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 epidemic 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 [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 ≥30 kg/m² 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 gluco toxicity 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 signaling 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 signalling 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.

**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 findings call for...
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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.

FIGURE 2: Obesity-associated pathways in the development of CKD.
Metabolic acidosis in renal transplantation: neglected but of potential clinical relevance

Pier Giorgio Messa, Carlo Alfieri and Simone Vettoretti

Unit of Nephrology-Dialysis, Urology and Renal Transplantation, IRCCS Fondazione Ca’ Granda-Ospedale Maggiore-Policlinico, Milano, Italy

Correspondence and offprint requests to: Pier Giorgio Messa; E-mail: piergiorgio.messa@policlinico.mi.it

ABSTRACT

Chronic metabolic acidosis (CMA) is a common complication of the more advanced stages of chronic kidney diseases (CKD), and is associated with morbidity and mortality of CKD patients and possibly with the progression of renal disease. Nevertheless, there is limited evidence or information on the prevalence, the potential causal factors, the clinical impact and the effects of correction of CMA in kidney transplant recipients. In this review, we briefly look at the more relevant, though scanty, studies which have, over time, addressed the above-mentioned points, with the hope that in the future the interest of transplant nephrologists and surgeons will grow towards this unreasonably neglected issue.

Keywords: allograft dysfunction, metabolic acidosis, renal transplantation

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