# Relationship of para- and perirenal fat and high-density lipoprotein and its function in patients with type 2 diabetes mellitus

**Jing Ke**
Beijing Luhe Hospital
**Yan Wang**
Beijing Luhe Hospital
**Simo Liu**
Beijing Luhe Hospital
**Kun Li**
Capital Medical University
**YueChao Xu**
Beijing Luhe Hospital
**Longyan Yang**
Beijing Luhe Hospital
**Dong Zhao** ( zhaodong@ccmu.edu.cn )
Beijing Luhe Hospital

**Original investigation**

**Keywords:** para-perirenal fat, high density lipoprotein, cholesterol efflux capacity, type 2 diabetes

**Posted Date:** March 10th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-16512/v1



**Version of Record:** A version of this preprint was published at International Journal of Endocrinology on December 22nd, 2021. See the published version at https://doi.org/10.1155/2021/9286492.

# Abstract

Background Para- and perirenal fat is a fat pad surrounding the kidneys. Recent researches have showed the association between para- and perirenal fat and cardiovascular diseases including atherosclerosis, hypertension and so on. Limited studies have explored the relation between para- and perirenal fat and serum high density lipoprotein (HDL) level, but the results were inconsistent. We aimed to assess the relationship between para-perirenal ultrasonographic fat thickness and serum HDL level and cholesterol efflux capacity of HDL in patients with type 2 diabetes mellitus (T2DM). Methods We recruited 58 subjects with T2DM and collected anthropometric indices including height, weight, waist circumference and so on. Para-perirenal ultrasonographic fat thickness (PUFT) was measured via ultrasound. Serum lipid profile and other metabolic indices were determined as well. Then we analyzed the relationship between PUFT and HDL level and cholesterol efflux capacity in all patients and subgroups divided by gender and body mass index (BMI). Results Patients with higher PUFT have lower serum HDL level but increased cholesterol efflux capacity of HDL. Further analysis showed that PUFT negatively correlated with serum HDL level in all patients, with no difference in group divided by BMI. While subgroup analysis divided by gender indicated that the relationship only existed in males. In addition, PUFT was positively correlated with cholesterol efflux capacity in all patients. However, subgroup analysis showed that PUFT did not significantly correlated with cholesterol efflux capacity in males and BMI ≥28kg/m 2 . Multiple stepwise regression analysis showed an independent association of PUFT and serum HDL level and cholesterol efflux capacity. Conclusions PUFT is closely correlated with serum HDL level and cholesterol efflux capacity in patients with T2DM.


# Background

Adipose tissue is commonly divided into visceral fat tissue (VAT) and subcutaneous fat tissue based on the anatomy and physiological features[1]. It has been thought that visceral fat was more related with metabolic and cardiovascular diseases[2, 3]. Previous research has demonstrated that adipose tissue in various locations had different enzyme histochemical traits[4], further studies showed that tissue-specific adipocytes were likely to associate with various diseases such as cardiovascular diseases, autoimmune diseases, infectious diseases, cancers, and so on[5]. Para- and perirenal fat is a fat pad surrounding the kidneys. It has complete system of blood supply, lymph fluid drainage, and innervation[6]. Several studies have reported the close relationship between para- and perirenal fat and cardiovascular diseases, including atherosclerosis, blood pressure, endothelial damage[7–10].

High density lipoprotein (HDL) carries the cholesterol in the surrounding tissue, and then converts it into bile acid or directly excretes it from the intestine[11]. Except lipid metabolism, accumulating evidence has showed that HDL was involved in the pathophysiology of diabetes, metabolic syndrome and cardiovascular diseases[12]. Patients with type 2 diabetes mellitus (T2DM) always accompanied by dyslipidemia, which is characterized by increased serum total cholesterol and decreased HDL level[13]. Lower serum HDL cholesterol level has been confirmed to be associated with increased risk of coronary artery diseases, while HDL has not been successfully exploited for therapy. One possible reason is its

complex functions[14]. Our previous work has suggested that HDL dysfunction including cholesterol efflux capacity and inhibitory on endothelial lipase existed in patients with T2DM[15]. Some investigators have explored the possible mechanism of the reduction of HDL level and its function in T2DM. Our further research has showed that patients with T2DM have lower serum HDL level and different components compared with non-T2DM patients[16]. In addition, adipokines including angiopoietin like proteins, have been thought to play important role in the regulation of HDL metabolism and its function[15, 16]. Para- and perirenal fat, as an unique fat tissue in its anatomy and biological functions, whether it has some association with HDL level and its cholesterol efflux capacity.

Limited studies have explored the relation between para- and perirenal fat and serum HDL level in obese subjects as well, while the results showed inconsistent. One study in obese patients found that perirenal fat thickness was lower and HDL cholesterol was higher after sleeve-gastrectomy surgery[17]. While another study in obese animal found the contrary results[18]. Based on the above background, this study aimed to explore the relationship between para- and perirenal fat and serum HDL level and cholesterol efflux capacity in patients with T2DM.

## Methods And Materials

# Study subjects

In this cross-sectional study, we recruited a total of 58 Han Chinese subjects from Beijing Luhe Hospital from September 2019 to January 2020. All subjects were diagnosed with T2DM according to the 1999 WHO criteria. The exclusion criteria were as follows: 1) acute or chronic hepatitis. 2) severe abnormal liver function, defined as liver enzyme ≥ 3 times normal value. 3) usage of lipid-lower medicine. 4) severe abnormal renal function, defined as estimated glomerular filtration rate (eGFR) < 30 ml/min per 1.73 $m^2$. 5) In pregnancy or lactation.

# Clinical And Laboratory Evaluation

Anthropometric and physical examinations were performed to collect body weight, height, waist and hip circumference in all subjects. Glycated hemoglobin $A1_C$ ($HbA_{1C}$), serum lipid profile, renal function, liver function, and albuminuria level were measured in the clinical laboratory of our hospital. The area of VAT at the level of the umbilicus was measured via an abdominal dual BIA machine with DUALSCAN HDS-2000 (OMRON Healthcare Co., Kyoto, Japan). eGFR were calculated using Chinese population-specific formula derived from the Modification of Diet in Renal Disease (MDRD) equation [GFR (mL/min/1.73 $m^2$) = 175 × $(Scr/88.4)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female)].

# Ultrasonographic Evaluation

Ultrasound examinations were performed by a single well-trained operator through a duplex Doppler (HITACHI Preirus, Hitachi, Japan). The operator was unaware of clinical data of all subjects. Para- and perirenal fat thickness was measured via a 1-to-5 MHz transducer on the abdomen in the subjects with inspiration state in supine position. The probe was slowly moved laterally until the optimal position, at which the surface of the kidney was almost parallel to the skin. The pressure exerted on the probe was as minimal as possible so that the fat layers were not compressed. Then, the para- and perirenal fat thickness was measured from the inner side of the abdominal musculature to the surface of the kidney. The average of measurements on both sides was defined as the para-perirenal ultrasonographic fat thickness (PUFT).

# Cholesterol Efflux Rate Examination

Cholesterol efflux assay was performed following the manual instruction (Biovision, CA, USA). RAW264.7 macrophages were plated at the density of 1 × 105 cells/well in a 96-well white plate and maintained in DMEM plus 10% FBS (Sigma-Aldrich) for 2 h. The adherent cells were incubated with labeled cholesterol for 16 h and then exposed to 100 μg/mL HDL for 4 h. The supernatant was transferred to a 96-well plate to measure the fluorescence (Ex/Em = 482/515 nm). The adherent cells were solubilized by cell lysis buffer to measure the fluorescence (Ex/Em = 482/515 nm). Cholesterol efflux % = fluorescence intensity of the media/(fluorescence intensity of the cell lysate + media) × 100%.

# Statistical analysis

Statistical analysis was first performed in the whole population, and then in two groups divided based on PUFT (PUFT < 2.08 cm, n = 29, PUFT ≥ 2.08 cm, n = 29 respectively). Continuous variables were expressed as mean ± standard deviation (SD), and the significance was tested by t-test. Triglycerides and uric acid were expressed as median and interquartile range because of its skewed distribution, and significance was tested by Mann Whitney U test. Chi-square test were used to analyzed the differences between male and female. The correlation between PUFT and anthropometric parameters with HDL level and cholesterol efflux rate was expressed by Pearson correlation coefficients (r). In addition, subgroup analysis was performed according to gender and BMI. Multiple linear regression analysis was used to evaluate the multivariate relationships. The stepwise multiple regression models were built on the whole population considering HDL and cholesterol efflux rate as response variables respectively, and including PUFT, BMI, WHR, VAT and these variables regarded as explanatory variables. Collinearity was assessed by calculating the variance inflation factor (VIF): Variables with VIF ≥ 2 were excluded from the models. $P < 0.05$ was considered statistically significant in all statistic analyses. The statistical analyses were performed using SPSS statistics software package, version 20.

## Results

# Clinical characteristics of subjects

The clinical characteristics of the whole population were shown in Table 1. Then we compared the clinical characteristics of the population divided into two groups based on PUFT (< 2.08 cm, n = 29, PUFT ≥ 2.08 cm, n = 29). HbA1c, triglycerides, uric acid, lower density lipoprotein (LDL) and eGFR were not different in the two groups. Subjects in higher PUFT group had higher BMI, WHR, VAT and longer diabetes course. And females may more likely had higher PUFT. Moreover, subjects who have higher PUFT had lower HDL cholesterol level and total lower cholesterol (Table 1).

Table 1
The basic clinical characteristics of the population.

| | **Whole population (n = 58)** | **PUFT < 2.08 cm (n = 29)** | **PUFT ≥ 2.08 cm (n = 29)** |
|---|---|---|---|
| Gender (M/F) | 29/29 | 10/19 | 19/10* |
| Age (years) | 54.69 ± 14.50 | 58.69 ± 12.29 | 50.69 ± 15.62* |
| Course of diabetes (years) | 7.47 ± 6.64 | 9.38 ± 6.73 | 5.55 ± 6.08* |
| BMI ($kg/m^2$) | 26.91 ± 4.75 | 24.65 ± 3.23 | 29.16 ± 5.00** |
| WHR | 0.97 ± 0.56 | 0.95 ± 0.41 | 0.98 ± 0.58* |
| VAT ($cm^2$) | 108.32 ± 40.31 | 90.31 ± 33.93 | 129.47 ± 37.33** |
| PUFT (cm) | 2.12 ± 0.82 | 1.46 ± 0.45 | 2.79 ± 0.51** |
| HbA1c (%) | 9.62 ± 2.13 | 9.52 ± 2.28 | 9.73 ± 2.01 |
| Total cholesterol (mmo/l) | 4.28 ± 1.32 | 4.65 ± 1.61.64 | 3.87 ± 0.66* |
| LDL cholesterol (mmol/l) | 2.78 ± 1.02 | 3.03 ± 1.25 | 2.52 ± 0.62 |
| HDL cholesterol (mmol/l) | 1.04 ± 0.24 | 1.13 ± 0.26 | 0.94 ± 0.19** |
| Cholesterol efflux rate (%) | 43.92 ± 9.17 | 40.76 ± 7.64 | 47.17 ± 9.49** |
| Triglycerides (mmol/l) | 1.56 (1.09, 2.12) | 1.29 (0.99, 2.06) | 1.77 (1.27, 2.17) |
| Uric acid (umol/l) | 333.00 (251.50, 399.75) | 306.83 ± 83.81 | 358.22 ± 112.31 |
| eGFR (ml/min per 1.73 $m^2$) | 97.92 ± 29.88 | 98.53 ± 33.96 | 97.31 ± 25.75 |
| BMI, body mass index; WHR, waist-to-hip ratio; VAT, visceral fat tissue; PUFT, para-perirenal ultrasonographic fat thickness; HbA1c, glycated hemoglobin $A1_C$; LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate. | | | |
| *P < 0.05; **P < 0.01 | | | |

Correlations between serum HDL and cholesterol efflux rate and anthropometric and metabolic parameters

The univariate correlations of HDL and cholesterol efflux rate and anthropometric and metabolic parameters in the entire population were shown in Table 2. Age and course of diabetes did not correlate with serum HDL level and cholesterol efflux rate. BMI, WHR and VAT were significantly negatively related with serum HDL level, while less than PUFT ($r = -0.42$, $P < 0.01$). BMI was not significantly associated with cholesterol efflux rate, while WHR and VAT were positively related with cholesterol efflux rate, even less than PUFT ($r = 0.43$, $P < 0.01$).

Table 2
Correlations between para-perirenal ultrasonographic fat thickness and anthropometric parameters with HDL level and cholesterol efflux rate in the whole population.

| | HDL level (mmol/l) | | Cholesterol efflux rate (%) | |
|---|---|---|---|---|
| | r | P | r | P |
| Age (years) | 0.20 | 0.14 | -0.12 | 0.39 |
| Course of diabetes (years) | 0.07 | 0.61 | -0.25 | 0.06 |
| BMI ($kg/m^2$) | -0.34 | 0.01 | 0.23 | 0.09 |
| WHR | -0.14 | 0.31 | 0.34 | < 0.01 |
| VAT ($cm^2$) | -0.24 | 0.10 | 0.31 | 0.03 |
| PUFT (cm) | -0.42 | < 0.01 | 0.43 | < 0.01 |

BMI, body mass index; WHR, waist-to-hip ratio; VAT, visceral fat tissue; PUFT, para-perirenal ultrasonographic fat thickness; HDL, high density lipoprotein.

Table 3
Independent multiple linear regression analysis of serum HDL level and cholesterol efflux rate. The other variables included in the models are described in the text.

| | β | P |
|---|---|---|
| HDL (mmol/l)[a] | | |
| Model ($R^2$ = 0.176) | | |
| PUFT (cm) | -0.115 | 0.009 |
| Cholesterol efflux rate (%)[b] | | |
| Model ($R^2$ = 0.121) | | |
| PUFT (cm) | 4.027 | 0.013 |
| HDL, high density lipoprotein; PUFT, para-perirenal ultrasonographic fat thickness. | | |

Then we separately analyzed the relationship between serum HDL and cholesterol efflux rate and anthropometric and metabolic parameters in males and females (Supplementary table 1). In males, PUFT were negatively related with serum HDL level (r = − 0.49, P < 0.01) but not cholesterol efflux rate (Fig. 1). In females, BMI was negatively related with serum HDL level (r = − 0.40, P < 0.05), which is more related than PUFT (r = − 0.28, P = 0.16). However, PUFT were positively correlated with cholesterol efflux rate (r = 0.65, P < 0.01) (Fig. 1B), which is more than BMI, WHR and VAT.

In addition, we performed a subgroup analysis of BMI (Supplementary table 2). WHR was positively related with cholesterol efflux rate in patients with lower BMI (r = 0.39, P = 0.02), which is less than PUFT (r = 0.53, P < 0.01). While no obvious relationship was seen in the patients with high BMI (Fig. 2).

# Multivariate Model For Hdl And Cholesterol Efflux Rate

Finally, we built multiple linear regression model considering serum HDL level as response variable and including PUFT, BMI, WHR, Visceral fat as explanatory variables. Only PUFT were independently associated with serum HDL level (β =- 0.115,P = 0.009). Similarly, another multiple linear model was built considering Cholesterol efflux rate as response variable, only PULT was left in stepwise procedure (β = − 4.027，P = 0.013). For the two models, collinearity was assessed by calculating VIF of the models, and there was no VIF > 10.

## Discussion

HDL cholesterol level and cholesterol efflux function of HDL play important roles in diabetes, metabolic syndrome and cardiovascular disease[12]. Previous studies on different diet or materials regulating lipid

metabolism indicated that the changes of plasma HDL cholesterol level and para- and perirenal fat content always inconsistent. For example, Lactobacillus fermentum CQPC05 isolated from Sichuan pickles could decrease perirenal fat index in high-fat diet mice, meanwhile plasma HDL cholesterol level reduced obviously[18]. Low dose doxycycline treated 6-week-old male db/db mice for 10 weeks showed that perirenal/epididymal fat index, and liver cholesterol reduced, but blood HDL cholesterol level increased[19]. A study about the potential variations after sleeve-gastrectomy of morbidly obese patients found that perirenal fat thickness was lower and HDL cholesterol was higher in postsurgery compared with presurgery[17]. The above study showed that there may be a certain relationship exist between HDL cholesterol and perirenal fat. Carlo Manno and colleagues reported that para- and perirenal fat but not epicardial adipose tissue was independently associated to insulin resistance and lower HDL cholesterol in a cohort of 102 uncomplicated overweight and obese patients[20]. In our study, we found the independent and negative association between PUFT and serum HDL level, and subgroup analysis showed the relation was more significant in male and obese diabetes. The results suggested that adipocytokines derived from para- and perirenal fat may lead to abnormal HDL metabolism and then affect HDL cholesterol level.

Besides reduced HDL level, the dysfunction of HDL in patients with T2DM has been revealed in our previous work[15]. Recent study indicated that high level of HDL cholesterol did not led to expected clinical benefits of cardiovascular system, which may due to the HDL dysfunction or altered HDL functions[14]. HDL function includes cholesterol efflux capacity, anti-inflammatory, antithrombotic, antioxidant, and vascular protective effects[21]. The cholesterol efflux capacity of HDL has been considered as the cardiovascular disease risk predictor independent of HDL cholesterol[22]. We evaluated cholesterol efflux capacity of HDL by in-vitro assay which measured the ability of an individual's HDL to promote cholesterol efflux from cholesterol donor cells such as macrophages. In this study, we found that PUFT was positively correlated with cholesterol efflux capacity of HDL in 58 subjects. PUFT was positively correlated with cholesterol efflux capacity of HDL in subjects with BMI $< 28$ kg/m$^2$, but has no correlation in subjects with BMI $\geq 28$ kg/m$^2$. Moreover, this positive relationship can also be seen in female subgroup but not in males. The reason may be that the increase of PUFT could stimulate the cholesterol efflux capacity of HDL in the condition of normal perirenal fat distribution. However, when perirenal fat accumulated abnormally, the cholesterol efflux capacity of HDL decreased due to the change of HDL components such as reduced levels of apoAI, apoAII, and higher levels of serum amyloid A (SAA). apoAI is a main component in cholesterol efflux capacity of HDL. SAA is an inhibitor of HDL anti-inflammatory function. It was reported that HDL function was decreased in CKD patients. HDL components isolated from CKD patients were changed by biochemical and mass spectrometry analyses, which demonstrated that levels of apoAI, apoAII, apoM, paraoxonase were decreased, and levels of serum amyloid A (SAA), apoCII, lipoprotein-associated phospholipase A2 were increased[23]. Our previous work indicated that the decrease of angiopoietin-like protein 3 level might contribute to the reduced capacity of cholesterol efflux in female T2DM patients[16]. It has been confirmed that angiopoietin-like protein 3 derived from liver and fat tissue, therefore, we guess the different distribution of para- and perirenal fat tissue may influence the HDL and its function via adipokines.

# Conclusions

In summary, our study showed that PUFT was independently and negatively associated with serum HDL level. And PUFT was independently and positively related with cholesterol efflux capacity. However, the underlying mechanism still need further research to illuminate it.

# List Of Abbreviations

T2DM, type 2 diabetes mellitus; BMI, body mass index; WHR, waist-to-hip ratio; VAT, visceral fat tissue; PUFT, para-perirenal ultrasonographic fat thickness; HbA1c, glycated hemoglobin $A1_C$; LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate.

# Declarations

### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Ethics Committee of Beijing Luhe Hospital. This article does not contain any studies with animals performed by any of the authors.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analysed 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

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Authors' contributions

SML recruited the subject and collected the clinical data. YCX measured the para- and perirenal fat thickness via the ultrasound. YW and LYY performed the cholesterol efflux experiments. JK and KL

performed the statistical analysis, JK and DZ were the major contributors in writing the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

Not applicable

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# Figures

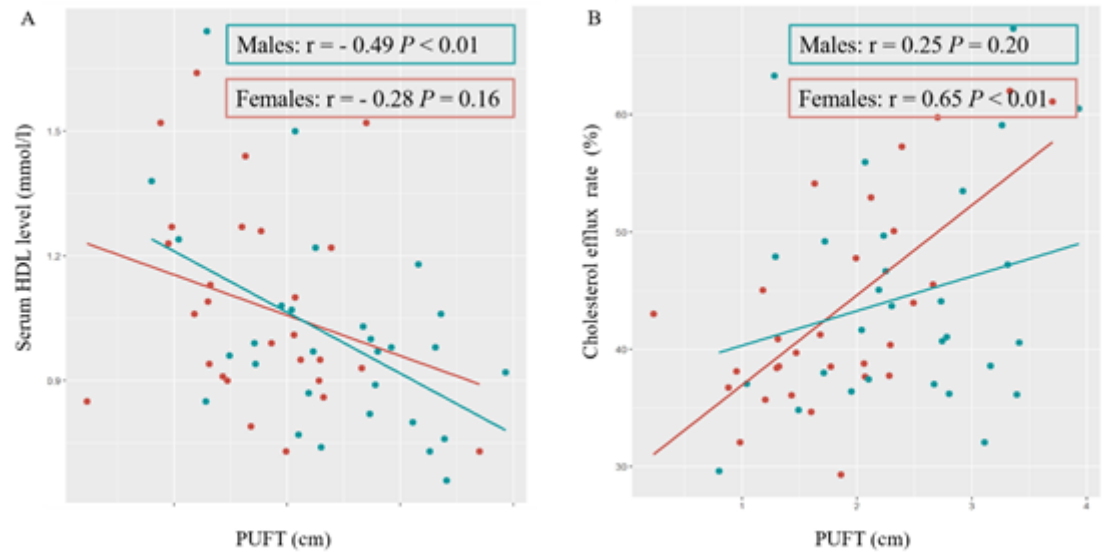


**Figure 2**

Correlations between para-perirenal ultrasonographic fat thickness (PUFT) and serum high density lipoprotein (HDL) level (A) and cholesterol efflux capacity (B) in the subgroup divided by gender.

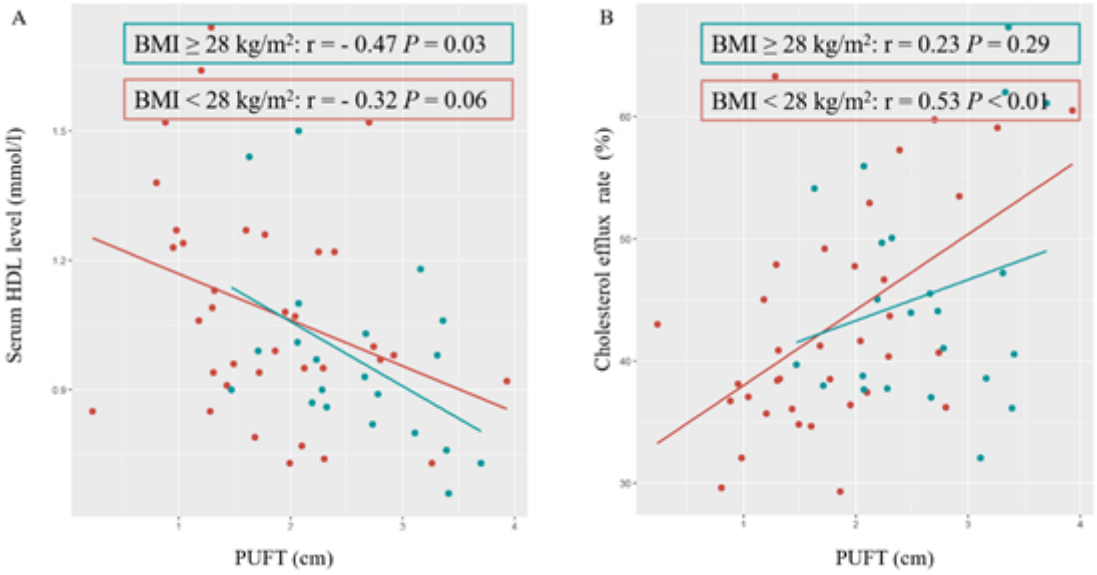


**Figure 4**

Correlations between para-perirenal ultrasonographic fat thickness (PUFT) and serum high density lipoprotein (HDL) level (A) and cholesterol efflux capacity (B) in the subgroup divided by body mass index (BMI).

# Supplementary Files

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