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INVITED PAPER

OVERWEIGHT, OBESITY AND METABOLIC ALTERATIONS IN CHRONIC KIDNEY DISEASE

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A b s t r a c t: There is now solid knowledge for associating overweight and obesity with CKD. The risk for ESRD is progressively higher at increasing body mass index (BMI) levels and in extremely obese individuals such risk is 5 times higher than that in persons with normal body mass. Visceral fat, insulin resistance and inflammation are nicely inter-correlated in cross sectional studies in CKD patients but it is still untested whether the association between waist circumference or waist-hip ratio and CKD underlies a causal connection. Notwithstanding knowledge on the quantitative relationship between risk factors implicated in kidney damage is still limited, evidence derived from clinical series in patients with various renal diseases (IgA nephropathy, renal agenesia or post-nephrectomy) supports the hypothesis that obesity is an important factor in the progression and perhaps even in the initiation of CKD. Hyperfiltration is commonly found in obese persons. Due to high sympathetic activity, high levels of angiotensin II and hyperinsulinemia, obese persons display enhanced sodium reabsorption in the proximal tubule and are unable to rapidly increase sodium excretion. Enhanced proximal salt reabsorption determines a reduced delivery of sodium to the macula densa and therefore promotes afferent vasodilatation and enhanced renin synthesis. As a result of high local angiotensin II levels, the efferent arteriole is constricted in the obese. Glomerulomegaly and focal glomerulosclerosis represent the anatomical counterparts of glomerular hyperfiltration-hypertension. Hyperfiltration apart, evidence is emerging that inflammatory cytokines produced by fat cells trigger inflammation in the kidney and that this mechanism contributes to reduce renal function in the obese.

Key words: obesity, CKD, ESRD, waist circumference, BMI, hypertension, insulin resistance, inflammation.

Observational studies now provide a solid knowledge base for associating overweight and obesity with CKD. Well conceived analyses based on the Kaiser Permanente clinical database adjusting for blood pressure, diabetes and other risk factors [1] have demonstrated that overweight persons have a 72% risk excess of ESRD. The risk of ESRD is progressively higher at increasing body mass index (BMI) levels and in extremely obese individuals such risk is 5 times higher than that in persons with normal body mass. Similar associations were reported in a study in Japan [2] and in a Swedish nationwide, population-based, case-control study [3]. Thus, there is a strong link between obesity and CKD and ESRD and this link is incompletely accounted for by hypertension and type-2 diabetes. Visceral fat, insulin resistance and inflammation are nicely inter-correlated in cross-sectional studies in CKD patients [4]. However, until now there has been no cohort nor intervention study testing whether the association between waist circumference or waist-hip ratio and CKD or ESRD underlies a causal connection.

Metabolic syndrome and CKD

The separate and combined relationship between the metabolic syndrome components and CKD has been only sparsely investigated. In a survey in non-diabetic native Americans (the inter-tribal heart project), the metabolic syndrome was associated with a twofold increased prevalence of microalbuminuria [5]. In NHANES III analyses adjusting for age, race, ethnicity, sex, anti-inflammatory drug use, education, physical inactivity, smoking and BMI, the independent excess risk for CKD of hypertension, low HDL Cholesterol, hypertriglyceridaemia, fasting hyperglicemia and large waist circumference ranged from 16% (serum glucose > 110 mg/dl) to 239% (BP > 130/85 mmHg) [6]. However, the combined effect of these risk factors was less than additive suggesting that the pathways whereby these risk factors are conducive to CKD overlap to an important extent. Although the cross-sectional design of the NHANES III study by Chen [6] does not allow making inferences about causality, this is the first study suggesting that at population level even mildly elevated blood pressure (> 130/85 mm Hg) or mild hyperglycaemia may portend an increased risk of CKD and microalbuminuria. Furthermore NHANES III confirms previous observations in the Modification Diet Renal Disease (MDRD) cohort indicating that low HDL cholesterol predicts faster CKD progression [7]. On the other hand, both high serum triglyceride and low HDL cholesterol levels predicted an increased risk of renal dysfunction in a community study (the Atherosclerosis Risk in Communities study, ARIC) in people aged 54–64 years [8]. Observational findings in these studies implicating dyslipidaemia in CKD are corroborated by a large combined analysis of three major pravastatin trials [9] and by a

secondary analysis of an atorvastatin-based trial [10] indicating that lipid lowering may help to preserve glomerular filtration rate in patients with coronary heart disease. Importantly, in line with experimental data in animal models, the NHANES III study by Chen [6] also suggest that visceral fat, as defined on the basis of a larger than normal waist circumference, is implicated in chronic kidney disease.

Very limited information based on follow-up or longitudinal studies is yet available. In the above-mentioned ARIC study the multivariable adjusted odds ratio (OR) of developing CKD over a 9-year follow-up in patients with the metabolic syndrome was 1.43 [11]. After adjusting for the subsequent development of diabetes and hypertension, metabolic syndrome entailed a 24% risk excess for incident CKD. Insulin resistance and hyperinsulinaemia in the absence of diabetes were associated with CKD in another NHANES III cross-sectional analysis [8]. Collectively these data suggest that renal dysfunction may start independently of hypertension or diabetes in patients harbouring risk factors which are also components of the metabolic syndrome and support the contention that, hypertension and diabetes apart, other metabolic risk factors also may underlie the current CKD epidemics.

Nephrosclerosis and the CKD epidemics

As previously alluded to, nephrosclerosis is a common histology picture in hypertension, diabetes, hypercholesterolaemia and obesity. Renal registries data point to hypertensive nephrosclerosis as the main factor explaining the expansion of the dialysis population of the last few decades. However, knowledge supporting a cause-and-effect relationship between hypertension *per se* and the ascendancy of ESRD is flimsy, particularly in Caucasians [12]. The definition of hypertensive nephrosclerosis does not take into proper account the fact that risk factors for hypertension and CKD (like obesity and diabetes) may cause nephrosclerosis by BP-dependent and independent mechanisms. Over 50% of hypertensive patients are obese and vice versa and the risk of diabetes in morbid obese individuals is 7 times higher than in normal weight subjects [13]. Studies published so far do not allow discriminating the independent effect of hypertension on kidney structure and function from those of obesity and diabetes. As previously mentioned, features commonly observed in classical nephrosclerosis are also frequently seen in these two diseases. On the other hand, glomerulomegaly and focal glomerulosclerosis are currently considered as features peculiar to nephropathy associated with obesity [14]. However, information on renal histopathology in the obese has been mainly derived from studies in case-series with an over-representation of proteinuric patients [15]. Intriguingly, at comparable levels of proteinuria, obese patients display less severe podocyte dama-

ge and progress at a slower pace than patients with the idiopathic form of Focal Glomerulo Sclerosis (FGS) [16]. Most likely glomerulomegaly and FGS in the obese with proteinuria underlie altered renal microcirculatory control eventuating in high glomerular flow and hyperfiltration (see below). These alterations occur at an early stage in obesity [17] and the contention that glomerulomegaly is a precocious renal alteration in the obese is also supported by the finding that obese kidney donors (i.e. subjects with no or minimal clinical evidence of renal dysfunction) display a glomerular surface area higher than that in well-matched non-obese donors [18].

Notwithstanding the fact that knowledge of the quantitative relationship between risk factors implicated in kidney damage and ESRD is still limited, evidence derived from clinical series in patients with IgA nephropathy [19], renal agenesia [20] or nephrectomy [21] or in recipients of kidneys harvested from overweight or obese donors [22] supports the hypothesis that obesity is an important factor in the progression and perhaps even in the initiation of CKD. Indeed in all the above-mentioned studies, a higher BMI (including a higher BMI in kidney donors) portended a relatively faster renal function loss.

Kidney damage in overweight and obesity

Inflammation appears associated with metabolic risk factors and obesity not only in patients with atherosclerosis but also in patients with CKD [23–24] and it is well known that patients with atherosclerotic complications are at a higher risk of CKD and vice versa. That inflammation driven by metabolic factors is implicated in renal damage is nicely suggested by a study showing that the LDL receptor gene and other genes regulating lipid metabolism (fatty acid binding protein-3 and sterol regulatory element binding protein) as well as inflammatory genes (TNF-α and its receptors, IL-6 signal transducer and interferon-γ) and genes implicated in insulin resistance (glucose transporter-1 and vascular endothelial growth factor) are over expressed in glomeruli of patients with obesity-related nephropathy [25]. Although investigations on the link between adipokines and kidney damage have been started only in recent years, there is mounting evidence that lipids accumulation and alterations in fat cells cytokines can translate into inflammatory changes in the kidney.

Lipids

A parallelism between atherosclerosis and glomerulosclerosis was suggested about 20 years ago by Diamond, who envisaged the foam cell, the lipid overloaded macrophage, as the pivotal factor both in atherosclerosis and in glomerulosclerosis [26]. The pro-inflammatory and toxic effects of lipids on the kidney are summarized in Figure 1. Free fatty acids (FFA) accumulation increases

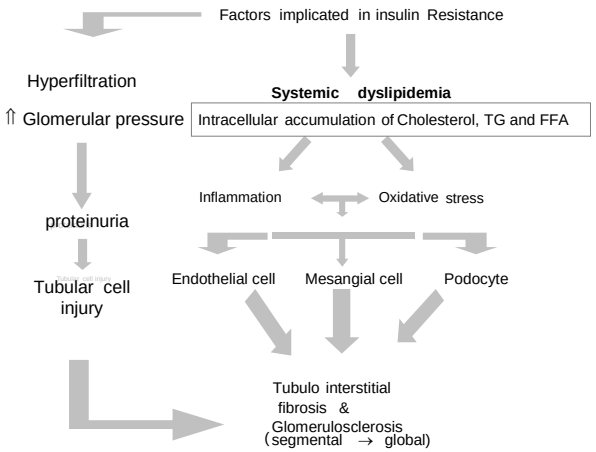

Fig.1

Figure 1 – Mechanisms whereby metabolic factors may cause renal damage. Isolated dyslipidemia may directly start the pathogenetic chain leading to tubulo-interstitial damage and glomerulosclerosis. Insulin resistance is a multifactorial phenotype which may be generated by altered major cytokines and adipokines profile (i.e. high IL-6, TNF-α and MCP-1, low adiponectin, high Resistin). Intracellular accumulation of triglycerides may impair insulin sensitivity. High angiotensin and Leptin resistance can contribute to reduced insulin sensitivity. High Leptin may per se engender kidney damage. Mechanisms summarised in the figure are described in more detail in the main text.

Слика 1 – Механизми со кои метаболните фактори можат да предизвикаат бубрежно оштетување. Изолирана дислипидемија може директно да го започне патогенетскиот синџир водејќи до тубуло-интерстицијално оштетување и гломерулосклероза. Отпорноста на инсулин е мултифакторијален фенотип кој може да биде генериран со променети главни цитокини и со профилот на адипокините (т.е. висок IL-6, TNF-α и MCP-1, low adiponectin, high Resistin). Интрацелуларната акумулација на триглицериди може да ја намали осетливоста кон инсулин. Високата отпорност кон ангиотензин и лептин може да придонесе за намалена сензитивност кон инсулинот. Високиот лептин може сам за себе да поттикне бубрежно оштетување. Механизмите претставени на сликата се опишани во повеќе детали во главниот текст

the synthesis of triglycerides (TG) and Very Low Density Lipoproteins (VLDL) which gives rise to atherogenic LDL and oxidized LDL in the liver. Hyperinsulinaemia and hyperglycaemia [27] induce organ damage by a variety of mechanisms including protein kinase C activation, oxidative stress, NF-kB activation

and other mechanisms eventuating in inflammation, apoptosis, and cell necrosis [28–29]. The transcription of many lipogenic genes is controllled by Sterol-Regulator Element-Binding Proteins (SREBP). SREBP-1 regulates fatty acid synthesis, whereas SREBP-2 is mainly involved in the control of cholesterol synthesis [30]. Peroxisome proliferator–activated receptors (PPAR) are present in virtually all organ systems, including the kidney [31]. When stimulated, these receptors promote adipogenesis and insulin sensitivity. Thiazolidinediones, a class of drugs with PPAR-γ agonist property, are currently used to treat insulin resistance in type 2 diabetics. As discussed below, both alterations in SERBP and in PPAR appear relevant to organ damage in experimental models. High-fat feeding in obesity-prone mice triggers obesity, hyperglycaemia and hyperinsulinaemia [32]. These mice show renal TG and cholesterol accumulation in glomerular and tubule-interstitial cells as well as over-expression of SREBP-1 and SREBP-2 proteins, PAI-1, type IV collagen and fibronectin and develop glomerulosclerosis and proteinuria [33]. FFA accumulation is responsible for endothelial dysfunction in a well-established model of visceral obesity such as the Zucker rat.

VLDL, intermediate-density lipoprotein (IDL) and LDL all enhance IL-6, TNF-α, and TGF-ß synthesis and induce mesangial cell proliferation [34]. Oxidized LDL stimulates extracellular matrix and MCP-1 and PAI-1 synthesis in these same cells [35]. IGF-I determines TG accumulation in mesangial cells which transform into foam cells and such a transformation impairs their ability to phagocyte and migrate [36]. Importantly, up-regulation of mesangial cell VLDL receptors (and hence enhanced TG entry) and down regulation of TG efflux from mesangial cells may be triggered by a reduction in PPAR-δ [37]. In proteinuric nephropathies and in full-blown nephrotic syndrome, albumin-saturated FFA appear causally implicated in tubulo-interstitial inflammation [38]. Overall these studies support a role of lipotoxicity in renal damage in dyslipidaemia and in obesity.

Cytokines

Besides T cells and macrophages, IL-6 is ubiquitously represented in fat cells being well expressed both in adipocytes and macrophages in visceral and peripheral adipose tissue. This cytokine is an autacoid, i.e. it acts locally, in the proximity of the site where it is synthesised, but also a hormone because it acts at distance where it exerts a variety of effects including amplification of the inflammatory process, stimulation of energy mobilization, hyperthermia and other effects including insulin resistance [39–40]. Circulating IL-6 is much increased in obese subjects and it predicts incident type 2 diabetes independently of other risk factors [41]. Interestingly, IL-6 increases Transforming Growth Factor-ß1 (TGF-β1) receptor activity and by this action it may favour fibrosis. IL-6 is a marker of progressive renal function loss in patients with IgA nephropathy [42]

and may be involved in renal damage in obesity, a condition characterized by high circulating levels of this cytokine.

Like IL-6, TNF-α is abundantly synthesised by macrophages in adipose tissue where it modulates insulin sensitivity by multiple mechanisms such as inactivation of insulin receptor and insulin receptor substrate-1, lipolysis and lipogenesis. Furthermore, TNF-α blunts the secretion of an important insulin sensitizer like adiponectin [43]. TNF-α has been shown to mediate inflammation and scarring in experimental crescentic glomerulonephritis [44], in acute renal failure in endotoxemia [45] and in renal fibrosis [46]. Similarly to IL-6, TNF-α may exert toxic effects on virtually all renal cell species including endothelial, mesangial and epithelial cells. However, it should be emphasised that until now there has been no study specifically testing the involvement of this cytokine or of IL-6 in the nephropathy associated with metabolic syndrome or with obesity in man.

Adipokines

Besides IL-6 and TNF-α, the adipose tissue makes up a variety of substances that may be implicated in kidney damage including plasminogen activator inhibitor-1 (PAI-1) and MCP-1. These factors may produce tissue damage by a direct pro-inflammatory mechanism or may act because implicated in insulin resistance [47].

Leptin is a fundamental adipose tissue hormone which modulates appetite and energy expenditure via pathways that modulate Neuropeptide Y in the hypothalamus. Circulating levels of leptin are strictly proportional to fat mass but obese subjects are resistant to the anorexigen effect of leptin [48]. Receptors for leptin are well expressed in the kidney [49]. In mesangial cells cultures of obese mice lacking the functional full-length leptin receptor (Ob-Rb), this adipokine enhances glucose uptake and augments TGF-ß type 2 receptor expressions, which eventually increases collagen production [50]. In the rat, leptin stimulates TGF-ß1 mRNA expression in glomerular endothelial cells and it is able to produce glomerulosclerosis and proteinuria by BP independent mechanisms [51]. This adipokine is implicated in hypertension and sodium retention secondary to obesity because it potently activates the sympathetic system, including sympathetic activity in the kidney [52]. Leptin is currently considered as a pro-inflammatory factor and a pro-oxidant implicated in endothelial dysfunction and atherosclerosis. Accordingly, the obese leptin-deficient mouse is protected from atherosclerosis despite the presence of other risk factors [53]. Hence, endothelial dysfunction represents an additional mechanism whereby this adipokine may induce renal damage. Collectively, these observations suggest that, also independently of hypertension, leptin may be involved in glomerulosclerosis in obese patients.

Adiponectin is an adipose tissue cytokine with well-characterized insulin-sensitizing, anti-inflammatory and anti-atherogenic properties. Adiponectin is inversely associated with body weight, with serum TG and LDL cholesterol levels and with various inflammation biomarkers. Plasma adiponectin concentration increases after weight loss [54–55]. Atherogenic changes characterize adiponectin-deficient transgenic mice [56]. Hypoadiponectinaemia is associated with endothelial dysfunction and with coronary events in patients with cardiac disease or with ESRD [57]. In spite of the fact that the evidence that adiponectin is a vasculoprotective factor is overwhelming, it remains still much debated whether this adipokine is cardiovasculoprotective or not in patients with CKD and ESRD. However, disparate results in current literature mainly reflect differences in the study populations, background risk factors and degree of statistical adjustment [58]. Very recent experimental studies strongly implicate low adiponectin in the pathogenesis of renal disease in obesity [59]. In this study albuminuria correlated inversely with plasma adiponectin in obese patients and the adiponectin-knockout mouse exhibits increased albuminuria and fusion of podocyte foot processes. In cultured podocytes, adiponectin increases the activity of AMP-activated protein kinase (AMPK), and both adiponectin and AMPK activation reduce podocyte permeability to albumin and podocyte dysfunction by decreasing oxidative stress. Furthermore, the adiponectin-deficient mouse treated with adiponectin shows normalization of albuminuria, improvement of podocyte foot process effacement, increased glomerular AMPK activation, and reduced urinary and glomerular markers of oxidant stress [59]. These intriguing results in a transgenic model and parallel observations in obese subjects suggest that adiponectin may prevent albuminuria, possibly by reducing oxidant stress in podocytes.

Glomerular hypertension and the renin angiotensin system

Substantial evidence has been accrued that the renin-angiotensin system and aldosterone are up regulated in obesity [60]. This phenomenon is attributable to sympathetic over activity (see above) and/or to hyperinsulinaemia and/or to enhanced synthesis of angiotensinogen in visceral fat. Both angiotensinogen and Angiotensin II type 1 receptor mRNA are over-expressed in visceral adipose tissue as compared to subcutaneous adipose tissue [61]. Weight loss in obese women is accompanied by a decrease in plasma angiotensinogen which is highly correlated with waist circumference reduction [62]. The renin-angiotensin system is of paramount importance in renal disease generation and progresssion in obesity because of its interference with glomerular hemodynamics (see below) and with inflammatory mechanisms. In a transgenic model of obesity, angiotensin-II blockade significantly reduces TNF-α, MCP-1 and oxidative stress and prompts increases in adiponectin levels [63]. Thus, inflammation and derange-

ment in adipokines levels may be additional mechanisms whereby the renin angiotensin system is conducive to renal damage in obese persons.

Hyperfiltration is commonly found in obese persons. Due to high sympathetic activity, high levels of angiotensin II and hyperinsulinaemia, obese persons display enhanced sodium reabsorption in the proximal tubule and are unable to rapidly increase sodium excretion. Enhanced proximal salt reabsorption determines a reduced delivery of sodium to the *macula densa* and therefore promotes afferent vasodilatation and enhanced renin synthesis. As a result of high local angiotensin II levels, the efferent arteriole is constricted in the obese. Glomerulomegaly and focal glomerulosclerosis represent the anatomical counterparts of glomerular hyperfiltration-hypertension. The Brenner theory linking low nephron number at birth with reduced intra-uterine growth [64] provides an explanation of why some individuals (those with a reduced nephron number) appear particularly prone to developing progressive renal damage later in life when overweight and obesity and other risk factors supervene. Severe obesity may alter renal haemodynamics also by mechanical compression of the renal vein [65]. Furthermore, morbidly obese patients frequently display sleep apnea, a sleep disorder engendering systemic and pulmonary hypertension [66]. Right ventricular overload in the obese with sleep apnea [67] may *per se* trigger and/or amplify venous hypertension in the kidney. Both left ventricular dysfunction (via reduced cardiac output) and right ventricular dysfunction (via increased venous pressure) may eventually impair renal perfusion, thereby further aggravating CKD in the obese.

Prevention and treatment issues

Metabolic risk factors and body weight excess – obesity independently contribute to nephrosclerosis, the most common histology pattern seen in patients with CKD. Lipotoxicity, inflammation and disturbances in the control of renal microcirculation all concur in engendering kidney damage in this condition but the precise causal involvement of these factors is still unknown. Interventions aimed at preventing overweight and obesity are fundamental to decreesing the burden of hormonal, inflammatory and haemodynamic factors implicated in the epidemics of cardiac and renal diseases. A meta-analysis has shown that, however achieved (by bariatric surgery, behavioural interventions or drug treatment) weight loss ameliorates the metabolic profile and reduces the inflammatory burden in obese patients [68]. However, the long-term effects of bariatric surgery are still unknown. Angiotensin antagonists have an almost ideal pharmacological profile for prevention and treatment of CKD progression in obesity but this contention is not supported by specific trials in this population. Thiazolidinediones, a class of PPAR-γ agonists, improve insulin sensitivity and

hyperglycaemia but a higher risk of progression toward heart failure has been reported in patients treated with Rosiglitazone [69]. Pravastatin and atorvastatin showed cardiovascular and nephroprotective actions [9–10] in CKD patients in secondary analyses performed in databases of large cardiovascular trials (see also chapter on dyslipidemia in chronic renal disease) and should be considered as a useful therapeutic option in patients with metabolic syndrome, obesity and CKD.

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Резиме

ПРЕКУМЕРНА ТЕЖИНА, ДЕБЕЛИНА И ПРОМЕНИ ВО МЕТАБОЛИЗМОТ КАЈ ХРОНИЧНА БУБРЕЖНА БОЛЕСТ

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Постои солидно знаење за поврзаноста на прекумерната тежина и дебелината со хроничната бубрежна болест (ХББ). Ризикот за терминална бубрежна болест (ТББ) прогресивно се зголемува со зголемување на нивоата на индекс на

маса на тело (ИМТ) и кај екстремно дебели поединци таквиот ризик е 5 пати поголем од лицата со нормална маса на телото. Висцералната маст, отпорноста на инсулин и воспалувањето се меѓусебно поврзани во студии на попречна анализа кај пациенти со ХББ, но сè уште не е испитано дали поврзаноста меѓу обемот на половината или соодносот половина/колк и ХББ предизвикува каузална поврзаност. И покрај тоа, знаењето за квантитативната врска меѓу факторите на ризик имплицирани во оштетувањето на бубрегот е сè уште ограничено, доказите што произлегуваат од клиничките серии кај пациенти со различни бубрежни болести (ИгА нефропатија, бубрежна агенезија или постнефректомија) ја поддржуваат хипотезата дека дебелината е важен фактор во прогресијата и можеби дури и во иницијацијата на ХББ. Хиперфилтрацијата обично се наоѓа кај дебелите лица. Поради големата симпатетичка активност, високите нивоа на ангиотензин II и хиперинсулинемија, дебелите лица покажуваат засилена реапсорпција на натриум во проксималните тубули и не се во можност брзо да го зголемат излачувањето на натриум. Засилената проксимална реапсорпција на сол утврдува намалена дистрибуција на натриум до макула денса и затоа ја поттикнува аферентната вазодилатација и зголемената синтеза на ренин. Како резултат на високите нивоа на локален ангиотензин II, еферентната артериола е контрахирана, стегната кај дебелите. Гломеруломегалијата и фокалната гломерулосклероза претставуваат анатомски пандани на гломеруларната хиперфилтрација-хипертензија. Освен хиперфилтрацијата, се јавува доказ дека инфламаторните цитокини создадени од масните ќелии предизвикуваат воспаление во бубрезите и дека овој механизам придонесува за намалување на бубрежната функција кај дебелите.

Клучни зборови: дебелина, ХББ, ТББ, обем на половина, ИМТ, хипертензија, отпорност на инсулин, воспаление.

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