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Full Review

Obesity and renal disease: not all fat is created equal and not all obesity is harmful to the kidneys

Norbert Stefan[1,2,3], Ferruh Artunc[1], Nils Heyne[1], Jürgen Machann[2,3], Erwin D. Schleicher[1,2,3] and Hans-Ulrich Häring[1,2,3]

[1]Department of Internal Medicine IV, University Hospital Tübingen, Tübingen, Germany, [2]Institute of Diabetes Research and Metabolic Diseases, Tübingen, Germany and [3]German Center for Diabetes Research (DZD), Tübingen, Germany

Correspondence and offprint requests to: Norbert Stefan; E-mail: norbert.stefan@med.uni-tuebingen.de

ABSTRACT

The prevalence of obesity is increasing worldwide and contributes to many health problems, including kidney disease. Unexpectedly, 10–30% of obese individuals are apparently not at increased risk of metabolic diseases, e.g. type 2 diabetes, cardiovascular disease and risk of renal disease. Their phenotype is labeled 'metabolically healthy obesity'. In the search for mechanisms explaining this unexpected condition, a favourable type of body fat distribution with low insulin resistance and with low subclinical inflammation has been identified. Furthermore, signalling pathways have been found that distinguish between metabolically benign and malignant obesity. In addition, the important roles of fatty acids, adipokines and hepatokines were identified. These factors regulate insulin resistance and subclinical inflammation. Onset and evolution of chronic kidney disease (CKD) are affected by obesity. CKD also increases the risk of insulin resistance and subclinical inflammation, two pathways that play an important role in the pathogenesis of renal malfunction. This brief review summarizes novel insights, specifically how distinct body fat compartments (including perivascular and even renal sinus fat) may have an impact on progression of CKD.

Keywords: chronic kidney disease, insulin resistance, metabolically healthy obesity, non-alcoholic fatty liver disease, subclinical inflammation

INTRODUCTION

The recent worldwide epidemic of obesity [1–4] is considered to be largely the cause of the recently increased incidence of type 2 diabetes, cardiovascular disease (CVD) and several types of cancer. Even the increasing prevalence of chronic kidney disease (CKD) has—to some extent—been attributed to the recent endemic of obesity and its metabolic complications [5]. Many studies have consistently documented that obesity is a risk factor for a decline of glomerular filtration rate as well as onset and progression of CKD [6–10]. Furthermore, in agreement with studies about the incidence of type 2 diabetes and CVD, the usual type of obesity is also associated with a higher risk of onset and/or progression of CKD. Estimates of visceral obesity, e.g. increased waist circumference, were found to be stronger predictors of end-stage renal disease (ESRD) than the elevated body mass index (BMI). While increased visceral obesity may cause and aggravate CKD by promoting metabolic diseases, recent studies indicate that even in the absence of the well-known risk factors such as hypertension or diabetes, obesity *per se* may be harmful to the kidney [11–13]. This conclusion is supported by the study of Nerpin *et al.* [14] which documents that insulin resistance, which often accompanies obesity, is a very strong marker of incident CKD. Thus, the assumption of a pathogenetic role is indeed reasonable. The authors showed that impaired insulin sensitivity at baseline predicted incident impairment of renal function independently of other risk factors, including age and fasting plasma glucose [14]. As a result, it has increasingly been postulated that insulin resistance (as well as factors promoting insulin resistance) plays a role in the development of CKD.

NEW ASPECTS CONCERNING THE ROLE OF INSULIN RESISTANCE IN CKD

Several mechanisms are known to impair insulin signalling in metabolic tissues, thus contributing to 'whole-body insulin resistance'. Among these mechanisms, genetic defects in skeletal muscle and the liver have been shown to result in decreased glucose disposal and increased hepatic glucose production [15]. These mechanisms eventually result in hyperglycemia and insulin resistance. It has also been documented, however, that the onset and progression of CKD may be independent of glycemia, so that other mechanisms may be critical as well, at least for the early stages of impaired renal function. In this context, humoral signals of metabolic tissues become relevant. The expansion of visceral adipose tissue, i.e. a target for infiltration by immune cells, is involved in the above process [16]. Furthermore, the decrease in adiponectin concentration is relevant: it is associated with reduced whole-body insulin sensitivity and possibly causes increased pro-inflammatory signalling in the kidney as well [17]. It must be admitted, however, that the renal biology and function of adiponectin, to-date considered the most important adipokine in metabolic diseases, has not been fully understood [18]. Furthermore, increased leptin-induced proteinuria and type 2 collagen expression by increased TGF-β1 production is thought to be involved in glomerusclerosis [19]. In addition, the metabolic syndrome is strongly associated with increased visceral obesity and contributes to onset and progression of CKD via hyperinsulinaemia, inappropriate activation of the renin angiotensin system and oxidative stress in the kidney. The resulting pathology includes impaired pressure/natriuresis relationship, increased salt sensitivity for blood pressure, aldosterone excess, glomerular hypertension, endothelial dysfunction and vasoconstriction as well as matrix expansion [10].

DOES METABOLICALLY HEALTHY OBESITY EXIST?

The recent proposal of the existence of 'metabolically healthy obesity' (MHO) has provoked some interesting novel hypotheses. It has been documented that a subgroup of obese individuals (∼10–30%) is apparently protected from the metabolic complications of obesity; at least the risk appears to be considerably lower than expected for the given level of obesity. This subgroup is thought to be not only at lower risk of cardiovascular morbidity, but also of mortality, compared with obese individuals with major cardiovascular risk factors [20, 21]. Furthermore, because the reduction of mortality and incidences of diabetes and CVD, that are being brought about by bariatric surgery, appear to depend on the presence and absence of MHO [20], this novel concept may also become important for the direction of obese people toward specific prevention and treatment programmes. However, the application of MHO concept in clinical practice may be limited by the fact that BMI, which is a component of the MHO definition, does not necessarily represent only fat mass, but also lean mass. Nevertheless, in relatively sedentary people BMI is still a good estimate of fat mass. In our initial study addressing MHO [22] we could show that when mostly sedentary middle-aged people with a BMI of $\geq$30 kg/m^2 were divided into a metabolically healthy and a metabolically at-risk group, both BMI and fat mass, measured by whole-body magnetic resonance imaging, were almost identical in both groups. Certainly, this may not necessarily be the case in physically active and younger individuals.

Furthermore, it is presently not clear as to whether MHO reflects an intermediate, rather than a truly low-risk state. Recent data from the North West Adelaide Health Study indicate that MHO might be a transient phenotype for a proportion of individuals [23]. From all individuals classified as having MHO in the beginning, one-third changed to a high-risk phenotype during the course of the study, but lower risk of type 2 diabetes and CVD was restricted to the subgroup of individuals with MHO maintaining this condition. Thus, having MHO during one clinical examination should not imply that there is no metabolic risk; however, keeping the MHO status may clearly be beneficial for metabolic health. In addition, the fact that currently there is no agreement about a universal definition of the MHO phenotype limits its use in daily clinical routine.

The most important characteristics of the MHO phenotype include low insulin resistance, low carotid intima-media thickness and lower prevalence of non-alcoholic fatty liver disease (NAFLD) [22]. Additionally, low levels of the hepatokine fetuin-A are found in subjects with MHO [22, 24]. Interestingly, visceral fat mass and adiponectin levels were, at the most, only mildly altered compared with metabolically unhealthy obese subjects [22, 24]. In >300 subjects with increased risk of type 2 diabetes, we found that high liver fat content and elevated fetuin-A levels were independent predictors of insulin resistance and impaired glucose regulation [25]. This finding leads to the question through which mechanism do NAFLD and fetuin-A have an impact on metabolism and cause subclinical inflammation.

ROLE OF NAFLD AND FETUIN-A IN METABOLISM

By regulating carbohydrate and lipid fluxes the liver can quickly adapt to extreme conditions of nutrient availability, e.g. prolonged fasting and chronic overfeeding. Insulin inhibits production and release of glucose by the liver as a result of blocking both gluconeogenesis and glycogenolysis. In adipose tissue as well as in the liver, increased energy intake and/or reduced energy expenditure result in accumulation of lipids, accompanied by infiltration and activation of immune cells, thus resulting in insulin resistance. Impaired insulin signalling in the liver increases endogenous glucose production, thus causing hyperglycaemia. Hyperglycaemia and glucotoxicity contribute to the development of type 2 diabetes and CVD [26]. Insulin is also a powerful regulator of hepatic lipid metabolism as a result impaired insulin signaling in the liver and might considerably contribute to the known atherogenic dyslipidaemia associated with insulin-resistant states. It is widely thought that such increased circulating lipid pool is a result of insulin resistance of the liver. It is also considered to be a prerequisite for atherosclerosis [26].

Apart from this conventional explanation, we have recently proposed a novel concept to explain how NAFLD affects lipid metabolism: if fat accumulates in the liver, proteins with signalling properties in other tissues (hepatokines) are released [27]. Fetuin-A is the best studied of these hepatokines. Its expression is increased in NAFLD [28–31]. Besides its well-known impact to inhibit insulin signalling [32], we could show that fetuin-A strongly induces cytokine expression in monocytes and adipose tissue [33]. In addition, we and others showed that fetuin-A predicts incident diabetes [34, 35] as well as CVD [36, 37]. More recently in animals as well as *in vitro* it was shown that fetuin-A serves as an adaptor protein for saturated fatty acids, allowing them to activate Toll-like receptor 4. This way, fetuin-A induces inflammatory signalling and insulin resistance [38], which are important factors driving the development of T2DM and CVD. In addition, fetuin-A is currently considered as the missing link to explaining lipid-induced inflammation [39]. These animal data and *in vitro* findings can be translated to humans *in vivo*: fetuin-A and fatty acids interact to induce insulin resistance [40].

IS FETUIN-A RELATED TO CKD?

Is there information that fetuin-A could also be involved in the pathogenesis of CKD? It is well known that in advanced CKD and in ESRD fetuin-A may inhibit ectopic calcification, thus perhaps even protecting the kidney [41]. We speculate that in early stages of CKD when ectopic calcification is not yet relevant, the pro-inflammatory effects of fetuin-A may prevail to a large extent. In this context, it is of interest that elevated fetuin-A levels had been found in women with normal glucose tolerance but with albuminuria; this relationship was independent of well-known predictors of albuminuria [42].

Because of the finding that fetuin-A induces pro-inflammatory signaling in adipose tissue [33, 38, 43], perivascular fat comes into the focus of research addressing the impact of fetuin-A on vessels and kidney. Perivascular fat is considered to play an important role in vascular function [44]. The renal function heavily depends on blood flow. One paracrine effect of increased pro-inflammatory signalling may be glomerular function—obviously relevant for the development of CKD. Perivascular fat is strongly associated with insulin resistance [45]. We recently also identified increased amounts of perivascular renal sinus fat (Figure 1), which was associated with exercise-induced albuminuria, independently of sex, age, visceral fat mass and blood pressure [46]. Furthermore, findings from the Framingham Heart Study Renal suggest that renal sinus fat may play a role in blood pressure regulation and CKD [47]. This neglected finding might become relevant if it turns out to be a predictor of CKD.

There is good evidence that not all fat is created equal. When characterizing perivascular fat, we found that adipocytes in this location differed substantially with respect to messenger RNA expression and protein production of angiogenic factors compared with fat cells from other sites [48]. Such difference may affect growth of fat tissue, contribute to complications of atherosclerotic plaques and be responsible for alterations in blood flow. Because fetuin-A strongly induces pro-inflammatory signalling in adipose tissue, it is indeed plausible that it may also have an impact on renal function by directly acting on perivascular renal sinus fat and potentially also on the endothelium. Currently studies addressing this issue are under way.

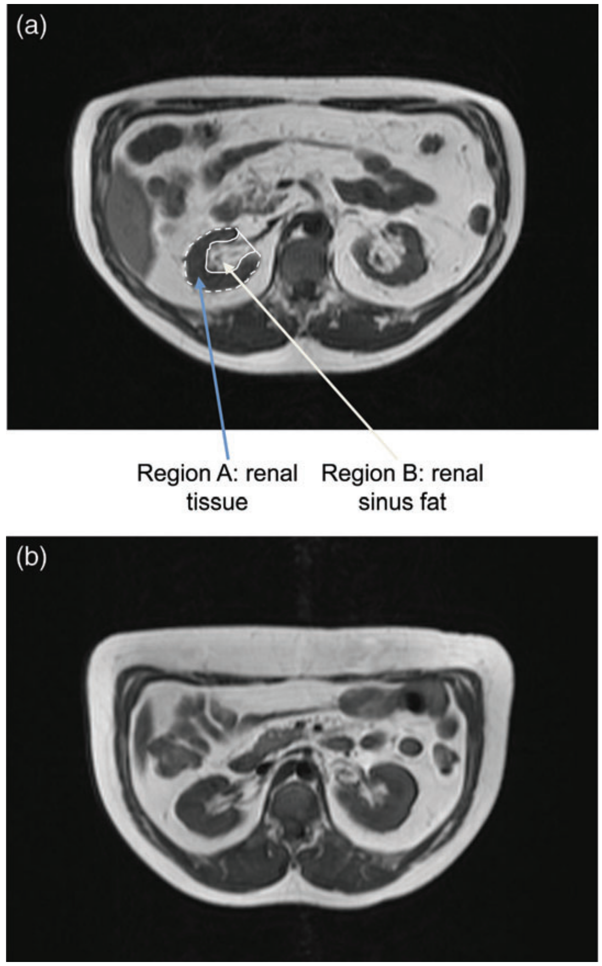

FIGURE 1: Perivascular renal sinus fat in humans. Axial T1-weighted magnetic resonance images taken at the level of entry of the renal arteries into the renal sinus in two subjects with comparable BMI. (**a**) Male volunteer (BMI 32.3 kg/m^2) with a high amount of perivascular adipose tissue in the renal sinus (RSF). Manually drawn regions of interest for quantification of total kidney area (region A, dashed line, blue arrow) and adipose tissue in the renal sinus (region B, continuous line, white arrow) are drawn in the right kidney. (**b**) Male volunteer (BMI 33.5 kg/m^2) with a low amount of RSF on both sides. RSF was calculated as the arithmetical mean of B/(A + B) left and right. From Wagner R *et al.* [46] (with permission for reproduction from Springer).

SUMMARY

Visceral adiposity and, more importantly, NAFLD, are strongly involved in the pathogenesis of type 2 diabetes, CVD and potentially also kidney disease; the latter is suggested by fat deposition in the renal sinus and is strongly supported by precise measurements of body fat distribution. The best marker of disturbed fat metabolism may be insulin resistance. Among the mechanisms of particular importance are presumably dysregulated release of cytokines, adipokines and hepatokines (as depicted in Figure 2). This conclusion is also in line with the novel finding of a putative critical role of perivascular renal sinus fat and its link to albuminuria. These

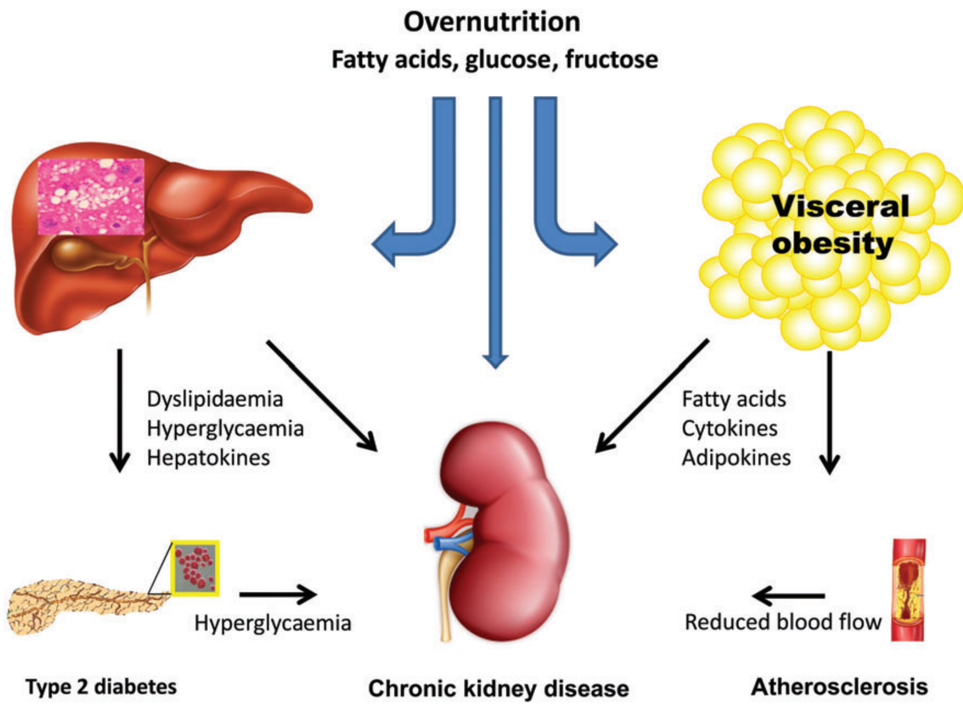

FIGURE 2: Obesity-associated pathways in the development of CKD.

findings call for further studies of the role of lipid metabolism in the pathogenesis of CKD.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole. Figure 1 was published in the Journal *Diabetologia* [46] and permission to present the figure in the present article has been granted by that journal.

REFERENCES

1. Finucane MM, Stevens GA, Cowan MJ *et al.* National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011; 377: 557–567
2. Hu FB, Willett WC, Li T *et al.* Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 2004; 351: 2694–2703
3. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol 2013; 9: 13–27
4. Pischon T, Boeing H, Hoffmann K *et al.* General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008; 359: 2105–2120
5. Eckardt KU, Coresh J, Devuyst O *et al.* Evolving importance of kidney disease: from subspecialty to global health burden. Lancet 2013; 382: 158–169
6. Fox CS, Larson MG, Leip EP *et al.* Predictors of new-onset kidney disease in a community-based population. JAMA 2004; 291: 844–850
7. Ejerblad E, Fored CM, Lindblad P *et al.* Obesity and risk for chronic renal failure. J Am Soc Nephrol 2006; 17: 1695–1702
8. Pinto-Sietsma SJ, Navis G, Janssen WM *et al.* A central body fat distribution is related to renal function impairment, even in lean subjects. Am J Kidney Dis 2003; 41: 733–741
9. Kanasaki K, Kitada M, Kanasaki M *et al.* The biological consequence of obesity on the kidney. Nephrol Dial Transplant 2013; 28(Suppl. 4): iv1–iv7
10. Ritz E. Metabolic syndrome and kidney disease. Blood Purif 2008; 26: 59–62
11. Cirillo M, Senigalliesi L, Laurenzi M *et al.* Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: the Gubbio Population Study. Arch Intern Med 1998; 158: 1933–1939
12. Tozawa M, Iseki K, Iseki C *et al.* Influence of smoking and obesity on the development of proteinuria. Kidney Int 2002; 62: 956–962
13. Chandie Shaw PK, Berger SP, Mallat M *et al.* Central obesity is an independent risk factor for albuminuria in nondiabetic South Asian subjects. Diabetes Care 2007; 30: 1840–1844
14. Nerpin E, Risérus U, Ingelsson E *et al.* Insulin sensitivity measured with euglycemic clamp is independently associated with glomerular filtration rate in a community-based cohort. Diabetes Care 2008; 31: 1550–1555
15. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001; 414: 799–806
16. Odegaard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science 2013; 339: 172–177
17. Adamczak M, Wiecek A. The adipose tissue as an endocrine organ. Semin Nephrol 2013; 33: 2–13
18. Sharma K, Ramachandrarao S, Qiu G *et al.* Adiponectin regulates albuminuria and podocyte function in mice. J Clin Invest. 2008; 118: 1645–1656
19. Wolf G, Hamann A, Han DC *et al.* Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: potential role in glomerulosclerosis [see comments]. Kidney Int 1999; 56: 860–872
20. Stefan N, Häring HU, Hu FB *et al.* Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol 2013; 1: 152–162
21. Stefan N, Kantartzis K, Machann J *et al.* Global trends in body-mass index. Lancet 2011; 377: 1917
22. Stefan N, Kantartzis K, Machann J *et al.* Identification and characterization of metabolically benign obesity in humans. Arch Intern Med 2008; 168: 1609–1616
23. Appleton SL, Seaborn CJ, Visvanathan R *et al.* Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care 2013; 36: 2388–2394

24. Klöting N, Fasshauer M, Dietrich A *et al*. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab 2010; 299: E506–E515
25. Kantartzis K, Machann J, Schick F *et al*. The impact of liver fat vs visceral fat in determining categories of prediabetes. Diabetologia 2010; 53: 882–889
26. Stefan N, Kantartzis K, Häring H-U. Causes and metabolic consequences of fatty liver. Endocr Rev 2008; 29: 939–960
27. Stefan N, Häring HU. The role of hepatokines in metabolism. Nat Rev Endocrinol 2013; 9: 144–152
28. Stefan N, Hennige AM, Staiger H *et al*. α2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. Diabetes Care 2006; 29: 853–857
29. Haukeland JW, Dahl TB, Yndestad A *et al*. Fetuin A in nonalcoholic fatty liver disease: in vivo and in vitro studies. Eur J Endocrinol 2012; 166: 503–510
30. Stefan N, Häring HU. The metabolically benign and malignant fatty liver. Diabetes 2011; 60: 2011–2017
31. Lehmann R, Franken H, Dammeier S *et al*. Circulating lysophosphatidylcholines are markers of a metabolically benign nonalcoholic fatty liver. Diabetes Care 2013; 36: 2331–2338
32. Auberger P, Falquerho L, Contreres JO *et al*. Characterization of a natural inhibitor of the insulin receptor tyrosine kinase: cDNA cloning, purification, and anti-mitogenic activity. Cell 1989; 58: 631–640
33. Hennige AM, Staiger H, Wicke C *et al*. Fetuin-A induces cytokine expression and suppresses adiponectin production. PLoS ONE 2008; 3: e1765
34. Stefan N, Fritsche A, Weikert C *et al*. Plasma fetuin-A levels and the risk of type 2 diabetes. Diabetes 2008; 57: 2762–2767
35. Ix JH, Wassel CL, Kanaya AM *et al*., Health ABC Study. Fetuin-A and incident diabetes mellitus in older persons. JAMA 2008; 300: 182–188
36. Weikert C, Stefan N, Schulze MB *et al*. Plasma fetuin-A levels and the risk of myocardial infarction and ischemic stroke. Circulation 2008; 118: 2555–2562
37. Fisher E, Stefan N, Saar K *et al*. Association of AHSG gene polymorphisms with fetuin-A plasma levels and cardiovascular diseases in the EPIC-Potsdam study. Circ Cardiovasc Genet 2009; 2: 607–613
38. Pal D, Dasgupta S, Kundu R *et al*. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. Nat Med 2012; 18: 1279–1285
39. Heinrichsdorff J, Olefsky JM. Fetuin-A: the missing link in lipid-induced inflammation. Nat Med 2012; 18: 1182–1183
40. Stefan N, Häring HU. Circulating fetuin-A and free fatty acids interact to predict insulin resistance in humans. Nat Med 2013; 19: 394–395
41. Schafer C, Heiss A, Schwarz A *et al*. The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Invest 2003; 112: 357–366
42. Li M, Xu M, Bi Y *et al*. Association between higher serum fetuin-A concentrations and abnormal albuminuria in middle-aged and elderly Chinese with normal glucose tolerance. Diabetes Care 2010; 33: 2462–2464
43. Siegel-Axel DI, Ullrich S, Stefan N *et al*. Fetuin-A influences vascular cell growth and production of proinflammatory and angiogenic proteins by human perivascular fat cells. Diabetologia. Epub ahead of print 4 February 2014
44. Yudkin JS, Eringa E, Stehouwer CD. 'Vasocrine' signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. Lancet 2005; 365: 1817–1820
45. Rittig K, Staib K, Machann J *et al*. Perivascular fatty tissue at the brachial artery is linked to insulin resistance but not to local endothelial dysfunction. Diabetologia 2008; 51: 2093–2099
46. Wagner R, Machann J, Lehmann R *et al*. Exercise-induced albuminuria is associated with perivascular renal sinus fat in individuals at increased risk of type 2 diabetes. Diabetologia 2012; 55: 2054–2058
47. Foster MC, Hwang SJ, Porter SA *et al*. Fatty kidney, hypertension, and chronic kidney disease: the Framingham Heart Study. Hypertension 2011; 58: 784–790
48. Rittig K, Dolderer JH, Balletshofer B *et al*. The secretion pattern of perivascular fat cells is different from that of subcutaneous and visceral fat cells. Diabetologia 2012; 55: 1514–1525

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