The CTRP5 Circulating Levels and the Ratio of CTRP1 to CTRP5 in Plasma are Significant Predictors for Carotid Intima-Media Thickness(cIMT) value in Patients with type 2 diabetes: A Preliminary Study

Ziba Majidi
Tehran University of Medical Sciences

Solaleh Emamgholipour
Tehran University of Medical Sciences

Abolfazl Omidifar
Shaheed Beheshti University of Medical Sciences

Soheil Rahmani Fard
Tehran University of Medical Sciences

Hossein Poustchi (✉ h.poustchi@gmail.com)
Tehran University of Medical Sciences

Mehmoosh Shanaki (✉ shanaki_m@sbmu.ac.ir)
Shaheed Beheshti University of Medical Sciences

Research

Keywords: Type 2 diabetes, CTRP1, CTRP5, carotid intima-media thickness

DOI: https://doi.org/10.21203/rs.3.rs-20710/v3

License: ☒ This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background: There is growing evidence that the C1qTNF-related protein (CTRP) family has a crucial role in the physiology and pathophysiology of metabolic disorders such as Type 2 Diabetes (T2D) and obesity. We sought to identify the association of CTRP1 and CTRP5 circulating levels with various obesity parameters such as visceral adipose tissue (VAT) thickness, visceral adiposity index (VAI), and with carotid intima-media thickness (cIMT) in patients with T2D and healthy subjects.

Methods: This preliminary study consisted of men with T2D (n=42) and men without T2D (n=42). cIMT and VAT thickness measurement was performed using an Accuvix XQ ultrasound. Circulating levels of CTRP1, CTRP5, and adiponectin were measured by enzyme-linked immunosorbent assay (ELISA).

Results: CTRP-1 and CTRP1/CTRP5 ratio were markedly higher in patients with T2D compared to controls (p < 0.0001 and p = 0.004 respectively). Interestingly, binominal logistic regression revealed that a higher circulating level of CTRP1 was associated with the presence of T2D (odds ratio [OR]: 1.009 [95% CI: 1.004-1.015]; P=.001). CTRP1 circulating levels were correlated with WHR, VAT, and HOMA-IR in the whole population study. Also, we observed that the ratio of CTRP1 to CTRP5 in plasma (β = 0.648, P=0.005) and CTRP5 circulating levels (β = 0.444, P=0.049) are significant predictors for cIMT value.

Conclusions: Our results indicated that CTRP1 and CTRP5 concentrations were correlated with atherosclerosis in men with T2D and these adipokines might have a causal role for cardiometabolic risk in T2D. However, more studies in large sample sizes are required to clarify the role of CTRPs in T2D pathogenesis.

1. Background

Type 2 Diabetes (T2D) is one of the most common diseases worldwide affecting about 9% of the world population. (1) As a complex disease, it affects the function of many organs, which implies the possible connection of T2D with multiple metabolic disorders (2-4). It is well-established that obesity and cardiovascular disorders (CVDs) are closely associated with T2D (5-7).

Obesity is a leading cause of insulin resistance, and thus it is considered as an important risk factor for T2D. Moreover, it is generally accepted that CVD is the leading cause of mortality among T2D patients, which results from several abnormalities in cellular metabolism and energy homeostasis. Recent years have seen an intense focus on the understanding of how T2D, obesity, and CVDs are associated together (8).

Adipose tissue plays a major role in regulating the overall metabolism of the body by using secreting a wide range of adipokines. Adiponectin and its paralogues, the family of C1q/TNF-related proteins (CTRPs), seems to be the crucial molecules in the cross-talk among metabolic disorders. (9)
There is growing evidence that adiponectin levels are inversely associated with insulin resistance. Adiponectin acts as an anti-inflammatory agent in the adipose tissue and improves metabolic status in peripheral tissues (10, 11). More importantly, accumulating evidence points toward the association between hypoadiponectinemia and increased risk of cardiovascular problems (12, 13).

The family of CTRPs consists of 15 protein members that play key roles in a variety of metabolic conditions (14, 15). The alteration in circulating levels of CTRPs has been reported in various metabolic diseases such as T2D, obesity, CVD, fatty liver disease, and metabolic syndrome (16-19).

CTRP1 is expressed in various tissues including adipose tissue, liver, muscles, kidneys, and heart (14). Muscles are primary targets for CTRP1 as it activates 5' AMP-activated protein kinase (AMPK) and the mitogen-activated protein kinase (MAPK) signaling pathways, promotes glucose uptake, ameliorates insulin resistance, and increases fat oxidation (20). The increased level of CTRP1 in T2D, prediabetes, coronary artery disease, congestive heart failure, and atherosclerosis is also reported in several studies (21, 22). Although there is evidence on the protective role of CTRP1 in murine heart injuries, the exact role of CTRP1 in these conditions is still not fully understood and requires further studies (23).

CTRP5, another member of the CTRPs family is also expressed in a wide range of tissues including adipose tissue, eye, testis, skeletal muscle, brain, spleen, uterus, and ciliary epithelium. However, adipose tissue is considered as the main secretor (21). CTRP5 increases glucose uptake via stimulating incorporation of the glucose transporter 4 (GLUT4) into the plasma membrane by a mechanism dependent on AMPK phosphorylation. Besides, phosphorylation of acetyl-CoA carboxylase (ACC) is mediated by CTRP5 which results in fatty acid oxidation in rat myocytes (14, 24, 25). Decreased levels of CTRP5 have been observed in metabolic syndrome, T2D, and coronary artery disease. The association between CTRP5 and metabolic disorders have been studied with contradicting results, either augmenting or ameliorating insulin resistance and atherosclerosis.

CVD is one of the most common causes of death in T2D patients. Moreover, there is a close association between T2D, obesity, and an increased occurrence of CVD risk factors. Hence, it is of great importance to detect the possible molecules which link among the aforementioned conditions.

To the best of our knowledge, there is no study to evaluate the correlation of circulating levels of CTRP1 and CTRP5 with various obesity indices including body mass index (BMI), waist, hip, waist-to-hip ratio (WHR), visceral adipose tissue (VAT), and visceral adiposity index (VAI) in T2D patients compared to the control group. In this study, we intended to address the association of circulating CTRP1 and CTRP5 with obesity indices and carotid intima-media thickness (cIMT) in patients with T2D and control subjects.

2. Methods

2.1. Study population
This study consisted of T2D patients (n=42) and control subjects (subjects without T2D) (n=42). All participants (T2D patients and controls) were men between the ages of 43 - 72 years. Informed written consent was obtained from all participants before the study, and the study was approved by the Ethics Committee of the Tehran University of Medical Sciences (TUMS).

Patients with T2D were consecutively recruited from the outpatient clinic of Shariati Hospital, affiliated from Tehran University of Medical Sciences, Tehran, Iran from March 2012 until November 2013. All patients in this study were clinically definite diagnosis of T2D based on the T2DM, the basis of American Diabetes Association (ADA) criteria which were fasting blood glucose (FBG) $\geq 126$ mg/dl (7.0 mmol/l) or 2 hours plasma glucose $\geq 200$ mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT) or random plasma glucose $\geq 200$ mg/dl (11.1 mmol/l) (26). T2D Patients with evidence of any (1) chronic or acute systemic diseases such as infectious disease, (2) acute or chronic renal failure, (3) malignancies, (4) congenital cardiac disease, and (5) type 1 diabetes (T1D) were excluded.

Subjects without T2D as the control group were selected from the same geographical areas and were selected among subjects attending the Shariati Hospital, Tehran, Iran for a routine check-up. The exclusion criteria for controls were as follows 1) T2D; 2) T1D;3) chronic or acute systemic diseases such as infectious disease;4) acute or chronic renal failure; 5) malignancies, and 6) congenital cardiac disease. It should be noted that none of the participants were current smoking. All controls were received a regular medical check-up by a physician.

We would like to stress that this study is reported in compliance with STROBE guidelines (Supplementary material).

2.2. Ultrasound methods

Ultrasound examinations for measurement of the cIMT and visceral adipose tissue thickness (VAT) were performed using an Accuvix XQ ultrasound unit (Medison, Seoul, Korea) equipped with a 3-7 MHZ curved-array and a 5-12 MHz linear-array transducer. The technique for measuring cIMT and VAT has been previously described (27, 28). In brief, cIMT measured at its thickest point on the distal wall of the carotid arteries, along a 1.5-2 cm proximal to the carotid bulb. cIMT on the left and right sides was evaluated and mean values of both sides were determined as carotid IMT. Also, VAT (in millimeter) was measured as the distance between the anterior wall of the aorta and the internal face of the rectus abdominis muscle perpendicular to the aorta.

2.3. Anthropometric and clinical characterization

Anthropometric indices of including age, weight, height, BMI, WC, hip, WHR, and blood pressure were examined. BMI was measured based on the ratio of weight in kg divided by height in m$^2$ to assess participants' obesity. WC using a flexible inch strip in the middle between the lowest rib and the iliac crest was calculated. Furthermore, the hip was measured at the maximum circumference of the buttocks. WHR was measured based on the ratio of WC in centimeters divided by hip circumference in centimeters. After
a 15-minute rest in sitting position, systolic and diastolic blood pressures were measured by a manual sphygmomanometer. VAI, as a gender-specific mathematical index was calculated based on simple anthropometric [BMI and WC] and metabolic [TG and HDL Cholesterol (HDL)] parameters (29).

\[
\text{Males: VAI} = \frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})} \times \frac{\text{TG}}{1.03} \times \frac{1.31}{\text{HDL}}
\]

2.4. Measurement of Biochemical and laboratory parameters

Fresh venous blood samples were collected into sterile tubes containing the EDTA-K2 after overnight fasting for measuring biochemical analyses. Fasting blood glucose (FBG), urea, creatinine, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (γ-GT) were measured by autoanalyzer using commercial kits (Pars Azmoon, Tehran, Iran). Additionally, fasting plasma insulin was calculated by enzyme-linked immunosorbent assay (ELISA) kit (Monobind Inc., USA). To examine the IR, homeostasis model assessment of IR (HOMA-IR) was calculated with the equation of fasting blood glucose (mg/dL) × fasting blood insulin (µU/mL) / 405.

2.5. Measurement of plasma level of adiponectin

Plasma levels of adiponectin were determined by using the ELISA Kit (Elabscience, Wuhan, China) according to the manufacturer’s protocol. Intra-assay and inter-assay Coefficients of Variability (CV) were <10%.

2.6. Measurement of plasma levels of CTRP5 and CTRP1

CTRP1 concentration was measured by ELISA kit (Biovendor research and diagnostic products) with a minimum detectable concentration of 0.016 ng/ml. Intra assay Coefficients of Variability (CV) was 2.7% and inter-assay CV was 8.5%. Plasma levels of CTRP5 were measured by immunoassay using the Cayman system kit according to the manufacturer's protocol. The inter-assay variability and intra-assay variabilities were 6.975 and 6.3 %, respectively.

2.7. Bias

Selection bias was addressed by closely matching cases to controls based on age. Moreover, all participants were men.

2.8. Statistical analysis

The sample size was calculated based on our previous studies. In detail, we estimated that considering alpha=0.05 and power=90%, a difference of 50% in the mean value of CTRP5 circulating levels between the two studied groups could be detected with a minimum of 30 subjects in each group. Here, we included 42 subjects in each group.
Continuous variables with normal distribution were presented as mean ± standard deviation (SD) and variables with non-normal distribution were presented as median (interquartile ranges (IQR)). Descriptive analysis was applied and normality was tested for all quantitative variables using the Shapiro-Wilk test. The student’s t-test and the Mann-Whitney U test were used to compare continuous variables between two groups for data with normal and non-normal distribution, respectively. A p-value <0.05 was applied to interpret all achieved data from analysis. All data analysis was performed using SPSS 20 (SPSS, Chicago, IL, USA).

3. Results

Anthropometric, clinical, and laboratory data of T2D patients and control subjects are shown in Table 1. All subjects were men and there is no statistical difference between two studied groups in terms of age (P =0.622). However, the T2D group had increased values of WC and WHR compared to controls (P=0.039 and P=0.012, respectively). However, other obesity parameters including hip, VAT, and VAI were not comparable between the two groups. We should be noted that BMI was higher in T2D in comparison with the control group but did not reach our threshold of statistically significant difference.

As expected, patients with T2D had higher FBG concentration, insulin levels, and HOMA-IR in comparison with controls. The concentration of TG, HDL-C, LDL- C showed no significant difference between patients and controls.

All liver function-related tests including AST and ALT with expect to GGT showed higher levels in the T2D group compared to controls. Moreover, cIMT as a measurement of subclinical atherosclerosis was higher in T2D patients compared to controls but did not reach our threshold of statistically significant difference (P=0.086).

The comparison of CTRP-5, CTRP-1, adiponectin circulating levels, and ratio of CTRP-1 to CTRP-5 between T2D patients and controls (Figure 1) revealed that CTRP-1 and CTRP1/CTRP5 ratio were significantly higher in patients with T2D rather than in controls (P < 0001 and P = 0004 respectively). While, plasma levels of both CTRP5 and adiponectin with a borderline significant, was lower in T2D patients in comparison with controls (P =0.09 and P =0.094 respectively).

We also performed binomial logistic regression to investigate whether the ratio of CTRP1 to CTRP5 and plasma levels of CTRP1, CTRP5, and adiponectin might predict the presence of T2D (Table 2). When all afore-mentioned items were inserted, we found the one unit increase in the circulating level of CTRP1 was associated with the presence of T2D (odds ratio [OR]: 1.009 [95% CI: 1.004-1.015]; P=.001). After adjustment for BMI, an increase in circulating levels of CTRP1 remained a significant risk factor of T2D (odds ratio [OR]: 1.009 [95% CI: 1.004-1.015]; P=.001).

To identify independent predictors of CTRP1 circulating levels, we performed multivariate stepwise linear regression analysis with age, BMI, WC, hip, WHR, VAI, and VAT as independent variables. Our results showed that WHR (β = 0.273, P=0.014) is the only predictor for CTRP1 concentration in all participants.
Also, we performed multivariate stepwise linear regression analysis with cIMAT as a dependent variable and ratio of CTRP1 to CTRP5 and plasma levels of CTRP1, CTRP5, and adiponectin as independent variables. Our results showed that the ratio of CTRP1 to CTRP5 in plasma ($\beta = 0.648$, $P=0.005$) and CTRP5 circulating levels ($\beta = 0.444$, $P=0.049$) are significant predictors for cIMT value.

The ROC curves analysis of CTRP1, CTRP5 and CTRP1/CTRP5 circulating levels in discriminating T2D from controls showed an area under the curve (AUC) of 0.75 ($p<0.0001$, 95% CI 0.65-0.85), 0.60 ($p=0.0945$, 95% CI 0.48-0.73) and of 0.73 ($p=0.0945$, 95% CI 0.61-0.83) in T2DM, respectively (Figure 2).

The results of the correlation analysis of CTRP1/CTRP5 and circulating levels of CTRP1 and CTRP5 with anthropometric and biochemical characteristics in all participants, T2D patients, and controls were depicted in Table 3 and Table 4. We found a positive significant correlation between CTRP1 levels with WHR, VAT, and HOMA-IR in the whole population study. Moreover, there was a correlation between CTRP1 circulating levels with cIMT ($P=0.062$) (Fig 3a), VAI ($P=0.093$), and VAT ($P=0.051$). Moreover, CTRP5 circulating levels inversely correlated with the HOMA-IR index ($p=0.008$). Furthermore, the ratio of CTRP1 to CTRP5 positively correlated with cIMT ($P=0.020$) (Fig 3b) and HOMA-IR ($P=0.015$) in all participants.

4. Discussion

A grown body of evidence highlights the crucial role of adiponectin and CTRP family members in the pathogenesis of metabolic disorders (30, 31). However, few studies have ever attempted to associate the CTRP1, CTRP5, and adiponectin circulating levels with unfavorable obesity indices including VAI, VAT, HOMA-IR, and also cIMT in T2D patients. In our study, we demonstrated that circulating levels of CTRP1 were higher in T2D patients compared to those in controls, in contrast to the reduced trend of adiponectin serum levels. Moreover, binominal logistic regression analysis revealed that elevated CTRP1 plasma levels were a possible indicator of T2D; suggesting the hypothesis that CTRP1 might be involved in the pathogenesis of T2D. Our results are consistent with observations reported by Bai B et al and Shanaki M et al (31, 32). They found higher plasma levels of CTRP1 in T2D and NAFLD patients in comparison with healthy participants. One possible explanation regarding the elevation of CTRP1 concentrations in T2D patients might be a self-protective or compensatory mechanism in response to abnormal glucose metabolism. Inconsistent with the above results, it was reported that CTRP1 levels did not significantly higher in diabetic subjects(33). The main reason for this discrepancy could be related to different samples as human and animal models (DIO or ob/ob mice) were investigated. There is also report that circulating CTRP1 in adiponectin- null mice were significantly enhanced relative to controls that confirms our finding concerning different serum pattern of CTRP1 and adiponectin(15). Also, CTRP1 may have specified overlapping roles as adiponectin. For instance, overexpression of recombinant CTRP1 could efficiently diminish serum levels of glucose in mice (15). Our data indicated that the differential pattern of CTRP1 and adiponectin in T2D condition might reflect an effective function in modulating glucose homeostasis, and the paradoxical elevation of CTRP1 circulating levels in T2DM subjects might exert a compensatory response to the abnormal glucose and lipid metabolism. However, more clinical studies are needed to establish this concept.
Interestingly, we found that CTRP1 markedly correlated with WHR and HOMA-IR and with VAI and VAT with a borderline significance. In line with our results, previous data reported that CTRP1 levels significantly increased in obese condition and associated with metabolic indices such as BMI and HOMA-IR (34-37). Moreover, in line with current literature, Bai et al. observed higher circulating levels of CTRP1 were significantly associated with hyperglycemia and HOMA-IR in T2D patients (38). However, another study indicated that CTRP1 circulating levels significantly decreased in diet-induced obese mice relative to normal diet mice (35, 39). Also, there is evidence that inhibition of CTRP1 impairs glucose homeostasis and insulin signaling which points into the possible contribution of CTRP1 in regulating energy metabolism and systemic insulin sensitivity (40, 41). Moreover, it has been noted that CTRP1 likely correlated with sex hormones and may affect systemic metabolism in a sex-dependent manner (40). Based on discrepancies in research data regarding the different patterns of CTRP1 in the context of obesity, future studies are needed to unravel underlying mechanisms in which CTRP1 regulates energy metabolism.

In the present study, a ROC curve analysis showed that circulating CTRP1 discriminated with high accuracy between T2D patients and controls. These findings point toward the contributory role of CTRP1 as a potential marker in men with T2D. However, future study with a larger sample size is necessary to establish this concept.

There is also ample evidence about the possible role of CTRP1 in coronary artery disease and atherosclerosis (42-44). Besides, it has been shown that the circulating level of CTRP1 is associated with coronary artery disorders and the atherosclerotic extent index. Also, the close associations of CTRP1 with an unfavorable metabolic profile can be considered as a possible reason for the relationship between CTRP1 and cardiovascular incidence risk. Here, we reported a positive correlation of CTRP1 with cIMT with a borderline significance. It has been noted that adiponectin (a paralogue of CTRP1) has potential anti-atherogenic properties and might be an independent factor correlated with atherosclerosis. Hence, it is tempting to speculate that a high level of CTRP1 is independently associated with subclinical atherosclerosis and vascular injury.

To put these findings together, our results along with others suggest that measurement of circulating CTRP1 concentrations may be valuable for assessment of cardiovascular risk. However, future researches are required to elucidate the impact of CTRP1 on cardiovascular homeostasis.

Recently, CTRP5 has been found as a mediator of metabolic pathways involved in T2D, insulin resistance, and also obesity-related cardiovascular abnormalities (45). Nevertheless, the previous results are inconsistent. There is a report about the low levels of circulating CTRP5 in T2D subjects, whereas another study argued that circulating levels of CTRP5 were significantly higher in obese and diabetic mice rather than lean group (45, 46). An in vivo study by Lei et al revealed that CTRP5 circulating levels were not significantly changed in ob/ob mice (47). Besides, we previously showed that plasma CTRP5 levels were significantly lower in NAFLD and T2D patients in comparison with healthy subjects (48). In the present study, circulating CTRP5 concentrations were lower in T2D patients with a borderline significant level. As
mentioned above, there is a discrepancy between animal model studies and human surveys that are
might be due to the different functions of CTRP5 in humans and mice; just as resistin plays different
roles in humans and mice(49). Another reason might be due to different genetic background that affects
phenotype since T2D in humans is a heterogeneous disease which is associated with environmental
factors, whereas ob/ob and db/db mice are only caused by leptin deficiency (50). Also, it is noteworthy
that we observed a negative correlation between CTRP5 and HOMA-IR, which suggests a link between
CTRP5 and insulin resistance. It has been shown that inhibition of CTRP5 action may result in the
alleviation of insulin resistance associated with obesity and diabetes (47). However, there is a limited
number of data on the correlation between CTRP5 and type 2 diabetes in humans and future clinical
studies are demanded.

As an important finding, we also found that CTRP5 circulating levels and CTRP1/CTRP5 ratio might be
two independent predictors for the cIMT index. It has been demonstrated that serum CTRP5 levels were
significantly increased in patients with CAD and positively correlated with the extent and severity of
atherosclerosis in these patients (51). It seems that decreased levels of CTRP5 may be linked to
cardiovascular complications in T2D patients. However, more research on this subject needs to be
undertaken.

Taken together, as a preliminary study, our study indicates that the CTRP1 to CTRP5 ratio in plasma may
be a predictor of cIMT among men with T2D. However, more studies in large sample sizes are required to
clarify the role of CTRPs in the pathomechanism of T2D and associated metabolic abnormalities. It is
also worth mentioning that the underlying mechanism of association between CTRP1 and CTRP5
alterations and metabolic abnormalities cannot be elucidated based on the current study. Although our
results accompanying available literature can provide novel information on the role of CTRP1 and CTRP5
in the pathomechanism of metabolic disorders, several limitations of the study should be considered.

The main limitation is the small number of patients enrolled in this study which precluded any definitive
conclusions on the exact role of CTRP1 and CTRP5 in the context of T2D, and cardiometabolic risk
factors. Moreover, the gender difference in cIMT was reported in several studies (52, 53). Hence, there is a
need for future work to determine if the CTRP1/CTRP5 ratio in women is also a predictor of cIMT.

5. Conclusions

In summary, it seems that the enhancement of CTRP1 levels along with reduced CTRP5 circulating levels
was associated with an increase in the risk of T2D in men. Moreover, the CTRP1 to CTRP5 ratio in plasma
may be a predictor of cIMT among T2D patients. We also noted that CTRP1 and CTRP5 concentrations
were associated with some metabolic abnormalities such as subclinical atherosclerosis in patients with
T2D. However, more investigations with a larger sample size in both men and women are needed to
confirm this concept.

6. Abbreviations
7. Declarations

Declarations Ethics approval and consent to participate

The procedures, used in the study, were approved by the Ethical Committee of the Tehran University of Medical Sciences (TUMS) and fully informed, written consent was obtained from the patients.
Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The study was funded by Tehran University of Medical Sciences, Tehran, Iran.

Authors contribution

Project administration: Mehrnoosh Shanaki, Solaleh Emamgholipour

Laboratory procedures: Ziba Majidi, Soheil Rahmani Fard

Data curation: Hossein Poustchi, Solaleh Emamgholipour

Formal analysis: Solaleh Emamgholipour, Abolfazl Omidifar

Funding acquisition: Hossein Poustchi

Writing of original draft: Solaleh Emamgholipour, Abolfazl Omidifar, Ziba Majidi

Writing -review & editing: Solaleh Emamgholipour, Abolfazl Omidifar, Ziba Majidi, Mehrnoosh Shanaki. All authors read and approved the manuscript.

Acknowledgments

We are grateful to all of our patients who participated in this study.

8. References

1. Khunti K, Alsifri S, Aronson R, Cigrovski Berković M, Enters-Weijnen C, Forsén T, et al. Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. Diabetes, obesity and metabolism. 2016;18(9):907-15.

2. Mukherjee A, Morales-Scheihing D, Butler PC, Soto C. Type 2 diabetes as a protein misfolding disease. Trends in molecular medicine. 2015;21(7):439-49.
3. Bharadwaj P, Wijesekara N, Liyanapathirana M, Newsholme P, Ittner L, Fraser P, et al. The link between type 2 diabetes and neurodegeneration: roles for amyloid-β, amylin, and tau proteins. Journal of Alzheimer's Disease. 2017;59(2):421-32.

4. Debnath S, Velagapudi C, Redus L, Thameem F, Kasinath B, Hura CE, et al. Tryptophan metabolism in patients with chronic kidney disease secondary to type 2 diabetes: Relationship to inflammatory markers. International Journal of Tryptophan Research. 2017;10:1178646917694600.

5. Borch D, Juul-Hindsgaul N, Veller M, Astrup A, Jaskolowski J, Raben A. Potatoes and risk of obesity, type 2 diabetes, and cardiovascular disease in apparently healthy adults: a systematic review of clinical intervention and observational studies. The American journal of clinical nutrition. 2016;104(2):489-98.

6. Bacha F, Gidding SS. Cardiac abnormalities in youth with obesity and type 2 diabetes. Current diabetes reports. 2016;16(7):62.

7. Abdul-Ghani M, DeFronzo RA, Del Prato S, Chilton R, Singh R, Ryder RE. Cardiovascular disease and type 2 diabetes: has the dawn of a new era arrived? Diabetes Care. 2017;40(7):813-20.

8. Patel TP, Rawal K, Bagchi AK, Akolkar G, Bernardes N, da Silva Dias D, et al. Insulin resistance: an additional risk factor in the pathogenesis of cardiovascular disease in type 2 diabetes. Heart failure reviews. 2016;21(1):11-23.

9. Schäffler A, Schölmerich J, Salzberger B. Adipose tissue as an immunological organ: Toll-like receptors, C1q/TNFs and CTRPs. Trends in immunology. 2007;28(9):393-9.

10. Turer A, Scherer P. Adiponectin: mechanistic insights and clinical implications. Diabetologia. 2012;55(9):2319-26.

11. Meier U, Gressner AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. Clinical chemistry. 2004;50(9):1511-25.

12. Renaldi O, Pramono B, Sinorita H, Purnomo LB, Asdie RH, Asdie AH. Hypoadiponectinemia: a risk factor for metabolic syndrome. Acta Med Indones. 2009;41(1):20-4.

13. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arteriosclerosis, thrombosis, and vascular biology. 2003;23(1):85-9.

14. Schäffler A, Buechler C. CTRP family: linking immunity to metabolism. Trends in Endocrinology & Metabolism. 2012;23(4):194-204.

15. Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Revett T, Gimeno R, Lodish HF. Molecular, biochemical and functional characterizations of C1q/TNF family members: adipose-tissue-selective expression patterns, regulation by PPAR-γ agonist, cysteine-mediated oligomerizations, combinatorial associations and metabolic functions. Biochemical Journal. 2008;416(2):161-77.

16. Moradi N, Fadaei R, Emamgholipour S, Kazemian E, Panahi G, Vahedi S, et al. Association of circulating CTRP9 with soluble adhesion molecules and inflammatory markers in patients with type 2 diabetes mellitus and coronary artery disease. PLOS ONE. 2018;13(1):e0192159.
17. Emamgholipour S, Moradi N, Beigy M, Shabani P, Fadaei R, Poustchi H, et al. The association of circulating levels of complement-C1q TNF-related protein 5 (CTRP5) with nonalcoholic fatty liver disease and type 2 diabetes: a case–control study. Diabetology & metabolic syndrome. 2015;7(1):108.

18. Fadaei R, Moradi N, Baratchian M, Aghajani H, Malek M, Fazaeli AA, et al. Association of C1q/TNF-related protein-3 (CTRP3) and CTRP13 serum levels with coronary artery disease in subjects with and without type 2 diabetes mellitus. PloS one. 2016;11(12):e0168773.

19. Wang S, Ling Y, Liang W, Shen L. Association of serum C1q/TNF-related protein-3 (CTRP-3) in patients with coronary artery disease. BMC Cardiovasc Disord. 2017;17(1):210-.

20. 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. Journal of Biological Chemistry. 2012;287(2):1576-87.

21. Wang Y-J, Zhao J-L, Lau W, Liu J, Guo R, Ma X-L. Adipose tissue-derived cytokines, CTRPs as biomarkers and therapeutic targets in metabolism and the cardiovascular system. Vessel Plus. 2017;1:202-12.

22. Chalupova L, Zakovska A, Adamcova K. Development of a novel enzyme-linked immunosorbet assay (ELISA) for measurement of serum CTRP1: a pilot study: measurement of serum CTRP1 in healthy donors and patients with metabolic syndrome. Clinical biochemistry. 2013;46(1-2):73-8.

23. Yuasa D, Ohashi K, Shibata R, Mizutani N, Kataoka Y, Kambara T, et al. C1q/TNF-related protein-1 functions to protect against acute ischemic injury in the heart. The FASEB Journal. 2015;30(3):1065-75.

24. Park S-Y, Choi JH, Ryu HS, Pak YK, Park KS, Lee HK, et al. C1q tumor necrosis factor α-related protein isoform 5 is increased in mitochondrial DNA-depleted myocytes and activates AMP-activated protein kinase. Journal of Biological Chemistry. 2009;284(41):27780-9.

25. Lee Y, Nair S, Rousseau E, Allison D, Page G, Tataranni P, et al. Microarray profiling of isolated abdominal subcutaneous adipocytes from obese vs non-obese Pima Indians: increased expression of inflammation-related genes. Diabetologia. 2005;48(9):1776-83.

26. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2010;33(Suppl 1):S62-9.

27. Ayonrinde OT, Olynyk JK, Beilin LJ, Mori TA, Pennell CE, de Klerk N, et al. Gender-specific differences in adipose distribution and adipocytokines influence adolescent nonalcoholic fatty liver disease. Hepatology. 2011;53(3):800-9.

28. Merat S, Poustchi H, Hemming K, Jafari E, Radmard AR, Nateghi A, et al. PolyPill for Prevention of Cardiovascular Disease in an Urban Iranian Population with Special Focus on Nonalcoholic Steatohepatitis: A Pragmatic Randomized Controlled Trial within a Cohort (PolyIran - Liver) - Study Protocol. Archives of Iranian medicine. 2015;18:515-23.

29. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010;33(4):920-2.
30. Ouchi N, Walsh K. Cardiovascular and Metabolic Regulation by the Adiponectin/C1q/Tumor Necrosis Factor–Related Protein Family of Proteins. Circulation. 2012;125(25):3066-8.

31. 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.

32. Shanaki M, Fadaei R, Moradi N, Emamgholipour S, Poustchi H. The Circulating CTRP13 in Type 2 Diabetes and Non-Alcoholic Fatty Liver Patients. PLOS ONE. 2016;11(12):e0168082.

33. Barbieri D, Goicoechea M, Sánchez-Niño MD, Ortiz A, Verde E, Verdalles U, et al. Obesity and chronic kidney disease progression—the role of a new adipocytokine: C1q/tumour necrosis factor-related protein-1. Clin Kidney J. 2018;12(3):420-6.

34. Wong GW, Wang J, Hug C, Tsao T-S, Lodish HF. A family of Acrp30/adiponectin structural and functional paralogs. Proc Natl Acad Sci U S A. 2004;101(28):10302-7.

35. Shabani P, Emamgholipour S, Doosti M. Chapter One - CTRP1 in Liver Disease. In: Makowski GS, editor. Advances in Clinical Chemistry. 79: Elsevier; 2017. p. 1-23.

36. 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. Clinical Biochemistry. 2013;46(1):73-8.

37. 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-e.

38. 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-e.

39. Han S, Park JS, Lee S, Jeong AL, Oh KS, Ka HI, et al. CTRP1 protects against diet-induced hyperglycemia by enhancing glycolysis and fatty acid oxidation. The Journal of Nutritional Biochemistry. 2016;27:43-52.

40. 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-E97.

41. Miller VM. Why are sex and gender important to basic physiology and translational and individualized medicine? Am J Physiol Heart Circ Physiol. 2014;306(6):H781-H8.

42. Yuasa D, Ohashi K, Shibata R, Takeshita K, Kikuchi R, Takahashi R, et al. Association of circulating C1q/TNF-related protein 1 levels with coronary artery disease in men. PloS one. 2014;9(6):e99846-e.

43. Muenlein A, Leiberer A, Saely C, Ebner J, Geiger K, Brandnter EM, et al. Data on the association between CTRP1 and future major adverse cardiovascular events in patients undergoing coronary angiography. Data Brief. 2019;25:104109-.

44. Shen L, Wang S, Ling Y, Liang W. Association of C1q/TNF-related protein-1 (CTRP1) serum levels with coronary artery disease. J Int Med Res. 2019;47(6):2571-9.
45. Zhang C, Luo Y, Liu R, Li X, Yang M, Zhang Y, et al. Circulating complement-1q tumor necrosis factor-α-related protein isoform 5 levels are low in type 2 diabetes patients and reduced by dapagliflozin. Journal of Diabetes Investigation. 2019;0(0).

46. Park S-Y, Choi JH, Ryu HS, Pak YK, Park KS, Lee HK, et al. C1q tumor necrosis factor alpha-related protein isoform 5 is increased in mitochondrial DNA-depleted myocytes and activates AMP-activated protein kinase. J Biol Chem. 2009;284(41):27780-9.

47. Lei X, Rodriguez S, Petersen PS, Seldin MM, Bowman CE, Wolfgang MJ, et al. Loss of CTRP5 improves insulin action and hepatic steatosis. Am J Physiol Endocrinol Metab. 2016;310(11):E1036-E52.

48. Emamgholipour S, Moradi N, Beigy M, Shabani P, Fadaei R, Poustchi H, et al. The association of circulating levels of complement-C1q TNF-related protein 5 (CTRP5) with nonalcoholic fatty liver disease and type 2 diabetes: a case-control study. Diabetology & metabolic syndrome. 2015;7:108-.

49. Park HK, Ahima RS. Resistin in rodents and humans. Diabetes Metab J. 2013;37(6):404-14.

50. Ling C, Groop L. Epigenetics: a molecular link between environmental factors and type 2 diabetes. Diabetes. 2009;58(12):2718-25.

51. Li C, Chen JW, Liu ZH, Shen Y, Ding FH, Gu G, et al. CTRP5 promotes transcytosis and oxidative modification of low-density lipoprotein and the development of atherosclerosis. Atherosclerosis. 2018;278:197-209.

52. Tabatabaei-Malazy O, Fakhrzadeh H, Sharifi F, Mirarefin M, Badamchizadeh Z, Larijani B. Gender differences in association between metabolic syndrome and carotid intima media thickness. Journal of diabetes and metabolic disorders. 2012;11(1):13.

53. Grimaud O, Lapostolle A, Berr C, Helmer C, Dufouil C, Kihal W, et al. Gender differences in the association between socioeconomic status and subclinical atherosclerosis. PLoS One. 2013;8(11):e80195.

9. Tables

Table 1. Anthropometric and laboratory characteristics of the study population.
| Characteristics       | Controls (n = 42)          | T2DM (n = 42)        | P value |
|----------------------|---------------------------|----------------------|---------|
| Age, years           | 51(48-57.25)              | 55(46.50-59.25)      | 0.622   |
| Waist, cm            | 99.52±10.21               | 104.45±11.30         | 0.039*  |
| Hips, cm             | 102.43±6.417              | 103.79±7.15          | 0.363   |
| WHR, -               | 0.97±0.05                 | 1.00±0.06            | 0.012*  |
| Height, cm           | 169.48±5.70               | 168.13±5.65          | 0.281   |
| Weight, kg           | 78.01±11.89               | 81.31±12.10          | 0.212   |
| BMI, kg/m2           | 27.13±3.72                | 28.78±4.33           | 0.064   |
| FBG, -               | 93.50(87.01-99.17)        | 146(123.45-183.07)   | 0.000*  |
| Insulin, μU/mL       | 8(3.50-10.10)             | 7.10(4.35-9.55)      | 0.906   |
| HOMA-IR, -           | 1.79(0.83-2.43)           | 2.61(1.58-3.77)      | 0.009*  |
| Triglycerides, mg/dL | 129.10(93.85-160.30)      | 142.30(108.28-184.40)| 0.214   |
| Cholesterol, mg/dL   | 196.50 (167.85-213.90)    | 202.60 (167.88-221.45)| 0.545   |
| HDL, mg/dl           | 50.10 (44.45-55.90)       | 55.90 (44.23-64.25)  | 0.225   |
| LDL, mg/dL           | 113.71±32.23              | 115.73±37.56         | 0.796   |
| LDL to HDL, -        | 2.26±0.67                 | 2.15±0.63            | 0.451   |
| Urea, mg/dL          | 30.46±7.58                | 32.20±6.55           | 0.272   |
| Creatinine, mg/dL    | 1.27±0.18                 | 1.21±0.18            | 0.164   |
| AST, U/L             | 18.70 (16.20-23.93)       | 20.20 (15.98-26.15)  | 0.679   |
| ALT, U/L             | 20.50 (14.30-29.65)       | 22.80 (14.98-40.20)  | 0.255   |
| ALP, U/L             | 227 (196.50-263)          | 220 (185.75-285)     | 0.810   |
| y-GT, U/L            | 24.33 (19.58-32.10)       | 28.34 (21.69-43.91)  | 0.045*  |
| SBP, mmHg            | 122 (113.75-140)          | 132 (120-150)        | 0.081   |
| DBP, mmHg            | 80(70-90)                 | 80 (74.25-90)        | 0.876   |
| Visceral Fat, %      | 60.76±22.35               | 66.26±21.90          | 0.258   |
| WBC, ×10⁹/L          | 5.40 (1.9)                | 6.70 (2)             | 0.029*  |
| cIMT, mm             | 0.79±0.10                 | 0.83±0.12            | 0.086   |
| VAI                  | 1.60(1.11-2.05)           | 1.67 (1.25-2.27)     | 0.577   |

*Continuous variables with normal distribution were described as mean ± SD and with non-normal distribution were described as Median (IQR)

Table 2. Binomial logistic regression for an odds ratio of T2D according to the ratio of CTRP1 to CTRP5 and plasma levels of CTRP1, CTRP5, and adiponectin (Model 1) and the ratio of CTRP1 to CTRP5 and plasma levels of CTRP1, CTRP5, and adiponectin (Model 2).

|          | B         | S.E. | Wald  | P-Value | OR      | 95% Cl. for EXP(B) |
|----------|-----------|------|-------|---------|---------|--------------------|
|          | Lower     | Upper|
| Model 1  |           |      |       |         |         |                    |
| CTRP1    | .009      | .003 | 11.432| .001    | 1.009   | 1.004 1.015        |
| CTRP5    | -.008     | .006 | 2.052 | .152    | .992    | .980 1.003        |
| Adiponectin | -.268 | .228 | 1.383 | .240    | .765    | .489 1.196        |
| CTRP1/CTRP5 | -.015 | .075 | .039 | .843    | .985    | .851 1.141        |
| Model 2  |           |      |       |         |         |                    |
| CTRP1    | .009      | .003 | 10.679| .001    | 1.009   | 1.004 1.015        |
| CTRP5    | -.008     | .006 | 1.758 | .185    | .992    | .981 1.004        |
| Adiponectin | -.231 | .233 | .987 | .321    | .793    | .503 1.253        |
| CTRP1/CTRP5 | -.008 | .076 | .012 | .911    | .992    | .855 1.150        |
| BMI      | .051      | .065 | .610  | .435    | 1.052   | .926 1.196        |

CI indicates confidence interval; S.E., standard error of the mean; OR, odds ratio.
Table 3. The correlation of CTRP1 & 5 circulating levels with anthropometric characteristics and biochemical data in T2D and controls

|                      | Diabetes | Non-diabetes | Diabetes | Non-diabetes | Diabetes | Non-diabetes |
|----------------------|----------|--------------|----------|--------------|----------|--------------|
|                      | CTRP 1, mg/mL | CTRP 5, mg/mL | CTRP 1/5 | CTRP 1, mg/mL | CTRP 5, mg/mL | CTRP 1/5 |
|                      | i | p | i | p | i | p | i | p | i | p |
| CTRP 1, mg/mL        | 1 | 1 | 0.147 | 0.371 | 0.017 | 0.916 | 1 | 1 | -0.186 | 0.000 | -0.865 | 0.000 |
| CTRP 5, mg/mL        | 0.094 | 0.568 | 0.196 | 0.235 | -0.866 | 0.000 | -0.865 | 0.000 | 1 | 1 |
| Adiponecin, µg/mL    | 0.039 | 0.856 | -0.175 | 0.430 | -0.716 | 0.186 | -0.085 | 0.603 | 0.331 | 0.157 | 0.162 | 0.319 |
| Age, years           | 0.073 | 0.646 | 0.209 | 0.184 | -0.075 | 0.650 | 0.128 | 0.433 | 0.048 | 0.772 | 0.049 | 0.782 |
| SBP, mmHg            | 0.315 | 0.171 | 0.030 | 0.900 | -0.097 | 0.557 | 0.145 | 0.571 | -0.008 | 0.970 | -0.081 | 0.921 |
| DBP, mmHg            | 0.027 | 0.789 | 0.118 | 0.384 | -0.072 | 0.684 | 0.010 | 0.900 | 0.073 | 0.600 | -0.071 | 0.662 |
| VAI                  | 0.213 | 0.186 | 0.142 | 0.384 | 0.028 | 0.568 | -0.287 | 0.881 | 0.080 | 0.403 | 0.037 | 0.567 |
| BMI, kg/m²           | 0.047 | 0.767 | 0.058 | 0.715 | 0.263 | 0.106 | -0.192 | 0.234 | -0.284 | 0.080 | 0.160 | 0.360 |
| WSR                  | 0.182 | 0.249 | 0.182 | 0.249 | 0.360 | 0.110 | -0.134 | 0.409 | -0.732 | -0.156 | 0.148 | 0.364 |
| HOMA-IR              | -0.001 | 0.996 | 0.043 | 0.603 | -0.292 | 0.072 | -0.267 | 0.096 | 0.225 | 0.169 | 0.274 | 0.087 |
| s-CAT, mm            | 0.091 | 0.509 | 0.200 | 0.205 | -0.396 | 0.013 | 0.211 | 0.192 | 0.435 | 0.004 | -0.045 | 0.781 |
| Visceral Fat, %      | 0.122 | 0.441 | 0.234 | 0.136 | 0.135 | 0.413 | -0.120 | 0.462 | -0.108 | 0.513 | 0.128 | 0.432 |
| FBG, mg/dL           | 0.005 | 0.957 | 0.051 | 0.746 | -0.187 | 0.256 | -0.238 | 0.139 | 0.095 | 0.563 | 0.117 | 0.473 |
| Urea, mg/dL          | 0.009 | 0.955 | 0.025 | 0.863 | -0.195 | 0.248 | 0.019 | 0.908 | 0.147 | 0.385 | 0.081 | 0.619 |
| Creatinine, mg/dL    | 0.213 | 0.187 | -0.024 | 0.881 | -0.224 | 0.158 | 0.014 | 0.834 | 0.250 | 0.136 | 0.212 | 0.190 |
| Triglycerides, mg/dL | 0.043 | 0.709 | 0.149 | 0.348 | 0.179 | 0.176 | 0.175 | 0.379 | 0.015 | 0.737 | 0.151 | 0.352 |
| Cholesterol, mg/dL   | 0.320 | 0.044 | 0.029 | 0.715 | -0.174 | 0.303 | -0.243 | 0.336 | 0.223 | 0.184 | 0.195 | 0.234 |
| LDL-C, mg/dL         | 0.310 | 0.052 | 0.051 | 0.751 | 0.248 | 0.139 | 0.132 | 0.423 | 0.311 | 0.061 | -0.194 | 0.236 |
| HDL-C, mg/dL         | -0.146 | 0.356 | -0.049 | 0.759 | -0.184 | 0.282 | 0.141 | 0.387 | 0.086 | 0.601 | -0.073 | 0.654 |
| LDL to HDL, mg/dL    | 0.379 | 0.016 | 0.080 | 0.617 | -0.305 | 0.066 | 0.188 | 0.408 | 0.012 | 0.215 | 0.189 |
| Insulin, µU/mL       | 0.143 | 0.365 | 0.141 | 0.006 | 0.200 | 0.071 | -0.201 | 0.160 | 0.300 | 0.262 | 0.103 |
| WBC, ×10³/µL         | 0.155 | 0.183 | -0.155 | 0.335 | 0.881 | 0.054 | 0.064 | 0.080 | 0.657 | 0.163 | 0.526 |

WHR, waist-to-hip ratio; BMI, body mass index; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; VAI, visceral adiposity index; WBC, white blood cells; cIMT, carotid intima-media thickness.
Table 4. The correlation of CTRP1 & 5 circulating levels with anthropometric characteristics and biochemical data in total study population.

|               | CTRP 1 ng/mL |       | CTRP 5 ng/mL |       | CTRP 1/5 |       |
|---------------|--------------|-------|--------------|-------|----------|-------|
|               | r  | p       | r  | p       | r  | p       |       |
| CTRP 1 ng/mL  | 1  | 0.015   | 0.897 | 0.198 | 0.080 |
| CTRP 5 ng/mL  | 0.015 | 0.897 | 1 |       |       |
| CTRP 1/5      | 0.198 | 0.080 | -0.873 | 0.000 | 1 |
| Adiponectin, μg/mL | -0.152 | 0.169 | -0.121 | 0.289 | 0.161 | 0.157 |
| Age, years    | 0.0083 | 0.470 | 0.013 | 0.906 | 0.061 | 0.593 |
| SBP, mmHg     | -0.077 | 0.006 | 0.099 | 0.914 | -0.018 | 0.873 |
| DBP, mmHg     | 0.065 | 0.559 | -0.011 | 0.926 | -0.013 | 0.910 |
| VAI            | 0.189 | 0.093 | -0.155 | 0.135 | 0.091 | 0.457 |
| BMI, kg/m²     | 0.133 | 0.226 | 0.015 | 0.894 | -0.053 | 0.643 |
| WHR            | 0.374 | 0.013 | 0.020 | 0.860 | -0.007 | 0.954 |
| HOMA-IR        | 0.292 | 0.007 | -0.296 | 0.008 | 0.277 | 0.015 |
| cIMT, mm       | 0.205 | 0.063 | -0.122 | 0.784 | 0.280 | 0.020 |
| Visceral Fat, % | 0.213 | 0.051 | -0.012 | 0.893 | 0.025 | 0.829 |
| FBG, mg/dL     | 0.0105 | 0.340 | -0.219 | 0.052 | 0.130 | 0.732 |
| Triglycerides, mg/dL | 0.068 | 0.541 | -0.085 | 0.461 | 0.128 | 0.767 |
| Creatinine, mg/dL | 0.169 | 0.129 | -0.178 | 0.121 | 0.184 | 0.110 |
| Total cholesterol, mg/dL | 0.032 | 0.769 | -0.171 | 0.131 | 0.090 | 0.429 |
| LDL-C, mg/dL   | 0.201 | 0.071 | -0.199 | 0.085 | 0.212 | 0.066 |
| HDL-C, mg/dL   | 0.183 | 0.101 | -0.065 | 0.574 | 0.094 | 0.417 |
| LDL to HDL     | 0.165 | 0.352 | -0.035 | 0.762 | 0.018 | 0.874 |
| Insulin, μU/mL | 0.112 | 0.311 | -0.218 | 0.054 | 0.191 | 0.092 |
| WBC, x10⁹/L    | -0.103 | 0.359 | 0.014 | 0.904 | -0.063 | 0.586 |

WHR, waist-to-hip ratio; BMI, body mass index; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; VAI, visceral adiposity index; WBC, white blood cells; cIMT, carotid intima-media thickness.

Figures
Figure 1

Plasma concentrations of adiponectin (a), CTRP1 (b), CTRP5 (c), and CTRP1/CTRP5 ratio (d) in non-T2D and T2D groups. The data are presented as median (Interquartile range). T2D: Type 2 diabetes. Independent Student’s t-test on logarithmically transformed data was used to determine the differences of the adipokines between two groups.
Figure 2

ROC curve analysis of plasma levels of adipokines including a) CTRP1; AUC of 0.75 (p<0.0001, 95% CI 0.65-0.85), b) CTRP5; AUC of 0.60 (p=0.0945, 95% CI 0.48-0.73), and c) CTRP1/CTRP5; AUC of 0.73 (p=0.0945, 95% CI 0.61-0.83). ROC curve analysis determined the diagnostic value of these adipokines for T2D. CI: confidence interval, AUC: area under the curve, T2D: type 2 diabetes.

Figure 3

Linear regression plot regarding the correlation of (a) CTRP1 circulating levels and (b) CTRP1/CTRP5 ratio with cIMT in the whole population. R coefficients and p-value were displayed. Data for CTRP1 circulating levels were logarithmically transformed.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistcasecontrol1.doc