



## Perirenal Adipose Tissue: Clinical Implication and Therapeutic Interventions

### Abstract

Perirenal adipose tissue (PRAT) has been identified as an important factor in local and general homeostasis of the human body and is especially important in regulating renal and cardiovascular functions. It has also been identified as a crucial risk factor to consider in cardiovascular and renal disorders, malignancies, and various other diseases. Having a concrete idea of the effects of therapeutic interventions on the size and metabolism of the PRAT could prove highly beneficial. This review summarizes what is known about the PRAT and provides a collection of studies on the effects of therapeutic interventions on PRAT and its related diseases. We used papers written on a variety of subjects, mainly concerning adipose tissue and the effects of therapeutic procedures on it. Our main challenge was to excerpt the information specifically related to the PRAT in these papers. These effects vary greatly, from an increase or decrease in mass or size of the PRAT to changes in metabolism and drug residue accumulation. The current studies often fail to consider PRAT as an individual subject of research and only examine the adipose tissue of the entire body as a whole. This leads us to believe this field could benefit greatly from further research.

**Keywords:** *Perirenal adipose tissue; Adipose tissue; Cardiovascular diseases; Obesity; Renal pathology; Interventions*

### Introduction

Adipose tissue typically represents 20–25% of the body weight in healthy adults. Its functions are: storing neutral fats (mainly triglycerides), acting as regulators of the body's energy metabolism, thermogenesis, and protection against trauma. Excessive adipose tissue leads to obesity, which can be treated by exercising, a healthy diet, and therapy.

The perirenal adipose tissue (PRAT) surrounds each kidney and is located between the kidney's capsule and fascia. PRAT's endocrine and paracrine activities play a significant role in local and systemic homeostasis. In addition, PRAT can affect the pathology of multiple diseases, which will be discussed later in this paper.

Although the anatomy and morpho-physiology of the PRAT itself and its implications in clinical complications such as whether abnormalities of the PRAT should be considered as risk factors in cardiovascular and renal diseases have been studied in detail, the effects that therapeutic interventions have on its size

and anatomy are relatively new fields of study and have much room for extensive research.

This study aims to compile the existing research on these subjects to identify better the fields that require further research.

### Materials and Methods

We review and summarize the current information about the PRAT, its role in causing diseases, and ways to prevent its adverse effects. The keywords "Perirenal adipose tissue; Adipose tissue; Cardiovascular diseases; Obesity; Renal pathology; Interventions" were searched in various databases, including ISI Web Of Science, PubMed, Google Scholar, and Scopus. Related English articles published till 2022 were reviewed. Because of this field's ever-changing knowledge, the focus was mainly on papers after 2010.

### The adipose tissue

There are three types of adipose tissue: white, brown, and beige. Each has specific

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morphological features. What they all have in common are adipocytes, preadipocytes, pericytes, inflammatory immune cells, blood vessels, and nerve endings.<sup>1</sup>

The human body fat is mainly made of white adipose tissue (WAT), found in subcutaneous and visceral areas [such as around the gonads, epicardium, retroperitoneum, mesentery, omentum, and the kidneys (perirenal)].<sup>2,3</sup> WAT stores energy in the form of triglycerides, which then can be decomposed into free fatty acids and glycerol during the lack of food.<sup>4</sup> WAT has also been associated with obesity and its relative complications.<sup>5</sup>

In adults, the brown adipose tissue (BAT) exists only in scattered areas around the kidneys, adrenal glands, aorta, and mediastinum. Its brown color is due to blood vessels and mitochondria filled with cytochrome pigmentations. BAT burns fatty acids which lead to heat production. Thermogenin or uncoupling protein-1 (UCP-1) is known to mediate this heat-producing process.<sup>6</sup> Contrary to prior knowledge about BAT, it is known today that this tissue is not only active in babies but has an essential role in adults as well. Some studies have shown that BAT plays a pivotal role in thermogenesis, clearance of triglyceride and glucose disposal, secreting adipokines, with a distinct inflammatory characteristics in comparison to WAT as well as thermogenesis.<sup>7</sup>

A new type of adipocyte has been discovered recently, which shows different gene expressions from white or brown adipocytes. These brown-like cells found among WAT, especially in the inguinal area, were named beige or brite (“brown in white” adipocytes or inducible brown adipocytes).<sup>5</sup>

WAT structures can gain BAT-like features. This process is called browning and is done in response to appropriate stimuli. The primary regulators of BAT development are PRDM16, PPAR $\gamma$ , and PGC-1 $\alpha$ . WAT adipocytes take on characteristics of BAT like expressing UCP-1, multilocular lipid, and many mitochondria.<sup>8</sup> This reverses their role as energy-storages to energy-releasing entities. Some regulators such as Irisin and FGF21 are secreted from muscles due to exercising.<sup>9-11</sup> FGF21 is a hormone mainly

produced in the liver, identified as a regulator for the browning process by affecting PGC-1 $\alpha$ .<sup>12</sup> It can increase by being exposed to cold.<sup>13</sup> Some characteristics of white and brown adipose tissues are mentioned in Table 1.<sup>14</sup>

**The PRAT**

There are three sections of visceral adipose tissue around each kidney. PRAT is the adipose tissue surrounding the kidney and the adrenal glands, situated between the renal capsule and the renal fascia in the retroperitoneum. The renal sinus fat is the adipose tissue situated in the medial border of the kidneys, encompassing the renal blood vessels, nerves, and lymphatic vessels, and could be considered a part of the body’s perivascular adipose tissue and has a role in controlling blood pressure.<sup>15,16</sup> Lastly, the paranephric adipose tissue surrounds the PRAT, being located outside of the renal fascia (Gerota’s fascia).<sup>8,17</sup>

PRAT has the exact fetal origin as typical visceral fat.<sup>18</sup> However, it has unique characteristics: a complete blood supply system, lymph drainage, and innervation.<sup>19-21</sup> This makes it similar to internal organs rather than other connective tissues. The abdominal aorta’s branches, including inferior adrenal, gonadal, left colic, renal, and lumbar, generate an anastomosing capillary network for the PRAT.<sup>22,23</sup> Its nerves originate from the celiac, superior mesenteric, ipsilateral inferior mesenteric, adrenal, aortic, renal, ovarian, and testicular nerves, and the ipsilateral sympathetic chain ganglia.<sup>24</sup> Perirenal lymphatic vessels end in subcapsular vessels and para-aortic nodes.<sup>25</sup> These features form the connection between the kidney and PRAT.<sup>26</sup> In addition, compared to subcutaneous adipose tissues, the proportion of saturated fatty acids is higher in PRAT.<sup>27</sup>

Studies on PRAT adipogenesis have shown that preadipocytes in the perirenal area do not express endothelial markers such as CD31 or hematopoietic stem cell markers like CD45, but are positive for CD90 and CD166.<sup>28</sup>

Morphologically speaking, PRAT consists of a combination of WAT and BAT, along with a combination of mesenchymal

**Table 1: Characteristics of white and brown adipose tissues<sup>14</sup>**

|                                  | White adipose tissue   | Brown adipose tissue   |
|----------------------------------|--|--|
| Morphology                       | Unilocular adipocytes<br>Fewer mitochondria compared to BAT                                      | Multilocular adipocytes<br>More mitochondria compared to WAT |
| Function                         | Energy storage, food supply during fasting   | Thermogenesis, inflammatory functions                        |
| Main origin                      | Myf5-negative cells  | Myf5-positive cells  |
| Association with diseases        | Increased risk of obesity-related diseases   | Decreased risk of obesity-related diseases                   |
| Proportion in adults vs. infants | Higher in adults   | Higher in infants  |
| Areas in the body                | Under the skin – around the gonads, epicardium, retroperitoneum, mesentery, omentum, and kidneys | Around the kidneys, adrenal glands, aorta, and mediastinum   |

BAT: brown adipose tissue, WAT: white adipose tissue

stem cells, inflammatory stem cells, preadipocytes, capillaries, and nerves.<sup>8</sup> In fetuses and babies younger than 11 months, BAT forms the majority of PRAT while WAT only exists as a thin outer layer;<sup>26</sup> that is, until the brown adipocytes start developing into unilocular white adipocytes, leading to brown cells only existing as small cellular clusters in the WAT. At this time, about 40% of PRAT has a typical brown adipocyte morphology, while about 30% expressed UCP-1.<sup>29</sup> Furthermore, in adults, these brown adipocytes are mostly in a dormant state and active brown adipocytes are only seen in areas with a high number of sympathetic nerve endings.<sup>28</sup> SPARC and CLSTN3 have been known for the dormant and multilocular BAT states, respectively.<sup>28</sup>

The adipocytes of the PRAT have a significant role in homeostasis due to their role in the secretion of various adipokines or cytokines (adiponectin, leptin, resistin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), visfatin, interleukin-6 (IL-6), and IL-1 $\beta$ ), which are regulators for the kidneys.<sup>8,30</sup> Leptin and adiponectin are also known to link obesity to high blood pressure and chronic kidney diseases (CKD).<sup>31</sup>

PRAT has a large number of mesenchymal stem cells (MSCs) and like other MSCs found in other fat tissue depots have the potential to differentiate into adipocytes, or otherwise, osteogenic, chondrogenic, and epithelial cells. Recent studies have shown that in the presence of inflammatory factors produced by the body's immune system, such as IL-1 $\beta$ , IFN $\gamma$ , and TNF- $\alpha$ , these MSCs express an immunoregulatory response. Moreover, secretion of IL-6 and IL-8 by these MSCs could be stimulated by TNF- $\alpha$  which is associated to enhanced angiogenesis in experimental model. The immunosuppressive features of the MSCs hosted in PRAT can be enhanced by IL-6, TNF- $\alpha$ , and IFN $\gamma$  in vitro. These observations may suggest a possibility of using MSCs in therapeutic interventions for inflammatory disease, tissue injuries, and cardiovascular and renal diseases.<sup>3</sup>

Quantifying PRAT's size is done by ultrasound, magnetic resonance imaging, and computer tomography;<sup>26</sup> the second and third options are considered unsuitable due to being expensive and time-consuming and exposing the patient to radiation. PRAT thickness in healthy people

is 7.95 mm on average.<sup>32</sup> And, amounts greater than 10 mm (or area greater than 100 cm<sup>2</sup>) are considered fat accumulation.<sup>33</sup>

Perirenal fat has weak relations with BMI.<sup>32</sup> Moreover, the PUFT measure (the thickness of perirenal fat, evaluated by ultrasound method) correlates more with total and visceral fat.<sup>34</sup>

### PRAT in the population

Men tend to have more significant perirenal fat than women.<sup>35</sup> However, PRAT in females has a higher potential to gain BAT-properties than males. The degree of the browning depends on sex-specific and environmental factors such as temperature (6). It was shown in a study that the presence of Y-chromosome suppresses the expression of UCP-1.<sup>36</sup>

Analyzing the UCP-1 gene expression revealed significant variations of the PRAT in the population. Both dormant and active BATs were detected in several individuals. This analysis identified 54 overexpressed genes in UCP-expressing cells. A set of genes with high correlation to UCP-1 had been revealed by Real-time PCR analysis of BAT. Some genes of transcription factor i.e. PRDM16, PGC1a, RXRc were highly correlated to each other.

Brown adipocytes showed nuclear immunoreactivity of RXRc. Brown adipogenesis was associated with increased gene expression of RXRc in human stem cells.<sup>37</sup>

### PRAT's association with other diseases

Obesity is associated with cardiovascular disease (CVD) and CKD.<sup>26</sup> Moreover, PRAT may be considered as a connection between these two. These complications, among others, will be discussed in the following.

### Renal diseases

PRAT has a closer relation with renal disease and CVD than other visceral fat. Furthermore, it is considered a risk factor for CKD making the risk 2–3 times greater.<sup>38</sup> It may even connect CVD and CKD.<sup>26</sup> Figure 1 demonstrates some possible pathways of PRAT causing CKD.

Para- and perirenal fat thickness can be considered predictors of renal dysfunction in type-2 diabetes, and

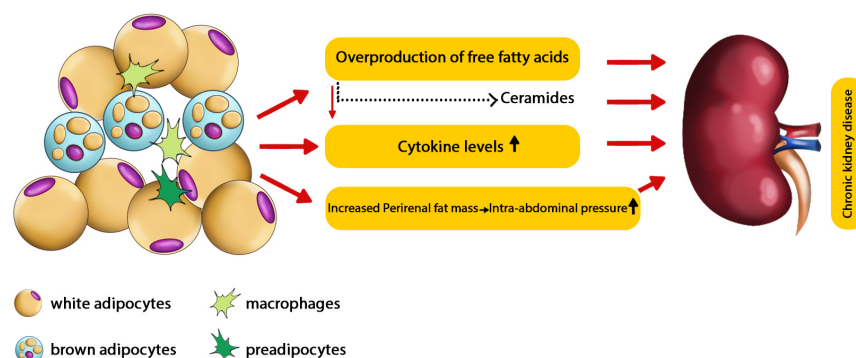


Figure 1: Possible pathways of perirenal adipose tissue causing chronic kidney disease.<sup>48</sup>

being an essential piece of the inter-individual variability of glomerular filtration rate (GFR), renal resistance index, and uricemia.<sup>39</sup>

High PUFT is associated with a low GFR<sup>34</sup> and shows the risk of developing arterial hypertension and chronic renal diseases.<sup>25</sup>

Obesity can cause proteinuria and glomerulopathy in nonproteinuria patients with renal dysfunction.<sup>40-42</sup> PRAT is larger in obese patients with albuminuria,<sup>23</sup> which is caused by the overproduction of free fatty acids (FFA).<sup>32,43</sup>

The amount of FFAs in renal and jugular venous blood was compared, and the results showed lower amounts of FFAs in the jugular vein, which indicated that the overproduced FFAs acted as kidney-damaging factors. This impact is caused either directly or indirectly via mediators.<sup>44</sup> These FFAs also cause lipotoxicity in kidneys (resulting in chronic inflammations) by FFA metabolites, such as ceramides.<sup>43</sup>

The inflammatory result of FFAs can lead to an imprudent amount of cytokine secretion,<sup>45,46</sup> causing NO imbalance in the endothelium and renal arterial dysfunction.<sup>47</sup>

Due to the fascia surrounding PRAT, an increase in perirenal fat accumulation and intra-abdominal pressure can compress the kidneys, increasing sodium absorption and blood pressure. It also leads to increased hydrostatic pressure of renal interstitial fluid and reduced flow rates of renal blood and tubular fluid.<sup>41,48</sup>

Radiological renal positioning<sup>49</sup> and staging clear cell renal carcinoma (ccRCC)<sup>50</sup> can be done by evaluating the PRAT. PRAT's measurement, tumor location, and age are notable predictors of clear cell renal carcinoma's histopathology.<sup>51</sup>

Fat stranding is an increase in attenuation, which can be seen in infections, inflammations, malignancies, or traumas.<sup>52</sup> Perinephric stranding is seen as the appearance of edema within the PRAT on CT or MRI.

Some degrees of symmetric bilateral perinephric stranding are common in older people. However, the asymmetric or unilateral form is an important sign of kidney inflammation or acute obstruction (like acute pyelonephritis and ureteric calculi). An association with bladder outlet obstruction has also been suggested.<sup>53</sup>

A study on 174 patients established a relation between PRAT size and ccRCC, caused by the anatomical relations between these two structures.<sup>54</sup> Another study has concluded that PRAT's high amounts of UCP-1 production make a bad prognosis for clear cell renal carcinoma. This study also compares PRAT's characteristics in healthy people and clear cell renal carcinoma patients, showing the following results: A reduction in HOXC8 and HOXC9 genes expression and an unchanged expression in TBX1, TMEM26, CD137, ADIPQ, and LEP. These results indicate a browning process in clear cell renal carcinoma patients' PRAT.<sup>55</sup>

### **Cardiovascular diseases**

Increased PRAT size is associated with a high risk for cardiovascular and metabolic complications.<sup>56,25</sup>

Many studies have shown a correlation between CKD and CVD; therefore, a connection between albuminuria and CVD can be assumed.<sup>57-59</sup>

Metabolic complications caused by PRAT such as diabetes or dyslipidemia tend to increase the risk of CVDs indirectly.<sup>26</sup>

This fat layer may relate to epicardial fat because of the common features it has with mesothelial layers of visceral organs enriched in WAT progenitors producing adipocytes.<sup>60</sup>

Fat storage in the renal sinus has been related to acute and chronic hypertension.<sup>61</sup> A study has shown that fat storage in the renal hilum and PRAT compresses the lymphatic and venous vessels and the ureters, resulting in the activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) activity; this will increase the hydrostatic pressure and lead to hypertension, resistance to insulin, and atherosclerosis.<sup>56,62,63</sup>

Adipose tissue nerves affect the SNS by a negative feedback loop (reflex). PRAT increases the renal sympathetic outflow by this means, causing higher arterial blood pressure.<sup>64</sup> A study has suggested that PRAT directly regulates the cardiovascular system. This was indicated as a result of leptin injection in PRAT, which activated the reflex without increasing the activator substances.<sup>65</sup>

However, endothelial injury is known to be the initiator for CVD,<sup>26</sup> which is caused by the same processes described in the subsection "Renal diseases."

### **Other complications**

Greater PRAT thickness measures tend to relate to dysfunction in the regulation of glucose homeostasis, such as impaired levels of fasting glucose increased insulin resistance and high triglyceride and uric acid levels in CKD patients.<sup>60,66</sup>

PRAT surface area, measured by CT scans, is used for preoperative assessments. Its median is calculated to be 24 cm<sup>2</sup>. A study showed that patients with bigger PRAT areas may have some risk by undergoing colon cancer surgery. Patients with PRAT  $\geq$  40 cm<sup>2</sup> had longer operations, bled more during the operation, had to undergo the operation twice, and suffered from surgical and nonsurgical complications. However, they didn't differ from PRAT < 40 cm<sup>2</sup> patients in terms of the need for intensive care or the time they stayed in the hospital.<sup>67</sup> However, another study concluded that the PRAT area is not an important indicator of negative results in rectum cancer patients who undergo laparoscopic surgery.<sup>68</sup>

Obesity has been known to be an important risk factor for cancer. Malfunction of the adipose tissue is a source for excessive amounts of cytokines, growth factors,

and adipokines that link to tumor cell growth in these patients.<sup>69-71</sup>

The factors involved in tumor progression induced by PRAT are high amounts of UCP-1, low amounts of HOXC8&9 expression, browning, and cachexia as a result and adipokines and cytokines produced by the dysfunctioning PRAT.<sup>55,48</sup>

Older male patients with symptoms in the lower urinary tract tend to show severe PRAT stranding in their CT scans. The stranding's severity is related to the level of bladder outlet obstruction and diminished kidney function.<sup>53</sup>

Peri- and pararenal fat thickness is a marker for the presence and severity of a fatty liver.<sup>33</sup>

Occlusive carotid artery disease is caused by atherosclerotic plaques that narrow or completely block the artery's blood flow and increase the risk of stroke. HIV infection can lead to this, and the ophthalmic artery resistance index (OARI) is an index of this disease in HIV-1 positive patients. A study indicated that assessing PRAT's thickness via ultrasound (PRFT) might indicate endothelial damage (particularly of the vascular area of the eyes) in these patients.<sup>72</sup>

In research about approaches to pediatric simple renal cysts (which included the PRAT wadding technique), the cysts were filled with perirenal fat tissue after deroofting and seemed to reduce recurrence.<sup>73</sup>

**PRAT's pathologies**

Perirenal aortic atherosclerosis starts in the early stages of life. Furthermore, it has similar plaque morphologies to

coronary atherosclerosis. However, its macrophage content tends to differ site-specifically.<sup>74</sup>

Nontraumatic perirenal hematoma is an uncommon condition in which severe cases can lead to shock. Bevacizumab treatment is known to be related to many bleeding complications; therefore, a study suggested an association between PRAT hematoma and Bevacizumab.<sup>75</sup>

Adherent perirenal fat (APF) is defined as an inflammatory fat that surrounds the kidney. Measuring PRAT's thickness via CT scan can predict APF. This condition challenges kidney surgery by making the dissection difficult, which increases the duration of PRAT dissection and surgery.<sup>76</sup> Figure 2 summarizes PRAT's association with other diseases.

**Therapeutic interventions**

As several studies have concluded, high PRAT mass leads to CVD, CKD, and other disorders. A series of materials, diets, diseases, and interventions which decrease PRAT mass are reviewed and categorized in the following sections and summarized in Table 2.

**Pharmaceuticals**

**Pharmaceuticals which were not proven to have any decreasing effect**

Animals chronically treated with olanzapine (±6.5 mg/kg/day, orally administered) had an increase in serum leptin and PRAT weight.<sup>77</sup>

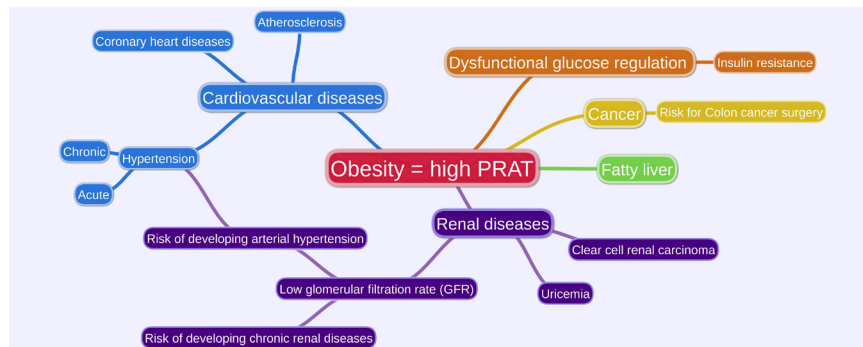


Figure 2: Perirenal adipose tissue (PRAT)'s association with other diseases.

Table 2: Currently known interventions reducing perirenal adipose tissue

| Pharmaceuticals                     | Herbals/others              | Complementary                        | Lifestyle          |
|-------------------------------------|-----------------------------|--------------------------------------|--------------------|
| Olanzapine                          | Kurozo                      | Acupuncture at the Fengiong Acupoint | Dining twice a day |
| Beta-3 adrenergic receptor agonists | Green tea                   | Electroacupuncture                   | Low-calorie diet   |
| Telmisartan                         | Lysimachiafoenum-graecum    | Cold exposure                        |                    |
| Betulonic acid                      | Palmiwon                    |                                      |                    |
| Evodiamine                          | C. Tumida                   |                                      |                    |
| Quasimodo                           | Nelumbiris semen            |                                      |                    |
|                                     | Fructus Schisandrae Aqueous |                                      |                    |
|                                     | Fish oil                    |                                      |                    |

Statins are used for treating hypercholesterolemia. A study scrutinized its effect on body fat and concluded that it does not decrease intra-abdominal fat (including PRAT).<sup>78</sup>

The thiazolidinediones are a class of compounds that lower blood glucose in diabetic rodent models. A study examined the effect of thiazolidinedione PIO (pioglitazone) on UCP mRNAs in brown PRAT of mice. The treatment caused the BAT, UCP, and  $\alpha 2$  mRNAs to increase in all models and also decreased the serum glucose and insulin levels, 2 and 5.5 times, respectively, in some of the mice (the ob/ob).<sup>79</sup>

Treatment with PIO has shown to increase bromodeoxyuridine (BrdU) levels in subcutaneous mature adipocytes (not visceral fat including PRAT) and increase the number of small adipocytes and proliferation in these areas. However, visceral adipocytes absorbed BrdU more actively than subcutaneous areas.<sup>80</sup>

Combination therapy with canagliflozin and pioglitazone has shown to reduce high levels of glucose and insulin in obese, type-2 diabetes patients. The addition of canagliflozin prevents glucotoxicity and reduces the weight gain caused by PIO; therefore, it improves insulin sensitivity.<sup>81</sup>

A study worked on the effects of liraglutide and PIO on mice. Perirenal, inguinal, and epididymal fats and body weight showed to be larger and more in PIO-treated mice rather than the mice which were treated with a vehicle. However, combining the two drugs caused the most weight gain amongst all models because of the glucosuria reduction causing improved balance in energy.<sup>82</sup>

Adipose tissues secrete leptin which can be used to indicate the total mass of adipose tissues along with the PRAT mass.<sup>83</sup> Anthocyanins (ACNs) from many ingredients have proven to reduce obesity in some animals. A study has compared the outcomes of purified black raspberry (BRB) ACNs and freeze-dried whole BRB feeding on developing obesity. But there was no decrease in serum leptin (related to the amount of adipose tissues) in purified ACN-treated models (which had a high-fat diet).<sup>84</sup>

#### **Pharmaceuticals with a decreasing effect**

Mice fed with a standard or high-fat diet were given intraperitoneal Standardized Quassinoids-enriched fraction (SQEL) at 5 mg/kg and 10 mg/kg doses concurrently for 12 weeks. The results indicated that SQEL suppresses weight gain and decreases PRAT mass.<sup>85</sup>

Erdheim-Chester disease (ECD) is a rare and fatal multi-system disease of adulthood. It is characterized by excessive proliferation and accumulation of histiocytes, a type of macrophage. Its most prominent cause of death is cardiovascular complications.<sup>86</sup> In 30% of cases, there is renal involvement due to fibrotic tissue being deposited in the PRAT. For this reason, analyzing the PRAT for infiltrates is the gold standard for ECD's diagnosis. A study on mice showed that oral administration of evodiamine, an alkaloidal chemical compound extracted from *Evodia* fruits

(*Evodia rutaecarpa*), at 0.03% and 0.02% of the diet for days resulted in a considerable reduction in the PRAT mass. Furthermore, increased lipolysis in the PRAT and specific GDP binding in BAT mitochondria (considered a biological index of increased heat production) were observed.<sup>87</sup>

Betulinic acid is a pentacyclic triterpenoid that has been a research target for anti-cancer usage. In research on CD-1 mice, the distribution of betulinic acid in PRAT after 24 hours of the intraperitoneal administration was the highest among other targeted tissues.<sup>88</sup>

Telmisartan is an oral medication for treating high blood pressure. A study on this medicine's effect on a high-fat diet has shown improvement in insulin resistance and dyslipidemia, and due to an increase in the expression of adiponectin mRNA, elevated serum adiponectin levels. Moreover, it caused a reduced PRAT mass (which would typically increase due to a high-fat diet). This study suggested a connection between PRAT and hypertension (caused by high fat intake), and Telmisartan has been suggested as a candidate choice for its treatment.<sup>89</sup>

#### **Complementary and herbal medicine**

In a study on rats, Kurozu concentrated liquid (KCL) was orally administered to them at a 100 mg/kg dose. It caused a decrease in the size of adipocytes by preventing fat absorption in the gastrointestinal tract and reducing the expression of PPAR $\gamma$  and  $\alpha 2$  mRNA in the fat cells. This resulted in a higher number of small adipocytes in the PRAT and, consequently, a reduction in PRAT size.<sup>90</sup>

Supplementation of green tea extract (GTE) significantly reduced perirenal and total WAT weights.<sup>91</sup>

Dose-dependent treatment of high-fat diet (HFD) mice with *Lysimachia foenum-graecum* extract (LFE) showed inhibition in adipogenesis and lipid metabolism and resulted in the reduction of the weight of WAT. This marks LFE as a therapeutic option for obesity.<sup>92</sup>

Palmiwon reduces perirenal fat accumulation by preventing lipid accumulation as a whole and, therefore, may be considered as a therapeutic option for hyperlipidemia.<sup>93</sup>

Dietary ingestion of immature *C. tumida* peels suppressed body weight gain following decreased perirenal fat weights.<sup>94</sup>

Nelumbinis semen (NS) powder supplementation has been shown to reduce the perirenal fat weights significantly.<sup>95</sup>

A study showed lower PRAT amounts in sorghum extract-administrated mice rather than the control group (which both were on a high-fat diet), and a higher PPAR- $\gamma$  and adiponectin expression. However, TNF- $\alpha$  was significantly expressed less in these mice.<sup>96</sup>

Feeding mice on agaropectin-derived oligosaccharides (SAOs) in a study has resulted in a decrease of body weight and adiposity index. SAOs also reduced lipid accumulation in the liver, PRAT, and epididymal fat tissues.<sup>97</sup>

In a study, Fructus Schisandrae aqueous extract (FSE) treatment alone reduced the weight gain and increase in fat pad mass (including PRAT) caused by dietary habits, which makes FSE a potential preventive substance for controlling weight.<sup>98</sup>

Electroacupuncture intervention (a form of acupuncture in which a small electric flow passes between two needles) has been proven to reduce weight. However, it has different amounts of effects based on gender. The effect on perirenal fat weight is more significant in male obese rats.<sup>99</sup>

### Preventive measures

By having a healthy lifestyle, regular exercise and a controlled diet, obesity can be prevented or treated.

Restricting calories, dining twice a day, having fish oil included in the diet, and etc., are some examples of dieting that can help reduce PRAT.<sup>100-102</sup>

A study on rats had them develop a metabolic syndrome by feeding them high-fat-salt food, and then some groups had to run on a treadmill. In conclusion, this aerobic exercise increased PPAR $\alpha$ mRNA and protein expression in the myocardium and LDL in the blood. It also reduced body mass and visceral fat mass (and PRAT's weight).<sup>103</sup>

In the case of preventive treatment, research on the effect of bilateral needling of the Fenglong acupoint plus having a high-fat diet in rats has shown that the measurement of PRAT in rats with Fenglong acupoint has been lower than rats with a high-fat diet (and no acupuncture). In conclusion, this preventive treatment (acupuncture at the Fenglong acupoint) can drastically prevent obesity in rats and help improve abnormal fat metabolism. This can be related to the improvement of leptin resistance and PPAR- $\gamma$  expression in the fat tissue. This type of intervention can also fall under the complementary medicine type.<sup>104</sup>

### Other

Since the activation of BAT can increase glucose uptake and energy usage<sup>105</sup> and considering the correlation of WAT with diseases, reactivating the dormant BAT into active BAT has been a suggestive treatment for increasing PRAT. This can be done by exposure to cold or stimulating the  $\beta$ 3-adrenoreceptors.<sup>29,106</sup>

lncRNAs are known to affect a process that is the opposite of browning, transforming BAT to WAT. Twenty-one thousand two hundred and thirty-two kinds of lncRNAs were found in goat PRAT's genome, of which 548 were identified in the mentioned process. Analysis of the lncRNA and mRNAs has shown that these genes may regulate the BAT to WAT process by affecting the AMPK signaling pathways, fatty acid metabolism, and cell respiratory chains.<sup>107</sup>

Heme-oxygenase (HO) reduces PRAT and mediators including (MIP-1 $\alpha$ ), (ET-1), TNF- $\alpha$ , IL-6, and IL-1 $\beta$ .<sup>108</sup>

In the past decade, PRAT's inherent anatomical and morphophysiological features have been researched sufficiently. It has been determined that the size and area of PRAT have significant direct and indirect effects on the pathologic path, risk, and prognosis of numerous cardiovascular, renal, and metabolic diseases and various malignancies. Different therapeutic interventions have varying effects on the anatomical and metabolic attributes of PRAT. Some cause an increase in mass and size, while some reduce it. Some pharmaceutical options even change the metabolic traits of the PRAT.

Due to the considerable ramifications that PRAT causes on the disorders mentioned above and their implications on their prognoses, having a good understanding of these effects is critical and could assist in making better therapeutic decisions. The research conducted on this matter has been scarce and often indirect, with the studies being primarily on the entire body's adipose tissue instead of directly focusing on the PRAT. Further research is needed to fully understand the effects of various therapeutic interventions on the PRAT as an individual part of the body's adipose tissue.

### Conflicts of interest

There are no conflicts of interest.

### References

- Hildebrand S, Stümer J, Pfeifer A. PVAT and its relation to brown, beige, and white adipose tissue in development and function. *Front Physiol* 2018;9:70.
- Lynes MD, Tseng Y-H. Deciphering adipose tissue heterogeneity. *Ann N Y Acad Sci* 2018;1411:5–20.
- Baer PC, Koch B, Hickmann E, Schubert R, Cinatl J, Hauser IA, et al. Isolation, characterization, differentiation and immunomodulatory capacity of mesenchymal stromal/stem cells from human perirenal adipose tissue. *Cells* 2019;8:1346.
- Porter RK. Uncoupling protein 1: A short-circuit in the chemiosmotic process. *J Bioenerg Biomembr* 2008;40:457.
- Torres N, Vargas-Castillo AE, Tovar AR. Adipose tissue: White adipose tissue structure and function. In: Caballero B, Finglas PM, Toldrá F, editors. *Encyclopedia of Food and Health*. Oxford: Academic Press; 2016. p. 35–42.
- van den Beukel JC, Grefhorst A, Hoogduijn MJ, Steenbergen J, Mastroberardino PG, Dor FJ, et al. Women have more potential to induce browning of perirenal adipose tissue than men. *Obesity* 2015;23:1671–9.
- Townsend K, Tseng Y-H. Brown adipose tissue. *Adipocyte* 2012;1:13–24.
- Lo Kinyui A, Sun L. Turning WAT into BAT: A review on regulators controlling the browning of white adipocytes. *Biosci Rep* 2013;33:e00065
- Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1- $\alpha$ -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012;481:463–8.
- Fenzl A, Kiefer FW. Brown adipose tissue and thermogenesis. *Horm Mol Biol Clin Investig* 2014;119:37–25

11. Laeger T, Henagan TM, Albarado DC, Redman LM, Bray GA, Noland RC, *et al.* FGF21 is an endocrine signal of protein restriction. *J Clin Invest* 2014;124:3913–22.
12. Harms M, Seale P. Brown and beige fat: Development, function and therapeutic potential. *Nat Med* 2013;19:1252–63.
13. Ohta H, Itoh N. Roles of FGFs as Adipokines in Adipose Tissue Development, Remodeling, and Metabolism. *Front Endocrinol (Lausanne)* 2014;5:18.
14. Liu B-X, Sun W, Kong X-Q. Perirenal fat: A unique fat pad and potential target for cardiovascular disease. *Angiology* 2019;70:584–93.
15. Spit KA, Muskiet MHA, Tonneijck L, Smits MM, Kramer MHH, Joles JA, *et al.* Renal sinus fat and renal hemodynamics: A cross-sectional analysis. *MAGMA* 2020;33:73–80.
16. Notohamiprodjo M, Goepfert M, Will S, Lorbeer R, Schick F, Rathmann W, *et al.* Renal and renal sinus fat volumes as quantified by magnetic resonance imaging in subjects with prediabetes, diabetes, and normal glucose tolerance. *PLOS ONE* 2020;15:e0216635.
17. Fang Y, Xu Y, Yang Y, Liu C, Zhao D, Ke J. The relationship between perirenal fat thickness and reduced glomerular filtration rate in patients with type 2 diabetes. *J Diabetes Res* 2020;2020:6076145.
18. Chau Y-Y, Bandiera R, Serrels A, Martínez-Estrada OM, Qing W, Lee M, *et al.* Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. *Nat Cell Biol* 2014;16:367–75.
19. Hausman GJ. Anatomical and enzyme histochemical differentiation of adipose tissue. *Int J Obes* 1985;9 Suppl 1:1–6.
20. Kim J-H, Han E-H, Jin Z-W, Lee H-K, Fujimiya M, Murakami G, *et al.* Fetal topographical anatomy of the upper abdominal lymphatics: Its specific features in comparison with other abdominopelvic regions. *Anat Rec (Hoboken)* 2012;295: 91–104.
21. Czaja K, Kraeling R, Klimczuk M, Franke-Radowiecka A, Sienkiewicz W, Lakomy M. Distribution of ganglionic sympathetic neurons supplying the subcutaneous, perirenal and mesentery fat tissue depots in the pig. *Acta Neurobiol Exp (Wars)* 2002;62:227–34.
22. Valero-Garrido D, López-Frías M, Llopis J, López-Jurado M. Influence of Dietary Fat on the Lipid Composition of Perirenal Adipose Tissue in Rats. *Annals of Nutrition and Metabolism* 1990;34:327–32.
23. Hamer DW, Santer RM. Anatomy and blood supply of the coeliac-superior mesenteric ganglion complex of the rat. *Anat Embryol (Berl)* 1981;162:353–62.
24. Hammoud SH, AlZaim I, Mougharbil N, Koubar S, Eid AH, Eid AA, *et al.* Peri-renal adipose inflammation contributes to renal dysfunction in a non-obese prediabetic rat model: Role of anti-diabetic drugs. *Biochem Pharmacol* 2021;186:114491.
25. Ricci MA, Scavizzi M, Ministrini S, De Vuono S, Pucci G, Lupattelli G. Morbid obesity and hypertension: The role of perirenal fat. *J Clin Hypertens (Greenwich)* 2018;20:1430–7.
26. Huang N, Mao E-W, Hou N-N, Liu Y-P, Han F, Sun X-D. Novel insight into perirenal adipose tissue: A neglected adipose depot linking cardiovascular and chronic kidney disease. *World J Diabetes* 2020;11:115.
27. Malcom GT, Bhattacharyya A, Velez-Duran M, Guzman M, Oalmann M, Strong J. Fatty acid composition of adipose tissue in humans: Differences between subcutaneous sites. *Am J Clin Nutr* 1989;50:288–91.
28. Jespersen NZ, Feizi A, Andersen ES, Heywood S, Hattel HB, Daugaard S, *et al.* Heterogeneity in the perirenal region of humans suggests presence of dormant brown adipose tissue that contains brown fat precursor cells. *Mol Metab* 2019;24: 30–43.
29. Efremova A, Senzacqua M, Venema W, Isakov E, Di Vincenzo A, Zingaretti MC, *et al.* A large proportion of mediastinal and perirenal visceral fat of Siberian adult people is formed by UCP1 immunoreactive multilocular and paucilocular adipocytes. *J Physiol Biochem* 2020;76:185–92.
30. Driscoll P. *Gray's Anatomy*, 39th Edition. *Emerg Med J* 2006;23:492
31. Argani H, Alirezaei A, Ghorbanihaghjo A, Azizi T, Asgharpour M, Bakhtiyari M. Comparing the serum levels of Adipocytokines in the renal transplant recipients and healthy individuals: A case-control study. *Iranian Red Crescent Medical Journal* 2018;20:3
32. Sun X, Han F, Miao W, Hou N, Cao Z, Zhang G. Sonographic evaluation of para- and perirenal fat thickness is an independent predictor of early kidney damage in obese patients. *Int Urol Nephrol* 2013;45:1589–95.
33. Kawasaki S, Hasegawa O, Satoh S, Numata K, Terauchi Y. Sonographic assessment of fatty liver infiltration using the measurement of para-and perirenal fat thickness. *J Clin Ultrasound* 2010;38:470–4.
34. Geraci G, Zammuto MM, Mattina A, Zanolli L, Geraci C, Granata A, *et al.* Para-perirenal distribution of body fat is associated with reduced glomerular filtration rate regardless of other indices of adiposity in hypertensive patients. *J Clin Hypertens (Greenwich)* 2018;20:1438–46.
35. Eisner BH, Zargooshi J, Berger AD, Cooperberg MR, Doyle SM, Sheth S, *et al.* Gender differences in subcutaneous and perirenal fat distribution. *Surgical and radiologic anatomy* 2010;32:879–82.
36. Chen X, McClusky R, Chen J, Beaven SW, Tontonoz P, Arnold AP, *et al.* The number of x chromosomes causes sex differences in adiposity in mice. *PLoS genetics* 2012;8:e1002709.
37. Svensson PA, Lindberg K, Hoffmann JM, Taube M, Pereira MJ, Mohsen-Kanson T, *et al.* Characterization of brown adipose tissue in the human perirenal depot. *Obesity* 2014;22:1830–7.
38. Foster MC, Hwang S-J, Porter SA, Massaro JM, Hoffmann U, Fox CS. Fatty kidney, hypertension, and chronic kidney disease: The Framingham Heart Study. *Hypertension* 2011;58:784–90.
39. Lamacchia O, Nicastro V, Camarchio D, Valente U, Grisorio R, Gesualdo L, *et al.* Para-and perirenal fat thickness is an independent predictor of chronic kidney disease, increased renal resistance index and hyperuricaemia in type-2 diabetic patients. *Nephrol Dial Transplant* 2011;26:892–8.
40. Tarzi RM, Cook HT, Jackson I, Pusey CD, Lord GM. Leptin-deficient mice are protected from accelerated nephrotoxic nephritis. *Am J Pathol* 2004;164:385–90.
41. Rea D, Heimbach J, Grande J, Textor S, Taler S, Prieto M, *et al.* Glomerular volume and renal histology in obese and non-obese living kidney donors. *Kidney int* 2006;70:1636–41.
42. Goumenos DS, Kowar B, El Nahas M, Conti S, Wagner B, Spyropoulos C, *et al.* Early histological changes in the kidney of people with morbid obesity. *Nephrol Dial Transplant* 2009;24:3732–8.
43. Adeosun SO, Gordon DM, Weeks MF, Moore KH, Hall JE, Hinds Jr TD, *et al.* Loss of biliverdin reductase-A promotes lipid accumulation and lipotoxicity in mouse proximal tubule cells. *Am J Physiol Renal Physiol* 2018;315:F323–F31.
44. Hou N, Han F, Wang M, Huang N, Zhao J, Liu X, *et al.* Perirenal fat associated with microalbuminuria in obese rats. *Int Urol Nephrol* 2014;46:839–45.



45. Montani JP, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AG. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. *Int J Obes Relat Metab Disord* 2004;28:S58–S65.
46. Katsiki N, G Athyros V, P Mikhailidis D. Abnormal peri-organ or intra-organ fat (APIFat) deposition: An underestimated predictor of vascular risk? *Curr Vasc Pharmacol* 2016;14:432–41.
47. Ma S, Zhu X-Y, Eirin A, Woollard JR, Jordan KL, Tang H, *et al.* Perirenal fat promotes renal arterial endothelial dysfunction in obese swine through tumor necrosis factor- $\alpha$ . *J Urol* 2016;195:1152–9.
48. Grigoraş A, Balan RA, Căruntu I-D, Giuşcă SE, Lozneau L, Avadanei RE, *et al.* Perirenal adipose tissue—current knowledge and future opportunities. *J Clin Med* 2021;10:1291.
49. Bosniak M. Spontaneous subcapsular and perirenal hematomas. *Radiology* 1989;172:601–2.
50. Tsili AC, Goussia AC, Baltogiannis D, Astrakas L, Sofikitis N, Malamou-Mitsi V, *et al.* Perirenal fat invasion on renal cell carcinoma: Evaluation with multidetector computed tomography—Multivariate analysis. *J Comput Assist Tomogr* 2013;37:450–7.
51. Okhunov Z, Mues AC, Kline M, Haramis G, Xu B, Mirabile G, *et al.* Evaluation of perirenal fat as a predictor of cT1a renal cortical neoplasm histopathology and surgical outcomes. *J Endourol* 2012;26:911–6.
52. Knipe H. Fat stranding (CT) Radiopaedia.org 2020 Available from: <https://doi.org/10.53347/rID-47438>.
53. Han NY, Sung DJ, Kim MJ, Park BJ, Sim KC, Cho SB. Perirenal fat stranding on CT: Is there an association with bladder outlet obstruction? *Br J Radiol* 2016;89:20160195.
54. Huang H, Chen S, Li W, Wu X, Xing J, editors. High perirenal fat thickness predicts a poor progression-free survival in patients with localized clear cell renal cell carcinoma. *Urologic Oncology: Seminars and Original Investigations*; 2018: Elsevier.
55. Li X, Wang G, Liu J, Ding G. Increased UCP1 expression in the perirenal adipose tissue of patients with renal cell carcinoma. *Oncol Rep* 2019;42:1972–80.
56. De Pergola G, Campobasso N, Nardecchia A, Triggiani V, Caccavo D, Gesualdo L, *et al.* Para-and perirenal ultrasonographic fat thickness is associated with 24-hours mean diastolic blood pressure levels in overweight and obese subjects. *BMC Cardiovasc Disord* 2015;15:1–7.
57. Wachtell K, Olsen MH, Dahlöf B, Devereux RB, Kjeldsen SE, Nieminen MS, *et al.* Microalbuminuria in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. *J Hypertens* 2002;20:3:12–405
58. Hillege HL. Prevention of renal and vascular end stage disease (PREVEND) study group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002;106:1777–82.
59. Tebbe U, Bramlage P, Thoenes M, Paar WD, Danchin N, Volpe M, *et al.* Prevalence of microalbuminuria and its associated cardiovascular risk: German and Swiss results of the recent global i-SEARCH survey. *Swiss Med Wkly* 2009;139:473–80.
60. Manno C, Campobasso N, Nardecchia A, Triggiani V, Zupo R, Gesualdo L, *et al.* Relationship of para-and perirenal fat and epicardial fat with metabolic parameters in overweight and obese subjects. *Eat Weight Disord* 2019;24.1:72–67
61. Chughtai HL, Morgan TM, Rocco M, Stacey B, Brinkley TE, Ding J, *et al.* Renal sinus fat and poor blood pressure control in middle-aged and elderly individuals at risk for cardiovascular events. *Hypertension* 2010;56:901–6.
62. Grima P, Guido M, Chiavaroli R, Zizza A. Ultrasound-assessed perirenal fat is related to increased ophthalmic artery resistance index in HIV-1 patients. *Cardiovasc Ultrasound* 2010;8:24.
63. Hall JE, Mouton AJ, da Silva AA, Omoto A, Wang Z, Li X, *et al.* Obesity, kidney dysfunction, and inflammation: Interactions in hypertension. *Cardiovasc Res* 2021;117:1859–76.
64. Shi Z, Chen W-W, Xiong X-Q, Han Y, Zhou Y-B, Zhang F, *et al.* Sympathetic activation by chemical stimulation of white adipose tissues in rats. *J Appl Physiol* (1985) 2012;112:1008–14.
65. Tanida M, Iwashita S, Ootsuka Y, Terui N, Suzuki M. Leptin injection into white adipose tissue elevates renal sympathetic nerve activity dose-dependently through the afferent nerves pathway in rats. *Neurosci Lett* 2000;293:107–10.
66. D’Marco L, Salazar J, Cortez M, Salazar M, Wetzel M, Lima-Martínez M, *et al.* Perirenal fat thickness is associated with metabolic risk factors in patients with chronic kidney disease. *Kidney Res Clin Pract* 2019;38:365.
67. der Hagopian O, Dahlberg M, Heinius G, Nordberg J, Gustafsson J, Nordenvall C, *et al.* Perirenal fat surface area as a risk factor for perioperative difficulties and 30-day postoperative complications in elective colon cancer surgery. *Colorectal Dis* 2018;20:1078–87.
68. Levic K, Bulut O, Schødt M, Bisgaard T. Increased perirenal fat area is not associated with adverse outcomes after laparoscopic total mesorectal excision for rectal cancer. *Langenbecks Arch Surg* 2017;402:1205–11.
69. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism* 2019;92:121–35.
70. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, *et al.* Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nat Med* 2011;17:1498–503.
71. Lee M-J, Wu Y, Fried SK. Adipose tissue heterogeneity: Implication of depot differences in adipose tissue for obesity complications. *Mol Aspects Med* 2013;34:1–11.
72. Grima P, Guido M, Chiavaroli R, Zizza A. Ultrasound-assessed perirenal fat is related to increased ophthalmic artery resistance index in HIV-1 patients. *Cardiovascular Ultrasound* 2010;18:9–1
73. Esposito C, Soria-Gondek A, Castagnetti M, Cerulo M, Del Conte F, Esposito G, *et al.* Laparoscopic or robotic deroofting guided by indocyanine green fluorescence and perirenal fat tissue wadding technique of pediatric simple renal cysts. *J Laparoendosc Adv Surg Tech A* 2020;30:471–6.
74. Van Dijk R, Virmani R, Von der Thüsen J, Schaapherder A, Lindeman J. The natural history of aortic atherosclerosis: A systematic histopathological evaluation of the peri-renal region. *Atherosclerosis* 2010;210:100–6.
75. Hayashi H, Okamoto I, Nakagawa K. Perirenal hematoma associated with bevacizumab treatment. *Invest New Drugs* 2012;30:808–9.
76. Ceyhan E, Ileri F, Aki FT, Yazici MS, Karcaaltincaba M, Ertoy Baydar D, *et al.* Pathology associated with adherent perirenal fat and its clinical effect. *Int J Clin Pract* 2021;75:e14518.
77. Girault EM, Guigas B, Alkemade A, Foppen E, Ackermans MT, La Fleur SE, *et al.* Chronic treatment with olanzapine increases adiposity by changing fuel substrate and causes desensitization of the acute metabolic side effects. *Naunyn Schmiedeberg Arch Pharmacol* 2014;387:185–95.
78. Aguirre L, Hijona E, Macarulla M, Gracia A, Larrechi I, Bujanda L, *et al.* Several statins increase body and liver fat accumulation

- in a model of metabolic syndrome. *J Physiol Pharmacol* 2013;64:281–8.
79. Foellmi-Adams LA, Wyse BM, Herron D, Nedergaard J, Kletzien RF. Induction of uncoupling protein in brown adipose tissue: Synergy between norepinephrine and pioglitazone, an insulin-sensitizing agent. *Biochem Pharmacol* 1996;52:693–701.
  80. Kajita K, Mori I, Hanamoto T, Ikeda T, Fujioka K, Yamauchi M, *et al.* Pioglitazone enhances small-sized adipocyte proliferation in subcutaneous adipose tissue. *Endocr J* 2012;59:1107–14.
  81. Watanabe Y, Nakayama K, Taniuchi N, Horai Y, Kuriyama C, Ueta K, *et al.* Beneficial effects of canagliflozin in combination with pioglitazone on insulin sensitivity in rodent models of obese type 2 diabetes. *PLOS ONE* 2015;10:e0116851.
  82. Larsen PJ, Wulff EM, Gotfredsen CF, Brand CL, Sturis J, Vrang N, *et al.* Combination of the insulin sensitizer, pioglitazone, and the long-acting GLP-1 human analog, liraglutide, exerts potent synergistic glucose-lowering efficacy in severely diabetic ZDF rats. *Diabetes Obes Metab* 2008;10:301–11.
  83. Ebal E, Cavalié H, Michaux O, Lac G. Visceral fat and total body fat mass correlate differently with hormones in rat. *Pathol Biol (Paris)* 2008;56:283–5.
  84. Prior RL, Wilkes S, Rogers T, Khanal RC, Wu X, Hager TJ, *et al.* Dietary black raspberry anthocyanins do not alter development of obesity in mice fed an obesogenic high-fat diet. *J Agric Food Chem* 2010;58:3977–83.
  85. Balan D, Chan KL, Murugan D, AbuBakar S, Wong PF. Antiadipogenic effects of a standardized quassinoids-enriched fraction and eurycomanone from *eurycoma longifolia*. *Phytother Res* 2018;32:1332–45.
  86. Shamburek RD, Brewer Jr HB, Gochuico BR. Erdheim-Chester disease: A rare multisystem histiocytic disorder associated with interstitial lung disease. *Am J Med Sci* 2001;321:66–75.
  87. Kobayashi Y, Nakano Y, Kizaki M, Hoshikuma K, Yokoo Y, Kamiya T. Capsaicin-like anti-obese activities of evodiamine from fruits of *Evodia rutaecarpa*, a vanilloid receptor agonist. *Planta medica* 2001;67:628–33.
  88. Udeani GO, Zhao GM, Geun Shin Y, Cooke BP, Graham J, Beecher CW, *et al.* Pharmacokinetics and tissue distribution of betulinic acid in CD-1 mice 1. *Biopharm Drug Dispos* 1999;20: 379–83.
  89. Wang Y, Song Y, Suo M, Jin X, Tian G. Telmisartan prevents high-fat diet-induced hypertension and decreases perirenal fat in rats. *J Biomed Res* 2012;26:219–25.
  90. Tong L-T, Katakura Y, Kawamura S, Baba S, Tanaka Y, Udono M, *et al.* Effects of Kurozu concentrated liquid on adipocyte size in rats. *Lipids Health Dis* 2010;9:1–9.
  91. Kim HJ, Jeon SM, Lee MK, Jung UJ, Shin SK, Choi MS. Antilipogenic effect of green tea extract in C57BL/6J-Lepob/ob mice. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives* 2009;23:467.71
  92. Seo JB, Choe SS, Jeong HW, Park SW, Shin HJ, Choi SM, *et al.* Anti-obesity effects of *lysimachia foenum-graecum* characterized by decreased adipogenesis and regulated lipid metabolism. *Exp Mol Med* 2011;43:205–15.
  93. Go H, Ryuk JA, Lee HW, Ko BS. Palmiton attenuates hepatic lipid accumulation and hyperlipidemia in a menopausal rat model. *Menopause (New York, NY)* 2015;22:872.
  94. Sato M, Goto T, Inoue E, Miyaguchi Y, Toyoda A. Dietary intake of immature citrus *tumida* hort. ex tanaka peels suppressed body weight gain and fat accumulation in a mouse model of acute obesity. *J Nutr Sci Vitaminol (Tokyo)* 2019;65:19–23.
  95. Hwang SB, Lee B-H. Anti-Obesity and antidiabetic effects of nelumbinis semen powder in high-fat diet-induced obese C57BL/6 Mice. *Nutrients* 2020;12:3576.
  96. Park JH, Lee SH, Chung I-M, Park Y. Sorghum extract exerts an anti-diabetic effect by improving insulin sensitivity via PPAR- $\gamma$  in mice fed a high-fat diet. *NRP* 2012;6:322.7
  97. Wang X, Jiang H, Cai C, Li G, Yu G. IDDF2021-ABS-0197 Delayed intervention of agaropectin-derived oligosaccharides alleviate lipid accumulation by modulating intestinal flora homeostasis. *BMJ Publishing Group*; 2021.
  98. Wat E, Ng CF, Wong ECW, Koon CM, Lau CP, Cheung DWS, *et al.* The hepatoprotective effect of the combination use of *Fructus Schisandrae* with statin—A preclinical evaluation. *Journal of ethnopharmacology* 2016;178:104–14.
  99. Tian L, Zhang S, Gao F, Sun X, DU X, Sun L, *et al.* Effect of electroacupuncture on serum ins and the fat content in male and female experimental obesity rats. *Shanghai Journal of Acupuncture and Moxibustion* 2017:94–7.
  100. Mateo-Gallego R, Marco-Benedí V, Perez-Calahorra S, Bea AM, Baila-Rueda L, Lamiquiz-Moneo I, *et al.* Energy-restricted, high-protein diets more effectively impact cardiometabolic profile in overweight and obese women than lower-protein diets. *Clinical Nutrition* 2017;36:371–9.
  101. Parrish C, Pathy D, Angel A. Dietary fish oils limit adipose tissue hypertrophy in rats. *Metabolism* 1990;39:217–9.
  102. Yan H, Cao S, Li Y, Zhang H, Liu J. Reduced meal frequency alleviates high-fat diet-induced lipid accumulation and inflammation in adipose tissue of pigs under the circumstance of fixed feed allowance. *Eur J Nutr* 2020;59:595–608.
  103. Zhang C, Liu S, Xia Z, Wang S, Ding X, Wang Q, *et al.* Effect of aerobic exercises and dietary intervention on lipid metabolism in rats with metabolic syndrome and mechanism mediated by peroxisome proliferator-activated receptor $\alpha$ . *Chinese Journal of Rehabilitation Theory and Practice* 2017:662–6.
  104. Jiajing W, Wenyan Z, Yinong S, Shipeng Z. Effects of preventive acupuncture at the fenglong acupoint on obesity prevention and PPAR- $\gamma$  expression level in rats fed a high-fat diet. *Chinese General Practice* 2019;22:707.
  105. Leitner BP, Huang S, Brychta RJ, Duckworth CJ, Baskin AS, McGehee S, *et al.* Mapping of human brown adipose tissue in lean and obese young men. *Proc Natl Acad Sci U S A* 2017;114:8649–54.
  106. Warner A, Kjellstedt A, Carreras A, Böttcher G, Peng X-R, Seale P, *et al.* Novel aspects of adipocyte biology: Activation of  $\beta$ 3-adrenoceptors increases in vivo free fatty acid uptake and utilization in brown but not white fat depots in high-fat-fed rats. *Am J Physiol Endocrinol Metab* 2016;311:E901.
  107. Wang L, Yang X, Zhu Y, Zhan S, Chao Z, Zhong T, *et al.* Genome-wide identification and characterization of long noncoding RNAs of brown to white adipose tissue transformation in goats. *Cells* 2019;8:904.
  108. Ndisang JF, Jadhav A, Mishra M. The heme oxygenase system suppresses perirenal visceral adiposity, abates renal inflammation and ameliorates diabetic nephropathy in Zucker diabetic fatty rats. *PLOS One* 2014;9:e87936.