/or obesity alone. CVD-related morbidity and mortality are markedly increased in individuals with T1D (1, 2), with 17 years of life lost when T1D is diagnosed at age 10 (12). Obesity is an increasingly prevalent problem in youth with T1D (13) and linked to CVD development (14). Obesity induces a progressive resistance to the anorexigenic effects of leptin, which promotes further weight gain and metabolic dysfunction (15). However, not all tissues are prone to leptin resistance (16). The pathophysiology underlying the relationship between elevated leptin and poor cardiopulmonary fitness remains unclear. Huby et al. demonstrated that leptin contributes to CVD by upregulating aldosterone synthesis leading to increased blood pressures, and by promoting endothelial dysfunction and the expression of profibrotic markers in the heart (16). Other possible mechanisms include adiposopathy (17) and leptin related mitochondrial dysfunction (18), but these pathways have to our knowledge not been examined in T1D.

The literature is conflicting regarding whether circulating leptin concentrations are affected by T1D status (19–23), and measurements of leptin in relation to VO_2peak in T1D youths have to our knowledge never previously been reported.

We previously demonstrated reduced VO_2peak, cardiac and vascular dysfunction in otherwise healthy, non-obese adolescents with T1D, compared with well-matched nondiabetic controls of similar BMI, pubertal stage, and habitual level of physical activity (8). Low fitness levels in adults with and without diabetes are associated with increased CVD mortality and decreased longevity (24). Furthermore, we previously found that IS correlated strongly with VO_2peak in youth with T1D (8), however the relationship between leptin, adiponectin/leptin ratio and VO_2peak in this analysis was independent of IS.

There are limitations to the present study, including the cross-sectional design, and the lack of a non-diabetic control group which prohibit determination of causality and whether the findings are specific to T1D Furthermore, fasting leptin concentrations may not capture the pulsatile nature of leptin. Although we adjusted for a variety of important confounding variables, we cannot rule out the presence of unknown factors that may have biased the present analyses.

In sum, these data suggest that leptin may influence VO_2peak by mechanisms independent of IR and adiposity. Further research and especially longitudinal studies are needed to better understand the role of leptin in cardiopulmonary fitness in youth with T1D.

Acknowledgments

Special thanks to the EMERALD Study Group and the research participants. This project was supported by the following: NIH T32 DK063687; NCRR K23 RR020038-01; NIH BIRCWH K12 5K12HD057022, R56 DK088971; ADA 7-11-CD-08, ADA 1-11-JF-23; JDRF Award #11-2010-343; K23DK107871; NIH/NCATS Colorado CTSI UL1 TR001082, Center for Women's Health Research, VA Merit. Its contents are the authors' sole responsibility and do not necessarily represent official NIH views.

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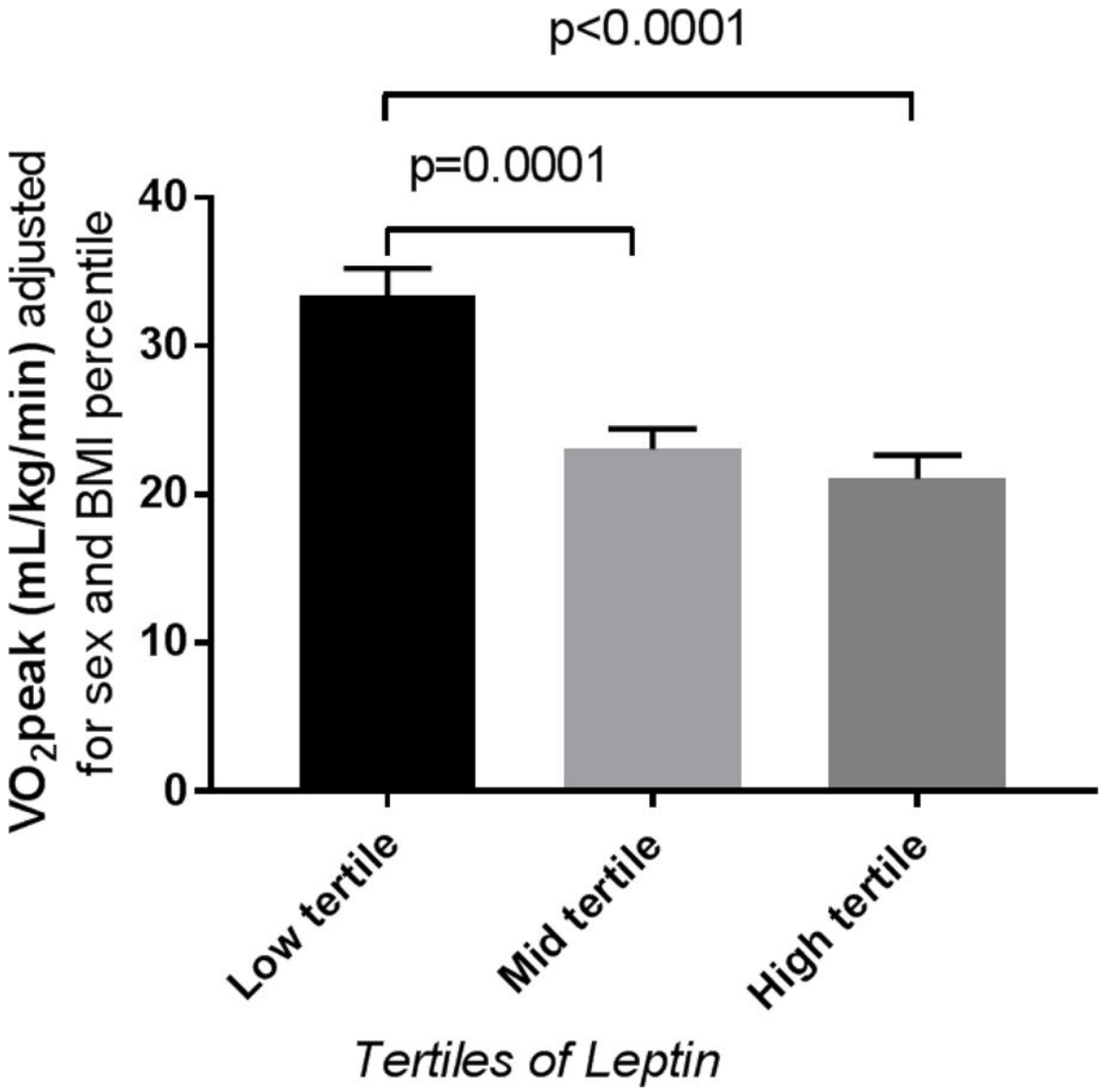

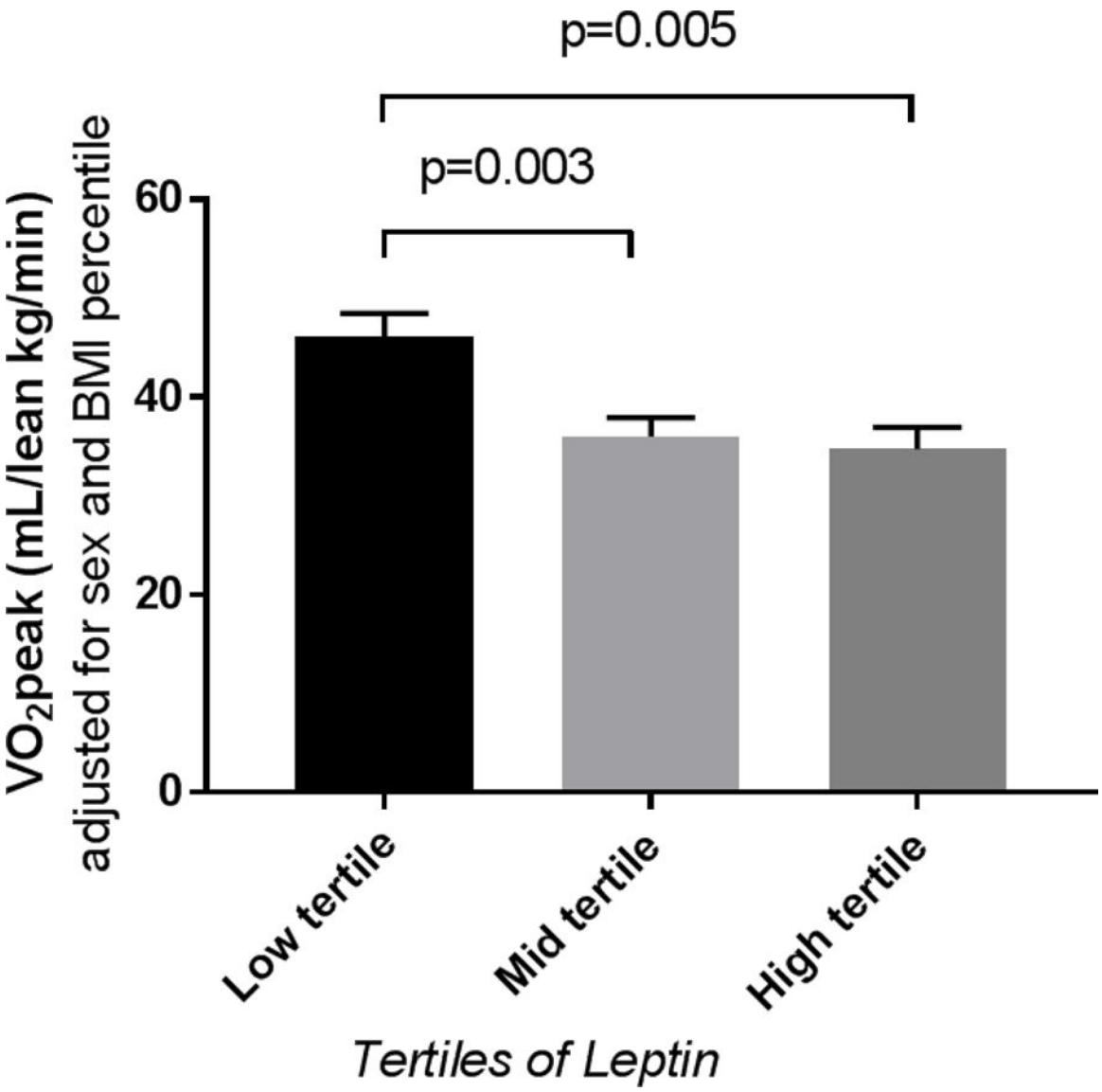

Figure 1.
Least square means and standard errors for VO_2peak across tertiles of leptin

Table 1

Clinical characteristics of adolescents with type 1 diabetes across tertiles of leptin

Variables	Low Leptin Tertile (<10.6ng/mL) [n=13]	Mid Leptin Tertile (10.6–26ng/mL) [n=13]	High Leptin Tertile (>26ng/mL) [n=14]	p-value
Age (years)	16.9±1.6	17.4±2.4	15.5±2.1 *	0.051
Weight (kg)	81.8±41.4	72.5±13.7	79.4±13.7	0.64
Height (cm)	158.7±36.3	165.3±7.2	162. ±16.8	0.77
Tanner Stage	5 (4–5)	5 (5–5)	5 (5–5)	0.53
Female (%)	15%	62%	79%	0.003
Fasting glucose (mg/dL)	114±16	110±19	112±17	0.80
HbA1c (%)	9.2±1.6	8.3±0.9	8.8±1.7	0.30
BMI (%tile)	59±26	81±21 *	92±8 ‡	0.0005
Resting HR (min^{-1})	65±11	72±14	76±8	0.01
Rate Pressure Product (mm Hg * min^{-1})	7614±1461	8887±1352	9407±1492	0.008
SBP (mm Hg)	117±8	122±10	124±10	0.19
DBP (mm Hg)	68±6	74±5	74±8	0.03
SBP (%tile)	51±26	77±19 *	80±20 ‡	0.002
DBP (%tile)	48±20	74±14 *	72±20 ‡	0.001
LDL-C (mg/dL)	78±18	81±20	94±17 ‡	0.07
HDL-C (mg/dL)	43±9	46±10	48±10	0.34
Total cholesterol (mg/dL)	136±24	142±24	160±27	0.04
Triglycerides (mg/dL)	74±26	73±27	90±52	0.42
Lean mass (kg)	49.8±9.0	45.7±8.5	45.9±7.6 †	<0.0001
Fat mass (kg)	15.5±5.4	24.9±5.9	31.3±6.9	0.37
Leptin (ng/mL)	4.6±2.7	17.1±4.9	39.2±12.0 †	<0.0001
Adiponectin	9.4±4.4	11.8±4.5	10.6±5.6	0.47
Adiponectin/leptin ratio ¥	2.3 (1.6–3.2)	0.7 (0.5–1.0)	0.2 (0.2–0.3) †	<0.0001
IS (mg/kg/min)	9.5±3.1	7.2±3.3	4.5±2.1 †	0.0007
IS (mg/lean kg/min)	12.8±4.1	12.3±4.6	7.8±3.6 †	0.009
Average insulin at steady state	180.2±48.3	156.5±26.5	223.0±89.8 *	0.03
IS (mg/kg/mn)/steady state insulin	0.05±0.02	0.05±0.03	0.02±0.01	0.0006
IS (mg/lean kg/mn)/steady state insulin	0.07±0.02	0.09±0.04	0.04±0.03	0.001
VO_2peak (mL/kg/min)	33.5±6.7	22.9±3.4 ‡	20.9±3.9 ‡	<0.0001
VO_2peak (mL/lean kg/min)	44.6±6.5	36.3±6.9 ‡	35.9±6.5 ‡	0.002

* p<0.05 compared to mid tertile

† p<0.05 compared to mid and low tertiles

‡ p<0.05 compared to low tertile

[¥] **Geometric means and 95% CI**

Table 2

Univariable and multivariable linear regression models

Variables	VO_2peak (mL/lean kg/min) β±SE	RPP (mm Hg * min^{-1}) β±SE
Leptin (ng/dL)	−0.20±0.07 (R^2 = 18.4%) p=0.006	47.49±13.68 (R^2 = 24.1%) p=0.001
Adiponectin	−0.18±0.45 (R^2 = 1.4%) p=0.46	−45.59±51.73 (R^2 = 1.9%) p=0.38
Ln adiponectin/leptin	3.13±1.00 (R^2 = 20.4%) p=0.003	−848.24±189.25 (R^2 = 34.6%) p<0.0001
Leptin* (ng/dL)	−0.23±0.11 p=0.04	61.63±22.26 p=0.009
Adiponectin *	−0.01±0.25 p=0.98	−57.42±54.07 p=0.30
Ln adiponectin/leptin *	4.25±1.45 p=0.006	−1125.46±289.02 p=0.0004
Leptin (ng/dL)**	−0.22±0.10 p=0.04	50.78±19.77 p=0.01
Adiponectin **	−0.04±0.26 p=0.89	−33.35±54.35 p=0.54
Ln adiponectin/leptin **	3.36±1.25 p=0.01	−849.27±245.02 p=0.002

* Adjusted for age, sex and BMI percentile

** Adjusted for age, sex and IS

Similar relationships also observed with VO_2peak (mL/kg/min)