HHS Public Access

Author manuscript

Horm Res Paediatr. Author manuscript; available in PMC 2022 November 21.

Published in final edited form as:

Horm Res Paediatr. 2022 ; 95(1): 43–50. doi:10.1159/000522665.

Novel Adipokines *CTRP1*, *CTRP9*, and *FGF21* in Pediatric Type 1 and Type 2 Diabetes: A Cross-Sectional Analysis

Alexander Arking[a,b,c], **Dylan C. Sarver**[b,c], **Sheela N. Magge**[a], **G. William Wong**[b,c], **Risa M. Wolf**[a,b,c]

[a]Department of Pediatric Endocrinology and Diabetes, Johns Hopkins University School of Medicine, Baltimore, MD, USA;

[b]Department of Physiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;

[c]Center for Metabolism and Obesity Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Introduction: Pediatric obesity and diabetes has increased over the last several decades. While the role of common adipokines on metabolic parameters has been well studied in adults, the relationship of novel adipokines and hepatokines in pediatric type 1 (T1D) and type 2 diabetes (T2D) is not well understood. This study assessed novel adipokines C1q/TNF-related proteins (*CTRP1* and *CTRP9*), and hepatokine fibroblast growth factor 21 (*FGF21*) in youth with T1D and T2D diabetes.

Methods: Participants (n = 80) with T1D (n = 40) enrolled in the Pediatric Diabetes Consortium (PDC) T1D NeOn registry, and T2D (n = 40) from the PDC T2D registry. Cross-sectional analysis compared adipokines (*CTRP1*, *CTRP9*, *FGF21*) between T1D and T2D, and regression models assessed adipokine relationship with clinical characteristics.

Results: The mean age of the participants was 14.9 ± 2 years, and 50% were female. T2D participants had a shorter diabetes duration (p = 0.0009), higher weight (p < 0.0001), and BMI (p < 0.0001) than T1D participants. *CTRP9* levels were higher in T1D (13,903.6 vs. 3,608.5 pg/mL, p = 0.04) than T2D, and *FGF21* levels were higher in T2D (113.1 vs. 70.6 pg/mL, p = 0.03) than T1D, with no differences in *CTRP1*. In regression analysis of T1D, *CTRP9* was positively associated with C-peptide (p = 0.006), and *FGF21* was positively associated with hemoglobin A1c

Correspondence to: Risa M. Wolf, rwolf@jhu.edu.

Author Contributions

R.M.W., S.N.M., and G.W.W. designed the study. R.M.W., D.C.S., and G.W.W. performed the laboratory work. A.A., R.M.W., S.N.M., and D.C.S. analyzed the data. A.A. and R.M.W. wrote the manuscript. All authors critically reviewed and revised the manuscript.

Statement of Ethics

The PDC protocol was approved by the Institutional Review Board at each participating center, according to the Declaration of Helsinki. Written informed consent was obtained from parents with written assent in participants <18 years of age, and informed consent was obtained from participants ≥18 years of age. This study protocol was reviewed and approved by the Johns Hopkins IRB, approval number: IRB00219817.

Conflict of Interest Statement

The authors have nothing to disclose.

($p = 0.04$). In T2D, *CTRP1* was positively associated with HbA1c ($p < 0.001$) and glucose ($p = 0.004$), even after controlling for age, sex, and BMI.

Conclusions: *CTRP9* levels are higher in youth with T1D compared to T2D, and *FGF21* levels are higher in youth with T2D than T1D. Novel adipokines are related to metabolic homeostasis in the inflammatory milieu of pediatric diabetes.

Keywords

Type 1 diabetes; Type 2 diabetes; Adipokines; Fibroblast growth factor 21; C1q/TNF-related protein-1; C1q/TNF-related protein-9

Introduction

The prevalence of obesity has increased tremendously over the last several decades [1], with a concurrent increase in the incidence of pediatric diabetes over the last 2 decades [2]. Despite the long-held notion that children with type 1 diabetes (T1D) have a thin body habitus, there has also been an increase in obesity and insulin resistance in this population of children [3, 4], such that the specific type of diabetes at diagnosis can often be difficult to distinguish [5]. While type 2 diabetes (T2D) is directly related to obesity, and up to 80% of youth with T2D are obese [5], often with insulin resistance and signs of metabolic syndrome, the impact of overweight and obesity on youth with T1D is just starting to be explored [6, 7].

Our understanding of the role of adipokines in the cross-talk of the immune, endocrine and cardiovascular systems in the setting of obesity and insulin resistance is evolving in this young population. Previous studies have demonstrated higher leptin levels in obese individuals with T1D compared to lean T1D controls [8], similar to trends seen in other obese populations [9–12], and obese youth with T2D [13]. Further, lower adiponectin levels have been shown with increasing BMI in T1D youth [8], although this relationship is not consistent as other studies have demonstrated paradoxically high adiponectin levels in youth with T1D even in the setting of insulin resistance [14]. Common adipokines such as leptin and adiponectin have been well studied in obese youth with and without metabolic syndrome and T2D [8, 15–21], but given the increase in obesity even in the setting of T1D, it is also important to consider the role of other adipokines and inflammation in this cohort of youth as well.

Novel adipokines including the C1q/TNF-related proteins (CTRPs) family of proteins and the hepatokine, fibroblast growth factor 21 (*FGF21*) have been implicated in glucose and/or lipid metabolism in the adult population, but there is less data in pediatrics [22–28]. *CTRP9* has been shown to be elevated in adults with obesity and T2D [12, 29, 30], but this same relationship has not been shown in the pediatric population [13]. *CTRP1* is higher in adults with obesity and hyperglycemia [24, 31, 32], and has been shown to be higher in adolescents with obesity and hyperglycemia compared to normoglycemic obese youth [13]. The hepatokine, *FGF21* has been shown to be higher in adults with obesity and T2D [27, 33–39]. Our group previously showed that obese youth with impaired glucose tolerance have higher *FGF21* levels compared to obese youth with normal glucose tolerance [13], but that it

may be due to a compensatory mechanism as longitudinal studies of children demonstrating weight loss had a decrease in *FGF21* levels [40].

While most studies have focused on youth with obesity and T2D, with the increase in overweight and obesity affecting youth with T1D and the potential risk for cardiovascular complications as a result of the additive impact of obesity, it is also important to understand the inflammatory milieu in this population. We sought to determine the differences in adipokine levels between youth with T1D and T2D and how they relate to clinical characteristics.

Methods

Pediatric Diabetes Consortium Registry

This was a cross-sectional study utilizing samples from the Pediatric Diabetes Consortium (PDC) Registry in a secondary analysis. A cohort of youth with newly diagnosed T1D was enrolled in the PDC T1D NeOn registry by 7 US pediatric diabetes centers between 2009 and 2011, and a cohort of youth with T2D was enrolled by 8 pediatric diabetes centers between 2012 and 2014. A detailed description of the PDC T1D NeOn registry has been published [41, 42]. The PDC T2D registry included participants who were <21 years of age, and were diagnosed with T2D using the criteria of the American Diabetes Association including being negative for T1D associated autoantibodies (including insulin autoantibody, glutamic acid decarboxylase antibody, islet antigen 2 antibody, islet cell antibody, and zinc transporter 8 antibody), BMI >85th percentile for age and sex prior to diabetes-associated weight loss and at least one of the following: (i) HbA1c ≥6.5% (≥48 mmol/mol), (ii) random glucose >200 mg/dL (11.1 mmol/L), (iii) fasting glucose ≥126 mg/dL (7.0 mmol/L), or (iv) 2-h OGTT glucose ≥200 mg/dL (11.1 mmol/L) [43]. The PDC protocol was approved by the IRBs at each participating center. Written informed consent was obtained from parents with written assent in participants <18 years of age, and informed consent was obtained from participants ≥18 years of age. This study protocol was reviewed and approved by the Johns Hopkins IRB, approval number: IRB00219817. The source of the data is the PDC registry, but the analyses, content, and conclusions presented herein are solely the responsibility of the authors and have not been reviewed or approved by the PDC.

Study Population and Procedures

This secondary analysis of participants from the PDC registries included a total of 80 randomly selected participants: 40 with T1D and 40 with T2D, who were pubertal males and females, sex and age matched between the two groups, with a range of BMI and hemoglobin A1c values. Data on enrollment into the Registry were collected via the medical record and interviews with participants and/or parents. Data included clinical (age, race/ethnicity, duration of diabetes), anthropometric variables (BMI, BMI%, and BMI Z-score), and metabolic variables (glucose, C-peptide, Hemoglobin A1c [HbA1c], and vitamin D). BMI was measured by the health care provider, and BMI percentile for age and gender was calculated using the 2000 CDC population growth chart data.

Laboratory Measurements

Human *CTRP9*, *CTRP1*, and *FGF21* were measured by ELISA (Biovendor, Czech Republic) per the manufacturer: *CTRP9* ELISA intra-assay variation 5.5%, inter-assay variation 7.9%; *CTRP1* ELISA intra-assay variation 2.7% inter-assay variation 8.5%; *FGF21* ELISA intra-assay variation 2% inter-assay variation 3.3%. Laboratory methods for metabolic variables are previously described [41–43] and are presented here in brief: Hemoglobin A1c levels were measured at each center by the DCA Vantage (Siemens, New York, NY, USA). Glucose levels were nonfasting random levels in 37 participants in both T1D and T2D groups, and fasting in 3 participants in both T1D and T2D groups.

Statistical Analysis

Initial comparisons between T1D and T2D groups were analyzed using Student's *t* test for normally distributed continuous variables. Variables that were non-normally distributed were either log transformed to fit a normal distribution or compared using the Wilcoxon rank-sum test. A logistic regression was used for sex and a Fischer's exact test was used for race/ethnicity. Multivariable regression was used to correlate variables across all 80 participants controlling for age, sex, BMI, diabetes duration when C-peptide was in the model, and glucose when *FGF21* was in the model. For each group, the novel adipokines *CTRP1*, *CTRP9*, and *FGF21* were correlated with each of the metabolic factors using a univariate and multivariable linear regression models. Variables significant in univariate regression models were controlled for in multivariable regression models additionally controlling for age, sex, BMI, diabetes duration when C-peptide was in the model, and glucose when *FGF21* was in the model. Data are reported as either mean ± SD if normally distributed or log transformed to fit a normal distribution or median with interquartile range if skewed. Statistical analyses were performed using the R statistical software package. p values <0.05 were considered statistically significant across all analyses.

Results

Patient Demographics and Clinical Characteristics

A total of 80 participants were included, 40 with T1D and 40 with T2D as shown in Table 1. By design, each group had 20 males and 20 females, with an average age of 14.9 ± 2 years. Patients with T1D had a mean duration of diabetes of 3.3 ± 0.7 years, and mean HbA1c was 9.2 ± 2.4%. T2D participants had a lower mean duration of diabetes of 2.3 ± 1.7 years ($p = 0.0009$) and lower mean HbA1c of 8.1 ± 2.9% ($p = 0.02$) when compared to T1D participants. Weight (61.9 ± 13.1 vs. 93.6 ± 24.8 kg, $p < 0.0001$), BMI (22.7 ± 3.6 vs. 33.9 ± 7.4 kg/m^2, $p < 0.0001$), BMI% (78.0 [61.0, 91.0] vs. 98.2 [96.6, 99.4] %, $p < 0.0001$), and C-peptide levels (0.1 [0.03, 0.3] vs. 4.2 [2.6, 6.4] ng/mL, $p < 0.0001$) were lower in participants with T1D compared to T2D, but there was no difference in BMI Z-scores. Glucose levels were higher in participants with T1D than T2D (198.8 ± 115.9 vs. 158.2 ± 113.7 mL/dL, $p = 0.04$).

Comparison of Adipokines in Pediatric T1D and T2D

CTRP9 was significantly higher in T1D compared to T2D participants (13,903.6 vs. 3,608.5 pg/mL, $p = 0.04$), *FGF21* was significantly higher in T2D compared to T1D (113.1 vs. 70.6 pg/mL, $p = 0.03$), but there were no differences observed in *CTRP1* between these two groups in unadjusted analysis (Fig. 1). Adjusting for age, sex, duration of diabetes, ethnicity, and BMI showed BMI to be the only confounder to the observed differences in *CTRP9* and *FGF21* levels between both groups, as BMI is collinear with diabetes type.

Association of Adipokines with Pediatric T1D

As shown in Table 2, *CTRP1* was not observed to be associated with any clinical variables in T1D. *CTRP9* was positively associated with C-peptide levels in univariate analysis ($p = 0.005$) and when adjusting for age, sex, BMI, and duration of diabetes ($p = 0.006$). *FGF21* was higher in females (152.9 vs. 72.1 pg/mL, $p = 0.009$) than males, and positively associated with HbA1c ($p = 0.04$) even when adjusting for age, sex, BMI, and glucose levels.

Association of Adipokines with Pediatric T2D

In participants with T2D, *CTRP1* was positively associated with HbA1c ($p = 0.0002$), glucose ($p = 0.004$), and *FGF21* ($p < 0.0001$) even when adjusting for age, sex, and BMI (Table 3). *CTRP9* was inversely associated with C-peptide ($p = 0.03$) and *FGF21* ($p = 0.005$), and remained significantly associated with *FGF21* on multivariable analysis ($p = 0.01$) adjusting for age, sex, BMI, glucose, and duration of diabetes. *FGF21* was positively associated with C-peptide levels ($p = 0.007$), which remained significant ($p = 0.02$) when adjusting for age, sex, BMI, diabetes duration, and other significant characteristics. In the multivariable analysis model, *FGF21* was positively associated with *CTRP1* ($p = 0.002$), but not with *CTRP9*.

Discussion

As the obesity epidemic continues [44], and the prevalence of T1D and T2D increases [2, 45, 46], it is important to understand the connection of adipokines and their relationship to metabolic factors in youth with diabetes. To our knowledge, this is the first comparison of the circulating novel adipokines *CTRP1*, *CTRP9*, and *FGF21* in pediatric patients with T1D and T2D. We demonstrate that *CTRP9* is higher in youth with T1D compared to T2D, and the hepatokine *FGF21* is higher in youth with T2D compared to T1D. Further, we show that in youth with T2D, the novel adipokine *CTRP1* is positively associated with HbA1c and glucose. The associations identified in this study of youth with T1D and T2D, while noting the absence of a control group, may help us begin to elucidate early alterations in adipokines and identify future research areas that may be able to inform future therapeutics and prevention of diabetes-related complications.

Similar to our prior study of *CTRP9* in obese adolescents with and without hyperglycemia, we did not see an association of *CTRP9* with obesity or measures of glycemia in the T2D cohort [13]. This is different than results from adult T2D studies demonstrating elevated *CTRP9* levels in the setting of obesity and diabetes [12, 30, 47]. Based on these data, one

could hypothesize that *CTRP9* levels are not yet elevated in the pediatric or adolescent T2D population and suggest that *CTRP9* levels may be changing in the course of T2D disease progression, but future longitudinal studies would be required to further evaluate this. Prior research suggests that *CTRP9* may have protective effects on diabetes-related complications. In vivo studies in diabetic mice demonstrate that administration of recombinant *CTRP9* attenuates development of diabetic nephropathy and development of kidney fibrosis [48], and reduces cardiac injury and infarct size [49]. In vitro studies also show that *CTRP9* overexpression attenuates hyperglycemia-induced oxidative stress in human retinal pigment epithelial ARPE-19 cells [50]. Thus, future research is needed to investigate *CTRP9*, as a potential biomarker for those at risk of developing diabetes, and what its role may be as a therapy to mitigate diabetes-associated complications. To our knowledge, this is the first study evaluating *CTRP9* levels in youth with T1D. *CTRP9* levels in youth with T1D were associated with C-peptide levels, even after adjusting for age, sex, BMI and diabetes duration, and suggests that *CTRP9* levels may be changing in the course of T1D disease progression, but future longitudinal studies would be required to further evaluate this.

While there were no differences in *CTRP1* levels between the T1D and T2D groups, *CTRP1* was positively associated with glucose and HbA1c in adolescents with T2D, consistent with our previous study [13]. In our recent study of *CTRP1* in obese adolescent youth with and without hyperglycemia, we found *CTRP1* to be positively associated with glucose levels, and higher in obese hyper-glycemic youth compared to obese normoglycemic adolescents, consistent with adult studies showing elevated *CTRP1* levels in T2D and the metabolic syndrome [29, 31, 32, 51, 52]. We also showed *CTRP1* to be positively associated with *FGF21*, consistent with prior research in adults [52]. Both *CTRP1* and *FGF21* are known to be elevated in adult subjects with T2D, which is posited to be a compensatory mechanism since administration of recombinant *CTRP1* lowers blood glucose in mice, and overexpression of *CTRP1* in transgenic mice improved insulin sensitivity [22]. Studies have shown that administration of *FGF21* also reduces plasma glucose, improves insulin sensitivity, and preserves β-cell function in diabetic animal models [32, 53].

Childhood obesity is associated with increased serum *FGF21* levels [36, 40, 54], consistent with our recent results illustrating increased *FGF21* levels in obese adolescents with hyperglycemia [13]. We also found T2D participants to have elevated *FGF21* levels when compared to T1D. This is consistent with a study by Xiao et al. [55] that found similar changes in serum *FGF21* levels in adults with different types of diabetes, including T1D, Latent Autoimmune Diabetes in Adults and T2D. These authors found a positive association between *FGF21* and C-peptide in adult subjects with all types of diabetes, which is consistent with our findings [55]. Interestingly, we found that *FGF21* levels were positively associated with HbA1c in youth with T1D, suggesting that *FGF21* levels are higher with worse glycemic control. As other studies have shown in T1D, this may be explained by an early-stage compensatory mechanism where hyperglycemia initially activates *FGF21* secretion by the liver or adipose tissue but is not sustained long term with subsequently declining levels of *FGF21* [55, 56]. Interestingly, an inverse relationship has been reported with studies suggesting that lower *FGF21* levels are associated with worse diabetes-associated complications. An in vivo study of *FGF21* deletion in diabetic mice demonstrated aggravated aortic remodeling and rescue with *FGF21* attenuated diabetes-

induced aortic damage [57]. Further, another study in humans showed that patients with T1D and retinopathy were shown to have lower *FGF21* levels than healthy controls [58], whereas other clinical studies suggest that *FGF21* administration may attenuate diabetes-related kidney disease [59]. Future longitudinal studies are needed to further investigate the compensatory mechanism and changing *FGF21* levels throughout the course of disease progression in diabetes.

Although these data are well characterized from an established registry, we acknowledge several limitations. This study is limited by the modest sample size and demographic variability between groups. Puberty staging was not available so it could not be adjusted for in analysis. Additionally, the lack of a control group in this cross-sectional design limits the generalization of results. Despite limitations, the uniqueness of this study still provides important results to serve as a benchmark for further research.

With the concurrent increase in obesity and diabetes in youth, it is important to understand the relationship between adipokines and the inflammatory milieu in this young population. Our results suggest that *CTRP9* levels are elevated in youth with T1D with intact C-peptide levels but longitudinal studies will need to determine how this changes over time and if *CTRP9* levels decrease as seen in the adult population. In youth with T2D, we found elevated *FGF21* levels similar to trends seen in adult T2D. While *CTRP1* was not different between youth with T1D and T2D, this novel adipokine's association with glucose and HbA1c that persists across studies and cohorts suggests it may play a role in the metabolome of youth with T2D. Future studies with larger cohorts and longitudinal follow-up may help further elucidate the relationship of adipokines and obesity in pediatric diabetes.

Funding Sources

There was no funding for this project. The authors report the following funding: NIDDK (DK084171 to GWW), NICHD (HD071981 to SNM), and NEI (EY033233 to RMW).

Data Availability Statement

Data are available upon request from the PDC.

References

1. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Centers for disease control and prevention 2000 growth charts for the USA: improvements to the 1977 National Center for Health Statistics version. Pediatrics. 2002; 109(1):45–60. [PubMed: 11773541]
2. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA. 2014; 311(17):1778–86. [PubMed: 24794371]
3. Libman IM, Pietropaolo M, Arslanian SA, La-Porte RE, Becker DJ. Changing prevalence of overweight children and adolescents at onset of insulin-treated diabetes. Diabetes care. 2003; 26(10):2871–5. [PubMed: 14514594]
4. Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, et al. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for diabetes in youth study. Pediatr Diabetes. 2010;11(1):4–11. [PubMed: 19473302]
5. American Diabetes Association. 13. Children and adolescents: standards of medical care in diabetes-2021. Diabetes care. 2021;44(Suppl 1): S180–99. [PubMed: 33298424]

6. Redondo MJ, Foster NC, Libman IM, Mehta SN, Hathway JM, Bethin KE, et al. Prevalence of cardiovascular risk factors in youth with type 1 diabetes and elevated body mass index. Acta Diabetol. 2016;53(2):271–7. [PubMed: 26077171]
7. Marlow AL, Rowe CW, Anderson D, Wynne K, King BR, Howley P, et al. Young children, adolescent girls and women with type 1 diabetes are more overweight and obese than reference populations, and this is associated with increased cardiovascular risk factors. Diabet Med. 2019; 36(11):1487–93. [PubMed: 31505060]
8. Tommerdahl KL, Baumgartner K, Schafer M, Bjornstad P, Melena I, Hegemann S, et al. Impact of obesity on measures of cardiovascular and kidney health in youth with type 1 diabetes as compared with youth with type 2 diabetes. Diabetes care. 2021;44(3):795–803. [PubMed: 33402367]
9. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J Am Coll Cardiol. 2008;52(15):1201–10. [PubMed: 18926322]
10. Vendrell J, Broch M, Vilarrasa N, Molina A, Gomez JM, Gutierrez C, et al. Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. Obes Res. 2004;12(6): 962–71. [PubMed: 15229336]
11. Wolf RM, Jaffe AE, Steele KE, Schweitzer MA, Magnuson TH, Wolfe A, et al. Cytokine, chemokine, and cytokine receptor changes are associated with metabolic improvements after bariatric surgery. J Clin Endocrinol Metab. 2019;104(3):947–56. [PubMed: 30544212]
12. Wolf RM, Steele KE, Peterson LA, Zeng X, Jaffe AE, Schweitzer MA, et al. C1q/TNF-related protein-9 (CTRP9) levels are associated with obesity and decrease following weight loss surgery. J Clin Endocrinol Metab. 2016;101(5): 2211–7. [PubMed: 26982010]
13. Wolf RM, Jaffe AE, Rodriguez S, Lei X, Sarver DC, Straub AT, et al. Altered adipokines in obese adolescents: a cross-sectional and longitudinal analysis across the spectrum of glycemia. Am J Physiol Endocrinol Metab. 2021;320(6): E1044–5. [PubMed: 33900848]
14. Nadeau KJ, Regensteiner JG, Bauer TA, Brown MS, Dorosz JL, Hull A, et al. Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. J Clin Endocrinol Metab. 2010;95(2):513–21. [PubMed: 19915016]
15. Bjornstad P, Truong U, Dorosz JL, Cree-Green M, Baumgartner A, Coe G, et al. Cardiopulmonary dysfunction and adiponectin in adolescents with type 2 diabetes. J Am Heart Assoc. 2016;5(3):e002804. [PubMed: 26994128]
16. Kelly AS, Ryder JR, Marlatt KL, Rudser KD, Jenkins T, Inge TH. Changes in inflammation, oxidative stress and adipokines following bariatric surgery among adolescents with severe obesity. Int J Obes. 2016;40(2):275–80.
17. Kim JY, Bacha F, Tfayli H, Michaliszyn SF, Yousuf S, Arslanian S. Adipose tissue insulin resistance in youth on the spectrum from normal weight to obese and from normal glucose tolerance to impaired glucose tolerance to type 2 diabetes. Diabetes Care. 2019;42(2):265–72. [PubMed: 30455334]
18. Li G, Xu L, Zhao Y, Li L, Fu J, Zhang Q, et al. Leptin-adiponectin imbalance as a marker of metabolic syndrome among Chinese children and adolescents: the BCAMS study. PLoS One. 2017;12(10):e0186222. [PubMed: 29020116]
19. Morales A, Wasserfall C, Brusko T, Carter C, Schatz D, Silverstein J, et al. Adiponectin and leptin concentrations may aid in discriminating disease forms in children and adolescents with type 1 and type 2 diabetes. Diabetes Care. 2004; 27(8):2010–4. [PubMed: 15277432]
20. Reinehr T, Woelfle J, Wiegand S, Karges B, Meissner T, Nagl K, et al. Leptin but not adiponectin is related to type 2 diabetes mellitus in obese adolescents. Pediatr Diabetes. 2016;17(4): 281–8. [PubMed: 25882767]
21. Peña AS, Harrington J, Peters Black SK, Gent R, Hirte C, Couper JJ, et al. Vascular function and distribution of adiponectin isomers during puberty in children and adolescents with obesity. Horm Res Paediatr. 2021;94(5–6):186–93. [PubMed: 34348299]
22. Peterson JM, Aja S, Wei Z, Wong GW. CTRP1 protein enhances fatty acid oxidation via AMP-activated protein kinase (AMPK) activation and acetyl-CoA carboxylase (ACC) inhibition. J Biol Chem. 2012;287(2):1576–87. [PubMed: 22086915]

23. Peterson JM, Seldin MM, Wei Z, Aja S, Wong GW. CTRP3 attenuates diet-induced hepatic steatosis by regulating triglyceride metabolism. Am J Physiol Gastrointest Liver Physiol. 2013; 305(3):G214–4. [PubMed: 23744740]
24. Rodriguez S, Lei X, Petersen PS, Tan SY, Little HC, Wong GW. Loss of CTRP1 disrupts glucose and lipid homeostasis. Am J Physiol Endocrinol Metab. 2016;311(4):E678–97. [PubMed: 27555298]
25. Wei Z, Lei X, Petersen PS, Aja S, Wong GW. Targeted deletion of C1q/TNF-related protein 9 increases food intake, decreases insulin sensitivity, and promotes hepatic steatosis in mice. Am J Physiol Endocrinol Metab. 2014;306(7):E779–90. [PubMed: 24473438]
26. Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Ge G, Spooner E, Hug C, et al. Identification and characterization of CTRP9, a novel secreted glycoprotein, from adipose tissue that reduces serum glucose in mice and forms heterotrimers with adiponectin. FASEB J. 2009;23(1):241–58. [PubMed: 18787108]
27. Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonenkov A, Flier JS, et al. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes. 2010;59(11):2781–9. [PubMed: 20682689]
28. Kliewer SA, Mangelsdorf DJ. A dozen years of discovery: insights into the physiology and pharmacology of FGF21. Cell Metab. 2019;29(2): 246–53. [PubMed: 30726758]
29. Bai B, Ban B, Liu Z, Zhang MM, Tan BK, Chen J. Circulating C1q complement/TNF-related protein (CTRP) 1, CTRP9, CTRP12 and CTRP13 concentrations in Type 2 diabetes mellitus: in vivo regulation by glucose. PLoS One. 2017;12(2):e0172271. [PubMed: 28207876]
30. Jia Y, Luo X, Ji Y, Xie J, Jiang H, Fu M, et al. Circulating CTRP9 levels are increased in patients with newly diagnosed type 2 diabetes and correlated with insulin resistance. Diabetes Res Clin Pract. 2017;131:116–23. [PubMed: 28743061]
31. Pan X, Lu T, Wu F, Jin L, Zhang Y, Shi L, et al. Circulating complement-C1q TNF-related protein 1 levels are increased in patients with type 2 diabetes and are associated with insulin sensitivity in Chinese subjects. PLoS One. 2014;9(5): e94478. [PubMed: 24827430]
32. Xin Y, Lyu X, Wang C, Fu Y, Zhang S, Tian C, et al. Elevated circulating levels of CTRP1, a novel adipokine, in diabetic patients. Endocr J. 2014; 61(9):841–7. [PubMed: 24965225]
33. Baek J, Nam HK, Rhie YJ, Lee KH. Serum FGF21 levels in obese Korean children and adolescents. J Obes Metab Syndr. 2017;26(3):204–9. [PubMed: 31089518]
34. Cuevas-Ramos D, Almeda-Valdes P, Aguilar-Salinas CA, Cuevas-Ramos G, Cuevas-Sosa AA, Gomez-Perez FJ. The role of fibroblast growth factor 21 (FGF21) on energy balance, glucose and lipid metabolism. Curr Diabetes Rev. 2009; 5(4):216–20. [PubMed: 19531026]
35. Hanks LJ, Gutiérrez OM, Bamman MM, Ashraf A, McCormick KL, Casazza K. Circulating levels of fibroblast growth factor-21 increase with age independently of body composition indices among healthy individuals. J Clin Transl Endocrinol. 2015;2(2):77–82. [PubMed: 26042208]
36. Li G, Feng D, Qu X, Fu J, Wang Y, Li L, et al. Role of adipokines FGF21, leptin and adiponectin in self-concept of youths with obesity. Eur Neuropsychopharmacol. 2018;28(8):892–902. [PubMed: 29891216]
37. Li G, Yin J, Fu J, Li L, Grant SFA, Li C, et al. FGF21 deficiency is associated with childhood obesity, insulin resistance and hypoadiponectinaemia: the BCAMS Study. Diabetes Metab. 2017;43(3):253–60. [PubMed: 28139438]
38. Reinehr T, Karges B, Meissner T, Wiegand S, Fritsch M, Holl RW, et al. Fibroblast growth factor 21 and fetuin-A in obese adolescents with and without type 2 diabetes. J Clin Endocrinol Metab. 2015;100(8):3004–10. [PubMed: 26052728]
39. Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes. 2008;57(5):1246–53. [PubMed: 18252893]
40. Reinehr T, Woelfle J, Wunsch R, Roth CL. Fibroblast growth factor 21 (FGF-21) and its relation to obesity, metabolic syndrome, and non-alcoholic fatty liver in children: a longitudinal analysis. J Clin Endocrinol Metab. 2012;97(6): 2143–50. [PubMed: 22438225]

41. Pediatric Diabetes Consortium. The pediatric diabetes consortium: improving care of children with type 1 diabetes through collaborative research. Diabetes Technol Ther. 2010;12(9):685–8. [PubMed: 20687862]
42. Redondo MJ, Connor CG, Ruedy KJ, Beck RW, Kollman C, Wood JR, et al. Pediatric diabetes consortium type 1 diabetes New Onset (NeOn) Study: factors associated with HbA1c levels one year after diagnosis. Pediatr Diabetes. 2014; 15(4):294–302. [PubMed: 23889707]
43. Klingensmith GJ, Connor CG, Ruedy KJ, Beck RW, Kollman C, Haro H, et al. Presentation of youth with type 2 diabetes in the Pediatric Diabetes Consortium. Pediatr Diabetes. 2016;17(4): 266–73. [PubMed: 25951940]
44. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. JAMA. 2018; 319(16):1723–5. [PubMed: 29570750]
45. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. N Engl J Med. 2017; 376(15):1419–29. [PubMed: 28402773]
46. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016–2018. Diabetes Technol Ther. 2019;21(2):66–72. [PubMed: 30657336]
47. Jung CH, Lee MJ, Kang YM, Jang JE, Leem J, Lee YL, et al. Association of serum C1q/TNF-related protein-9 concentration with arterial stiffness in subjects with type 2 diabetes. J Clin Endocrinol Metab. 2014;99(12):E2477–84. [PubMed: 25105737]
48. Hu H, Li W, Liu M, Xiong J, Li Y, Wei Y, et al. C1q/tumor necrosis factor-related protein-9 attenuates diabetic nephropathy and kidney fibrosis in db/db mice. DNA Cell Biol. 2020; 39(6):938–48. [PubMed: 32283037]
49. Su H, Yuan Y, Wang XM, Lau WB, Wang Y, Wang X, et al. Inhibition of CTRP9, a novel and cardiac-abundantly expressed cell survival molecule, by TNFalpha-initiated oxidative signaling contributes to exacerbated cardiac injury in diabetic mice. Basic Res Cardiol. 2013;108(1): 315. [PubMed: 23212557]
50. Cheng Y, Qi Y, Liu S, Di R, Shi Q, Li J, et al. C1q/TNF-related protein 9 inhibits high glucose-induced oxidative stress and apoptosis in retinal pigment epithelial cells through the activation of AMPK/Nrf2 signaling pathway. Cell Transplant. 2020;29:963689720962052.
51. Chalupova L, Zakovska A, Adamcova K. Development of a novel enzyme-linked immunosorbent assay (ELISA) for measurement of serum CTRP1: a pilot study: measurement of serum CTRP1 in healthy donors and patients with metabolic syndrome. Clin Biochem. 2013;46(1–2):73–8. [PubMed: 23000311]
52. Han S, Kim JD, Lee S, Jeong AL, Park JS, Yong HJ, et al. Circulating CTRP1 levels in type 2 diabetes and their association with FGF21. Int J Endocrinol. 2016;2016:5479627.
53. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, et al. FGF-21 as a novel metabolic regulator. J Clin Invest. 2005;115(6):1627–35. [PubMed: 15902306]
54. Giannini C, Feldstein AE, Santoro N, Kim G, Kursawe R, Pierpont B, et al. Circulating levels of FGF-21 in obese youth: associations with liver fat content and markers of liver damage. J Clin Endocrinol Metab. 2013;98(7):2993–3000. [PubMed: 23626003]
55. Xiao Y, Xu A, Law LS, Chen C, Li H, Li X, et al. Distinct changes in serum fibroblast growth factor 21 levels in different subtypes of diabetes. J Clin Endocrinol Metab. 2012;97(1):E54–8. [PubMed: 22013098]
56. Zibar K, Blaslov K, Bulum T, Ćuća JK, Smirčić-Duvnjak L. Basal and postprandial change in serum fibroblast growth factor-21 concentration in type 1 diabetic mellitus and in healthy controls. Endocrine. 2015;48(3):848–55. [PubMed: 25194937]
57. Yan X, Chen J, Zhang C, Zeng J, Zhou S, Zhang Z, et al. Fibroblast growth factor 21 deletion aggravates diabetes-induced pathogenic changes in the aorta in type 1 diabetic mice. Cardiovasc Diabetol. 2015;14(1):77. [PubMed: 27391008]
58. Rosell Rask S, Krarup Hansen T, Bjerre M. FGF21 and glycemic control in patients with T1D. Endocrine. 2019;65(3):550–7. [PubMed: 31372821]

59. Weng W, Ge T, Wang Y, He L, Liu T, Wang W, et al. Therapeutic effects of fibroblast growth factor-21 on diabetic nephropathy and the possible mechanism in type 1 diabetes mellitus mice. Diabetes Metab J. 2020;44(4):566–80. [PubMed: 32431116]

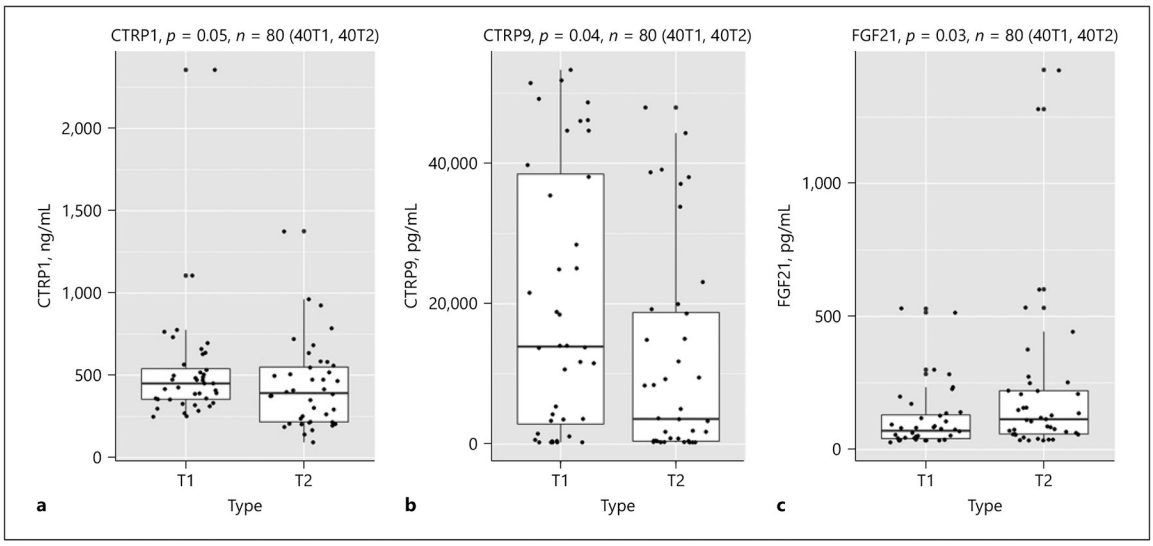

Fig. 1.

Comparison of adipokines in participants with T1D and T2D. All boxplots shown in the figures display the median as the center line, and interquartile range (25th and 75th percentiles) as the box ranges. In each group, there were 20 males and 20 females. Plots represent raw data before any transformations.

Table 1.

Baseline clinical characteristics of study participants with T1D and T2D

	Type 1 (*n* = 40)	**Type 2 (*n* = 40)**	***p* value**
Sex, male, *n* (%)	20 (50)	20 (50)	1
Race/ethnicity, *n* (%)			
White	18 (45)	1 (2.5)	**<0.0001***
Hispanic	16 (40)	30 (75)	
Black	1 (2.5)	8 (20)	
Other	5 (12.5)	1 (2.5)	
Age, years	14.7 (13.1, 16.1)	14.5 (13.4, 16.4)	0.9
Diabetes duration, years	3.3±0.7	2.3±1.7	**0.0009**
Weight, kg	61.9±13.1	93.6±24.8	**<0.0001**
BMI, kg/m^2	22.7±3.6	33.9±7.4	**<0.0001**
BMI, %	78.0 (61.0, 91.0)	98.2 (96.6, 99.4)	**<0.0001**
BMIZ	0.64±0.94	2.1±0.6	0.4
HbA1c, %	9.2±2.4	8.1±2.9	**0.02**
C-peptide, ng/mL	0.1 (0.03, 0.3)	4.2 (2.6, 6.4)	**<0.0001**
Glucose, mg/dL	198.8±115.9	158.2±113.7	**0.04**
Vitamin D, ng/mL	27.0±9.3	23.0±9.6	0.06
CTRP1, ng/mL	518.5±345.0	434.3±261.2	0.05
CTRP9, pg/mL	13,903.6 (2,878.1, 38,492.0)	3,608.5 (433.1, 18,759.8)	**0.04**
FGF21, pg/mL	70.6 (40.9, 129.8)	113.1 (58.0, 220.5)	**0.03**

p values calculated using Student's *t* test for normally distributed variables and variables log transformed to fit a normal distribution, and Wilcoxon rank-sum test for non-normally distributed variables. Fisher's exact was used for race/ethnicity. Data are reported as mean ± SD for normally distributed variables, and median and interquartile range for non-normally distributed variables. *p* values were 2-sided and not adjusted for multiple comparisons.

Table 2.

Univariate and multivariable analysis of adipokine levels with clinical characteristics in participants with T1D (n = 40)

T1D	*CTRP1*				*CTRP9*				*FGF21*			
	univariate		multivariable analysis		univariate		multivariable analysis		univariate		multivariable analysis	
	β ± SE	*p* value	β ± SE	*p* value	β ± SE	*p* value	β ± SE	*p* value	β ± SE	*p* value	β ± SE	*p* value
Age (years)	−0.06±0.03	0.09	–	–	2,233.36±1,495.44	0.1	2,103±1,434	0.6	0.06±0.06	0.4	0.06±0.06	0.4
Sex (M)	–	0.64	–	–	–	0.1	–	0.2	–	**0.009**	–	0.1
Weight (kg)	−0.27±0.32	0.4	–	–	1,803.40±14,221.90	0.9	–	–	0.26±0.60	0.7	–	–
Height (cm)	−3.31E-03±6.20E-03	0.60	–	–	335.49±269.12	0.2	–	–	−2.03E-09±0.01	0.9	–	–
BMI (kg/m^2)	−0.32±0.44	0.47	–	–	−17,445.89±19,228.51	0.4	−20,928±19,133	0.3	0.54±0.82	0.5	−0.89±0.83	0.3
BMI%	−0.12±0.28	0.66	–	–	−21,404.49±11,898.40	0.1	–	–	−0.12±0.53	0.8	–	–
BMIZ	−4.82E-03±0.19	0.98	–	–	13,358.32±8,144.51	0.1	–	–	−0.03±0.36	0.9	–	–
Diabetes duration (years)	0.07±0.10	0.5	–	–	−4,385.55±4,471.76	0.3	−1,277±4,098	0.8	0.27±0.19	0.2	–	–
C-peptide (ng/mL)	−0.12±0.27	0.65	–	–	31,629.63±10,583.56	**0.005**	30,661±10,480	**0.006**	−0.07±0.50	0.9	–	–
Glucose (mg/dL)	0.14±0.12	0.26	–	–	7,339.86±5,258.97	0.2	–	–	0.37±0.22	0.1	0.21±0.21	0.3
HbA1c (%)	−0.10±0.28	0.73	–	–	12,538.66±12,237.88	0.3	–	–	1.51±0.47	**0.002**	1.15±0.54	**0.04**
Vitamin D (ng/mL)	5.98E-03±7.40E-03	0.42	–	–	307.01±325.57	0.4	–	–	3.75E-03±0.01	0.8	–	–
CTRP1 (ng/mL)	–	–	–	–	−2,164.46±7,153.34	0.8	–	–	0.057±0.30	0.9	–	–
CTRP9 (pg/mL)	−1.11E-06±3.67E-06	0.76	–	–	–	–	–	–	8.06E-06±6.76E-06	0.2	–	–
FGF21 (pg/mL)	0.02±0.09	0.85	–	–	4,475.60±3,751.99	0.2	–	–	–	–	–	–

Factors significant on univariate analysis were included in a multivariable regression model and also adjusted for age, sex, and BMI. When C-peptide was significant, the model was also adjusted for diabetes duration. When *FGF21* was significant, the model was additionally adjusted for glucose levels.

Table 3.

Univariate and multivariable analysis of adipokine levels with clinical characteristics in participants with type 2 diabetes

Type 2 diabetes (T2D)	*CTRP1*				*CTRP9*				*FGF21*			
	univariate		multivariable analysis		univariate		multivariable analysis		univariate		multivariable analysis	
	β ± SE	*p* value	β ± SE	*p* value	β ± SE	*p* value	β ± SE	*p* value	β ± SE	*p* value	β ± SE	*p* value
Age (years)	0.04±0.05	0.4	0.008±0.03	0.8	2,335.01±1,151.87	0.05	2,373.5±1,339.0	0.09	0.06±0.08	0.4	0.07±0.07	0.3
Sex (M)	–	0.1	–	0.95	5,051.70±4,657.32	0.3	–	0.3	−0.11±0.31	0.7	–	0.5
Weight (kg)	−0.52±0.34	0.1	–	–	4,858.55±8,824.74	0.6	–	–	−1.52E-04±0.58	1	–	–
Height (cm)	−9.40E-03±9.58E-03	0.3	–	–	374.85±238.05	0.1	–	–	−0.04±0.01	**0.01**	−0.02±0.01	0.2
BMI, (kg/m^2)	−0.59±0.43	0.2	−0.34±0.25	0.2	−1,868.62±11,096.15	0.9	1,209.9±10,768.4	0.9	1.01±0.71	0.2	0.99±0.58	0.1
BMI%	−3.06±1.52	0.05	–	–	−1,343.19±40,462.41	1	–	–	−2.80±2.62	0.3	–	–
BMIZ	0.43±0.35	0.2	–	–	3,280.53±8,952.75	0.7	–	–	−0.67±0.58	0.3	–	–
Diabetes duration (years)	0.02±0.06	0.7	–	–	1,821.41±1,367.00	0.2	284.5±1,579.0	0.9	−6.72E-03±0.09	0.9	−0.02±0.08	0.8
C-peptide (ng/mL)	−0.09±0.13	0.5	–	–	−7,178.87±3,141.23	**0.03**	−3,237.6±3,484.6	0.4	0.57±0.20	**0.007**	0.50±0.20	**0.02**
Glucose (mg/dL)	0.72±0.12	**<0.0001**	0.35±0.11	**0.004**	629.62±4,212.32	0.9	498.8±3,788.4	0.9	−0.02±0.28	1	−0.77±0.32	**0.02**
HbA1c (%)	1.26±0.19	**<0.0001**	0.84±0.20	**0.0002**	7,957.25±6,984.75	0.3	–	–	−0.25±0.47	0.6	–	–
Vitamin D (ng/mL)	9.23E-03±9.75E-03	0.3	–	–	184.08±247.93	0.5	–	–	−0.01±0.02	0.5	–	–
CTRP1 (ng/mL)	–	–	–	–	−1,231.03±4,102.07	0.8	–	–	0.52±0.26	0.05	1.13±0.34	**0.002**
CTRP9 (pg/mL)	−1.92E-06±6.40E-06	0.8	–	–	–	–	–	–	−2.89E-05±9.57E-06	**0.005**	−1.55E-05±8.86E-06	0.09
FGF21 (pg/mL)	0.19±0.09	0.05	0.24±0.05	**<0.0001**	−6,692.59±2,217.20	**0.005**	−6,256.5±2,427.1	**0.01**	–	–	–	–

Factors significant on univariate analysis were included in a multivariate regression model and also adjusted for age, sex, and BMI. When C-peptide was significant, the regression model was also adjusted for diabetes duration. When *FGF21* was significant, the model was additionally adjusted for glucose levels.