Dear Dr. Ma and Dr. Ying Dou,

I would like to thank the editors and reviewers for their careful assessment of our study; their suggestions have strengthened the manuscript. I hope that our responses and modifications to the manuscript will render our study acceptable for publication in this excellent journal.

Yours sincerely,

Best regards,

Xiaodong Sun

Reviewer 1:

Q1. PRAT may be regarded as part of lipotoxicity, i.e., the deposition of fat in non-adipose tissue sites in the presence of excess fat turnover. The authors propose a series of possible pathogenic mechanisms linking PRAT with CKD, as expressed in the figure, but I would like a larger discussion on point 2-4, i.e., the action of FFA, inflammatory adipokines and insulin resistance. Contrary to liver fat – a classical example of lipotoxicity – where fat enters the parenchymal cells, PRAT remains external to parenchymal cells. The possibility of a paracrine action was so far documented only in experimental animals (see, Li et al, Hypertension, 2016), and the independent correlation with CKD is vague. The association with insulin resistance is also more dependent on visceral fat as a whole than with PRAT.

Answer: Thank you very much for your review with valuable suggestions and remarks. We greatly appreciate the time you have contributed to the review process. We hope

that amending the manuscript according to your suggestions would meet your acceptance and enable publishing of our study in this excellent Journal.

According to your comments, we first revised the section of "Relationship between PRAT and CKD". Specifically, some discussions on point 2-4 have been added. And then, we deleted the description of paracrine action according to your suggestion. We also agree that the association with insulin resistance is more dependent on visceral fat as a whole than with PRAT. However, PRAT is also a part of visceral fat displaying characteristic of white-fat. Moreover, greater PRAT thickness has been associated with hyperinsulinemia (*Eating and weight disorders: EWD. 2019. 24(1): 67-72*). We revised this section highlighted with red mark.

Q2. The association of CKD and CVD is also driven by micro-macrovascular disease involving both the CV system and the kidney. I am not sure that PRAT may have any additional role.

Answer: Thank you for the valuable suggestions. There are some differences between PRAT and traditional visceral fat. First, PRAT is the only adipose tissue that is surrounded by a multilayered fibrous membrane. Because PRAT is surrounded by fascia tissue, excess PRAT can tightly encapsulate the kidney and cause excessive renal compression. Second, despite its origination from preadipocytes, PRAT constitutes a combination of white adipose tissue and brown adipose tissue, suggesting that PRAT can be converted to brown adipose tissue in cold conditions. Third, perirenal lymphatic vessels communicate with renal subcapsular lymphatic vessels and then drain into para-

aortic lymph nodes. These features allow interrelationships between kidney and PRAT, as well as between body function and PRAT, via secretion of adipokines and cytokines.

Q3. A few more data on the methodology of PRAT measurement by ultrasonography is important to increase the interest towards this easy-accessible site of lipotoxicity. We need to have data on reproducibility of measurement, as derived from the literature.

Answer: Thank you for the valuable suggestions. We have added the method of measurement and the data of PRAT thickness derived from the literature including our own study in the section of "***Assessment of obesity and PRAT"***.

Measurement of PRAT can be performed as following: keep the patient in the supine position; place the ultrasound probe vertically to the abdominal lateral surface skin above the kidney; obtain the ultrasound longitudinal scan of the kidney which is almost parallel to the skin. Gender pressure of the probe should be noticed during image obtaining in order not to cause extra adipose tissue pressing. PRAT thickness were then measured from the kidney surface to inner side of abdominal musculature. Average measurement of the maximum thickness values of both sides by three times was regarded as ultrasound measure. Kawasaki *et al.*[39] showed that PRAT thickness was positively correlated with visceral adipose tissue area and that PRAT thickness >10 mm could be regarded as visceral fat accumulation (area >100 cm^2). In a separate analysis, our research group found that the average of PRAT thickness in healthy people was 7.95mm and that in obese patients was 26.54 mm[17]. And PRAT was positively associated with body mass index and waist circumference; thus, sonographic evaluation

of PRAT thickness could be used to assess visceral fat and predict early renal injury in patients with obesity[17]. Lamacchia *et al.* [22] measured PRAT thickness in normal subjects (8±2 mm for men and 5±2 mm for women), which were validated by computed tomography measurements. With the same method, De pergola *et al.*[40] found an average value of PRAT in obese patients with BMI above 30 kg/m^2 was 25.0 mm. Ricci *et al.*[41] verified that PRAT was statistically different between hypertensive and nonhypertensive patients, with average value of 13.6 and 11.6 mm, respectively.

Q4. The authors claim that PRAT might be a therapeutic target against obesity-related disease. They conclude that PRAT might be tackled by balanced diet, intermittent exercise, other therapeutic interventions. What is the difference between tackling PRAT and tackling any type of body fat?

Answer: Thank you for the valuable suggestions. This is really a good question. PRAT and abdominal visceral fat are different. Contrary to traditional visceral fat, PRAT have characteristic of both brown- and white-fat. PRAT is phenotypically close to brown adipose tissue, and shares its unique functional characteristics. We also have added a paragraph discussing about the effects of current therapeutics used to treat CKD and CVD on PART (**Prospective Therapeutic Strategies).**

References：

Efremova A, *et al*. A large proportion of mediastinal and perirenal visceral fat of Siberian adult people is formed by UCP1 immunoreactive multilocular and paucilocular adipocytes. Journal of physiology and biochemistry. 2019 .

Jespersen NZ, *et al*. Heterogeneity in the perirenal region of humans suggests presence of dormant brown adipose tissue that contains brown fat precursor cells. Molecular metabolism. 2019. 24: 30-43.

Warner A, *et al.* Activation of β3-adrenoceptors increases in vivo free fatty acid uptake and utilization in brown but not white fat depots in high-fat-fed rats. American journal of physiology. Endocrinology and metabolism. 2016. 311(6): E901-E910.

Q5. Ref. 73 should read “Ricci et al”

Answer: Thank you for the valuable suggestions. We are sorry for the error and have revised it.

Reviewer 2:

Q: This review focused on the relationships between perirenal adipose tissue (PART) and CKD and CVD. In addition, authors further summarized potential mechanism of actions. I think this manuscript is informative. However, if authors can provide a paragraph which is discussed about the effects of current therapeutics which are used to treat CKD and CVD on PART, the manuscript will become even more attractive for the readers in the field of drug development.

Answer: Thank you very much for your review with valuable suggestions and remarks. We greatly appreciate the time you have contributed to the review process. We hope that amending the manuscript according to your suggestions would meet your acceptance and enable publishing of our study in this excellent Journal.

According to your comments, we have added a paragraph discussing about the effects of current therapeutics used to treat CKD and CVD on PART (**Prospective Therapeutic Strategies).**

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