Adverse renal consequences of obesity

Karen A. Griffin, Holly Kramer, and Anil K. Bidani
Loyola University Medical Center and Hines Veterans Affairs Hospital, Maywood, Illinois
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Griffin KA, Kramer H, Bidani AK. Adverse renal consequences of obesity. Am J Physiol Renal Physiol 294: F685–F696, 2008. First published January 30, 2008; doi:10.1152/ajprenal.00324.2007.—Emerging evidence indicates that obesity per se, even in the absence of diabetes, contributes significantly to the development and progression of chronic kidney disease (CKD). Glomerular hyperfiltration/hypertrophy in response to the increased metabolic needs of obesity are postulated to lead to the development of glomerulosclerosis (GS) in a manner analogous to that in reduced renal mass states. Nevertheless, the individual risk for developing GS with obesity is very low. It is proposed that glomerular hyperfiltration/hypertrophy are per se not pathogenic in the absence of an enhanced glomerular blood pressure (BP) transmission, and the modest preglomerular vasodilation that is likely present in the large majority of obese individuals is not sufficient to result in such increased BP transmission. However, in the small subset of obese individuals who are also born with a substantially reduced nephron number, there is a greater risk of enhanced glomerular BP transmission due to the substantially greater preglomerular vasodilation. Of perhaps greater clinical importance, similar additive deleterious effects of obesity on BP transmission would be expected in individuals with reduced renal mass, either congenital or acquired, or with concurrent renal disease, leading to accelerated progression. Of note, a low birth weight may be a risk factor for not only reduced nephron numbers at birth, but also for obesity and hypertension, resulting in a clustering of risk factors for progressive GS. Therefore, even though the individual risk for developing obesity GS is low, the cumulative impact of obesity on the public health burden of CKD is likely to be large because of its huge prevalence.

chronic kidney disease; glomerulosclerosis; hyperfiltration; hypertrophy; hypertension

THE GROWING EPIDEMIC OF OBESITY in the United States and worldwide, with its associated health care burden, has been the subject of much recent literature. The contribution of obesity to diabetes, hypertension, the cluster of risk factors grouped together under the broad nomenclature of “metabolic syndrome” or “syndrome X,” and the attendant risks for cardiovascular disease have all been extensively described. More recently, the potential impact of the obesity epidemic for the development of chronic kidney disease (CKD) has been emphasized in numerous publications, reviews, and editorials (3, 9, 30, 31, 36, 37, 60, 61, 70, 85, 111, 148). Given that obesity is a major risk factor for diabetes and hypertension (36, 37, 60, 61, 85), which together account for ~70% of all cases of end-stage renal disease (ESRD) (141), most of the increasing prevalence of ESRD in the United States over the past two decades may be attributable to the rapid and parallel increases in obesity and diabetes during the same period (60, 85). However, there is growing evidence that obesity per se, even in the absence of diabetes, significantly increases the risk of CKD and adversely impacts its progression (37, 60, 85). Conversely, weight loss has been shown to reduce proteinuria in both diabetic and nondiabetic nephropathies (97, 110, 111). The present review is primarily addressed to a critical evaluation of the potential pathogenesis of obesity-associated glomerulosclerosis (GS), the lesion believed to be largely responsible for the development of progressive renal disease and/or ESRD in obese individuals in the absence of diabetes (3, 60, 76, 85, 111–113).

Obesity as an Independent Risk Factor for CKD

Multiple cross-sectional and cohort studies have consistently demonstrated epidemiological associations among obesity, metabolic syndrome components (defined as the presence of 3 of the following 5 traits: abdominal obesity, impaired fasting glucose, hypertension, hypertriglyceridemia, and a reduced HDL cholesterol), and early CKD, primarily increased albuminuria and/or a decreased glomerular filtration rate (GFR; <60 ml·min⁻¹·1.73 m⁻²) (32, 37, 49, 64, 84, 85, 90). However, the levels of association are small (odds ratio ~1.5) and may be biased by potential misclassification (85). However, of relevance to the present review, a strong graded association has also been observed between increasing obesity and more advanced CKD and/or ESRD even after adjusting for baseline blood pressure (BP) and/or the presence of diabetes (45, 70, 85).

Obesity-related glomerulopathy. While the pathological correlates of the early CKD described in epidemiological studies remain unknown clinical observations indicate that obese individuals who develop substantial proteinuria and progressive renal disease are likely to exhibit marked glomerulomegaly and the lesions of focal segmental glomerulosclerosis (FSGS) on
biopsy. Since the 1970s, isolated case reports have noted the association among severe obesity, proteinuria, striking glomerulomegaly, and FSGS (72, 77, 142–144). In some cases, heavy proteinuria had been documented in morbidly obese adults in the absence of other glomerular pathology aside from glomerulomegaly (3, 76, 77). This led some investigators to view glomerulomegaly per se, to be part of the histologic spectrum of what has been termed obesity-related glomerulopathy (3, 76). On the other hand, substantial glomerulomegaly has also been observed in obese individuals at autopsy without evidence of antemortem proteinuria (33, 78, 79), indicating that glomerulomegaly, proteinuria, and GS may be separately mediated. Nevertheless, in a single center review of 6,818 kidney biopsies collected over a 14-yr period, proteinuric patients with a body mass index (BMI) ≥30 kg/m² were considered to have obesity-related glomerulopathy if they had glomerulomegaly with FSGS in the absence of other causes of FSGS such as human immunodeficiency virus, heroin abuse, and reduced renal mass (n = 57), or glomerulomegaly alone (n = 14) (76). Foot process effacement was less prominent and glomerulomegaly tended to be greater in degree and was present in 100% of the obesity-associated FSGS cases vs. 10% of patients with idiopathic FSGS (76). Obese patients also tend to exhibit less proteinuria, hypoalbuminemia, and edema and progress more slowly than those with idiopathic primary FSGS (76, 113). For clarity, the secondary FSGS associated with obesity in the remaining text will be called GS.

Variability in individual risk for obesity-related glomerulopathy. It is important to recognize that despite the growing emphasis on obesity as a risk factor for CKD and its public health importance, the absolute risk for an obese individual to develop GS and ESRD is very low, as illustrated by the relative rarity of GS compared with the prevalence of obesity in the population. Even in individuals followed for massive obesity, little evidence of overt renal disease has been seen (78, 79). Similarly, autopsy studies, while documenting glomerulomegaly, have not shown a greater presence of GS in obese individuals (69, 78, 79). Thus obesity per se seems not to be sufficient to result in GS in most individuals, despite the presence of multiple mechanisms that are postulated to promote renal damage and GS in obesity. Such data suggest that either the pathogenesis of proteinuria and GS in obesity depends on potential mechanisms that are not uniformly distributed in the obese population or that there are differences in genetic susceptibility to develop GS despite similar degrees of exposure, or some combination thereof. The situation is somewhat akin to hypertensive renal damage. Although hypertension is the second leading cause of ESRD (140), the absolute risk of a hypertensive individual developing severe enough renal damage to result in ESRD is believed to be <1% (16).

However, unlike hypertension, where studies in experimental models have provided significant insights into the potential reasons for the susceptibility differences (15, 16, 52–57), studies in obesity models have thus far failed to elucidate the reasons for similar differences in susceptibility even though these models also exhibit a variable propensity to develop GS. For instance, a high-fat diet-induced model of obesity in the dog exhibits most of the metabolic and hormonal features of human obesity as well as glomerulomegaly, but does not develop overt proteinuria or GS (59, 62). By contrast, the genetically obese Zucker rat (OZR) with the leptin receptor mutation readily develops proteinuria and GS (34, 80, 81, 93) but displays other significant differences from human obesity (60, 62). A more recently described high-fat diet-induced obesity (DIO) model in the Sprague-Dawley rat, which may be more relevant to human obesity than the OZR model, has so far only been reported to exhibit modest glomerular pathology without definite GS, at least after ~3 mo (42). Similarly, a high-fat diet-induced obesity/metallic syndrome model in the C57BL/6J mouse has been reported to develop modest albuminuria, mesangial matrix expansion, and mild GS after 12 wk (73). However, the same diet in the A/J mouse strain failed to produce either obesity or renal pathology, suggesting a potential importance of genetic factors in the susceptibility to both obesity and obesity GS (73).

In any event, any consideration of the potential pathogenesis of GS in human obesity needs to account for this seeming resistance to GS in most obese patients. On the other hand, such a pathogenesis construct should also be able to accommodate the accumulating data showing the significant adverse impact of superimposed obesity and the opposite salutary effect of weight loss on proteinuria and progression of existent CKD (37, 50, 97, 110–114).

Pathogenesis of Obesity-Related Glomerulopathy

Most of the neurohumoral, metabolic, structural, and hemodynamic abnormalities that have been implicated in microalbuminuria and/or decreased renal function have a limited potential to initiate overt GS. By contrast, glomerular hyperfiltration/hypertrophy have been explicitly postulated to lead to segmental GS in obesity (3, 21, 28, 37, 60, 62, 76, 93, 107, 111–114) in a manner analogous to that described with reduced renal mass states (23, 67, 68, 101, 154). Indeed, the terms hyperfiltration glomerulopathy and/or nephropathy have been used to emphasize the histological and clinical similarity of obesity glomerulopathy to reduced renal mass states (37, 111–114). Similarly, hypertension has been postulated to play an important role in the pathogenesis and/or progression of secondary FSGS (118), the characteristic pathological lesion observed in obesity (60, 76, 111–114). Hypertension is extremely prevalent in the obese population, and several excellent reviews have recently addressed the pathogenesis of the elevated systemic pressures seen in obesity (36, 60, 61, 115). Therefore, hypertension is an obvious candidate mechanism in the pathogenesis of obesity-associated CKD. However, mild to moderate hypertension per se as is generally observed in obesity, does not lead to either substantial proteinuria or FSGS, in the absence of other facilitating mechanisms (15, 16, 52). The following discussion is therefore primarily addressed to a critical evaluation of these mechanisms and their potential interactions in the pathogenesis of obesity GS, although it is acknowledged that other mechanisms may also play a smaller, contributory role.

Glomerular Hyperfiltration and Hypertrophy in Obesity

Based on a large number of studies that have reported the frequent association of obesity and increased GFR both in experimental animal models and in humans, it is widely postulated that increased metabolic demands associated with obesity lead to glomerular hyperfiltration (3, 9, 21, 27, 28, 37, 93, 111–114), with increases in kidney mass and glomerular hypertension representing the structural components of this re-
sponse (3, 62, 76, 78–81, 111, 116). Hyperfiltration and/or an increased filtration fraction have been considered to be surrogate markers for elevated glomerular capillary pressures ($P_{Gc}$), and obesity GS is believed to represent the long-term adverse consequence of glomerular hyperfiltration and/or elevated $P_{Gc}$. Although the concept has received widespread acceptance because of its biological plausibility, it perhaps represents a considerable oversimplification and fails to account for the very low incidence of obesity GS, despite the expected wide prevalence of this postulated pathway in the obese population.

Should obesity be considered a “hyperfiltration” state? Renal blood flow (RBF) and GFR in humans are traditionally expressed {[1.73 m$^2$ body surface area (BSA)]} to normalize for differences in body size (90, 132). Indeed, the National Kidney Foundation’s definitions and classifications of CKD stages are based on GFR levels per 1.73 m$^2$ BSA (90). Although the underlying physiological basis for the relationship has not been definitively identified, scaling of the existing GFR data across mammalian species with large differences in body mass have indicated that GFR is closely related to the metabolic rate, and such relationships between body mass and metabolic rate can be expressed using allometric power law equations with an exponent of 0.75 (25, 44, 131, 145). However, some investigators have suggested that the data within a species exhibit a better agreement with an exponent of 0.67 (which is also the exponent relating body mass to BSA) (63). In any event, even though the use of BSA to normalize GFR and RBF has been questioned (117, 124, 140), the fairly strong correlation that has been observed between BSA and GFR, as long as body size dimensions do not deviate substantially from the average, suggests that BSA serves as a reasonably valid surrogate marker within a species for the individual metabolic/excretory needs, in the absence of other variables that may independently alter such metabolic/excretory needs such as aging, hyperthyroidism, etc. (121, 132). Therefore, it is important to note that the increases in absolute GFR observed in obesity are not disproportionate to the increases in BSA (21, 28, 99, 120). Accordingly, given that normalized RBF and GFR exhibit an inverse relationship with BMI and sometimes even with BSA in obese individuals, it may not be strictly accurate to consider obesity to be a “hyperfiltration” state in absolute terms, at least at the physiological or population level, without additional qualification/caveats (vide infra).

Similar considerations are likely applicable to the interpretations of glomerular hypertrophy. As noted earlier, glomerulomegaly has been emphasized as a consistent feature in obesity. However, the glomerular size data obtained in renal biopsy samples obviously reflect a selection bias as biopsies are only performed in patients with significant CKD and/or proteinuria. Moreover, absolute glomerular size is reported and/or compared with control groups without being indexed for BSA. By contrast, carefully performed autopsy studies have shown that kidney weight and glomerular volume are more strongly correlated with each other and to BSA rather than other body size parameters (body weight, BMI, or height) (69, 79, 102). In this context, it is of interest that obesity is also associated with an increase, albeit not proportionate, in lean body (muscle) mass, as indicated by the higher total 24-h creatinine excretion observed in obese individuals (135a) and its decrease after weight loss (24, 27, 99). Such data indicate that the increases in GFR in obesity may not per se be maladaptive but rather represent coordinated and regulated increases in renal size and function that are likely proportionate to the metabolic/excretory needs of the obese individual. Qualitatively and conceptually, these increases are not dissimilar to the increases in GFR in taller or more muscular individuals. Conversely, at least part of the decline in GFR that occurs with aging may also not be pathological but represent the decreasing metabolic/excretory needs of the aging individual (121).

Obesity as a state of relative hyperfiltration. On the other hand, these very same considerations also indicate that to the extent that increases in BMI result in increases in lean body mass and metabolic/excretory needs, absolute GFR is also expected to increase. Thus in a given individual the absolute GFR is likely to be higher in the obese state than it would be in the nonobese state. Accordingly, it may be more accurate to consider obesity as a state of relative hyperfiltration. Such interpretations are consistent with the data that show that most (21, 24, 27, 28, 99, 120) but not all (4, 21) measurements in severely obese individuals have found the absolute GFR to be higher than in their lean counterparts. Moreover, several of these studies have also shown declines in GFR after the weight loss following intestinal bypass surgery or gastrectomy (24, 27, 99). By contrast, with smaller BMI increases, the GFR results have been more inconsistent, perhaps not surprisingly given the modest GFR increases expected and the many variables that may impact it, including age and other coexistent conditions (21, 60). As noted in a recent review, the absolute GFR has been found to be higher in some studies but not in others, while still others have found differences in only subsets of obese individuals and only under certain specific conditions of altered salt intake, etc. (21, 86). A similar variability of results has been observed for studies that have measured renal perfusion or plasma flow with or without measurements of GFR and filtration fraction (21, 65, 117, 124). In this context, it is important to emphasize the limitations of the empirically derived renal function equations that are widely employed to estimate GFR from serum creatinine measurements in clinical and epidemiological studies. They are unreliable when the renal function (serum creatinine) is in the normal range and, not surprisingly, their performance additionally declines with increasing deviation from the average body size, muscle mass, fat content, and creatinine generation (90, 109, 122). The problem is illustrated by a recent publication reporting the presence of hyperfiltration as an early marker of metabolic syndrome but which used the weight-based Cockcroft-Gault equation to estimate the absolute creatinine clearance, making the finding of such a relationship with increasing BMI almost inevitable (137).

Of note, similar normalization and variability considerations apply to the data obtained in animal models. For instance, a high-fat diet-induced obesity model in the dog is consistently associated with increases in absolute GFR and kidney and glomerular enlargement (59, 62) but not when corrected for body weight or kidney size. By contrast, both the GFR and single-nephron GFR (SNGFR) data are substantially more variable in rodent models of obesity, perhaps in part due to methodological reasons. Increased, unchanged, and even decreased GFR (inulin or creatinine clearance) have been reported in the OZR, although kidney and glomerular enlargement are observed more consistently (34, 80, 81, 93, 104, 107, 119, 125). Similarly, attempts to confirm single-nephron hy-
perfiltration in obesity by direct micropuncture measurements in a limited number of studies in this model have also yielded inconsistent and variable data (104, 107, 125). Of note, for unclear reasons, kidney weight, glomerular volume, and GFR do not increase in an obesity model induced by bilateral hypothalamic electrolytic lesions in the Munich-Wistar rat, although the obese males do develop increased BP, proteinuria, and GS (12).

Mediation of hyperfiltration in obesity. Although, as noted earlier, substantial evidence links metabolic/excretory needs to GFR within and across species, the precise parameters that reflect these metabolic/excretory needs, the signals by which these needs are sensed and communicated to the kidney, and the mechanisms that eventually provide regulation of the ambient GFR in response to these needs all remain ill defined. Nevertheless, it seems unlikely that mechanisms specific to obesity such as insulin resistance/hyperinsulinemia are primarily involved. However, a pathway that may be particularly relevant as it can potentially contribute to both the hypertension and the hyperfiltration in obesity is that postulated by Hall and coworkers (41, 60, 61). Increased salt reabsorption proximal to the macula densa, mediated by increased sympathoadrenal activity, angiotensin II, and other mechanisms, leads to the relative suppression and/or resetting of the tubuloglomerular feedback (TGF) system (60, 61, 98, 126). This in turn is expected to result in relative afferent arteriolar vasodilation, increased PGC, and hyperfiltration. However, these investigators have also recently noted that aldosterone blockade with eplerenone not only blunted the increases in BP but also that in GFR in the obese dog model (41). The data were interpreted to indicate that although plasma aldosterone is only modestly elevated in obesity, it may nevertheless contribute to increased plasma volume and hyperfiltration through its effects on Na balance and TGF. In this context, it is of note that TGF resetting has also been postulated to mediate the hyperfiltration after renal ablation (123), diabetes (136), and with increased protein intake (129, 131, 151). The latter probably also contributes to the hyperfiltration of obesity, at least in some situations (9, 93, 120). For instance, dietary (and protein) restriction in the OZR to a level of food intake of the lean control rats results in a rapid decline in creatinine clearance to control levels, although the body weight in the obese rats is still twice that of lean control rats (93). Of interest, the TGF alterations have also been suggested as a mechanism for increased PGC and enhanced glomerular damage in African-Americans (8). Nevertheless, while these data clearly indicate that TGF resetting is present in states of chronically increased GFR, it remains to be established whether such resetting is causal or permissive. Moreover, the mechanisms that link such TGF resetting to the metabolic/excretory needs of an individual remain largely conjectural at the present time.

Single-nephron hyperfiltration in obesity. The pathophysiological consequences of hyperfiltration are postulated to stem from the stress imposed on glomerular capillaries (GS) by hyperfiltration at the single-nephron level (23, 67, 68, 101, 154). Given that nephron number does not increase, any obesity-associated increases in GFR need to be achieved by increased SNGFR. While such increases in SNGFR in humans can only be definitively inferred if the absolute normalized GFR is unambiguously elevated, the increases are expected to be fairly modest in most obese individuals, as discussed earlier. However, the results of recent autopsy studies using the physical dissociator/fractionator combination indicate that such interpretations may not always be valid (69, 71, 95, 102). These studies have shown that although there is a proportionality between GC area and functional/metabolic needs, there is a very large natural variability in the glomerular number (several-fold) between individuals that is unrelated to body size parameters. For instance, Nyengaard and Bendtsen (102) found a −4.3-fold range in glomerular number in a series of 37 autopsy cases. Even more strikingly, in a series of 67 autopsied adults from the United States and Australia, Hoy et al. (59) found an almost eightfold range for glomerular number (~230,000–1.8 million). Mean glomerular volume (GV) varied 5.6-fold, with a significant inverse correlation observed between GV and glomerular number, as would be predicted. Moreover, the total GV, the product of glomerular number and mean GV, exhibited the strongest correlation with kidney weight and BSA, indicating that the greatest degree of glomerular hypertrophy is observed in those individuals genetically endowed with the fewest glomeruli at birth. A major implication of these data is that the greatest increase in SNGFR, the pathogenically relevant parameter, is also expected to occur in this subset. In addition, such increases may be present even if the overall absolute GFR is not increased. It is also relevant to note that large increases in GV and SNGFR per se may have the potential to alter the GC barrier (large-pore and/or shunt pathway) and lead to microalbuminuria or mild overt proteinuria even in the absence of additional glomerular injury (38, 100). It may also be important to note that a growing literature on fetal programming, although controversial in some aspects, also suggests that prenatal nutritional factors and/or low birth weight may be important risk factors not only for a reduced nephron number at birth but also for hypertension, obesity, and the associated cardiometabolic complications in adult life (1, 9, 11, 22, 89, 92, 94, 95, 100, 106, 127, 134, 135, 147, 152, 154).

Glomerular Hyperfiltration/Hypertrophy as Mediators of Obesity GS

The initial observations linking glomerular hyperfiltration to GC injury and sclerosis were obtained two decades ago in models of severe (>5/6) renal mass reduction (RMR) by Brenner and colleagues (67, 68). The concept was formulated that “glomerular hyperfiltration, an adaptation seen in response to a reduction in functional nephron number whether induced genetically, surgically or by acquired renal disease” (23), was, in fact, maladaptive and eventually led to the progressive sclerosis of the initially normal remnant glomeruli (23, 67, 68). Based on micropuncture data, it was concluded that “the elevated single nephron glomerular filtration rate (SNGFR) common to these pathophysiologic conditions is usually caused by increases in the glomerular capillary plasma flow rate (QA) and mean glomerular capillary hydraulic pressure (PGC), which in turn are due to adaptive reductions in preglomerular and postglomerular arteriolar resistances” and “that . . . systemic hypertension is not required for glomerular capillary hyperfiltration and hypertension” (23). Additional support was derived from observations in experimental diabetes which also showed hyperfiltration, increased PGC, and GS (68, 101, 154). While these seminal studies and the “hyperfiltration theory” did undoubtedly provide new insights and the impetus for much investigation,
substantial evidence in the intervening years has suggested the need for a critical re-evaluation and modification.

Are pathogenic increases in $P_{GC}$ intrinsic to and necessary for chronic hyperfiltration? Such a concept is integral to the “hyperfiltration theory,” but a great deal of evidence indicates that substantial hyperfiltration can be achieved with very modest and likely nonpathogenic increases in $P_{GC} (≥5\,\text{mmHg})$, such as after uninephrectomy. Even with greater hyperfiltration, as after 5/6 renal ablation, the necessity for greater $P_{GC}$ increases is belied by the fact that the angiotensin-converting enzyme inhibitor enalapril almost normalizes $P_{GC} (53 ± 1\,\text{mmHg})$, but SNGFR is not reduced (5). That these effects are not specific to angiotensin II blockade but are a consequence of normotension is indicated by the fact that comparable increases in remnant kidney GFR, SNGFR, and glomerular volume are achieved with only modest ($−5\,\text{mmHg}$) increases in $P_{GC}$ when 5/6 ablation is performed in rat strains that do not develop subsequent hypertension due to genetic resistance (18, 51), or when surgical excision rather than infarction is used to achieve comparable 5/6 RMR without hypertension (18, 53, 57). The reasons for the lack of need for more substantial increases in $P_{GC}$ (>5 mmHg) for hyperfiltration can be readily inferred by an examination of the physical determinants of SNGFR (40, 138). A coordinated increase in GC surface area available for filtration (GC hypertrophy) and increases in single-nephron plasma flow (SNPF), achieved through proportionate decreases in afferent and efferent resistance, would be sufficient to result in hydraulic conductance (91). Such effects may account for the surprising finding that despite the marked anatomic increases in GC area, $K_f$ is not only not increased after 5/6 ablation but is in fact reduced (5, 22). However, when $P_{GC}$ is nearly normalized by therapeutic agents or only modestly increased as in normotensive models of $−5/6$ RMR, the increases in $K_f$ expected with the observed GC hypertrophy are indeed seen (5, 18, 57, 130). Thus more than very modest $P_{GC}$ increases are not only deleterious but are also not very effective in increasing SNGFR, as is also true for isolated increases in SNPF in the absence of increases in GC area ($K_f$). Thus it is not surprising that GC hypertrophy invariably accompanies states of chronic hyperfiltration including diabetes, even though the precise mechanisms regulating such hypertrophy remain to be defined.

Such data clearly suggest that large increases in $P_{GC}$ are not intrinsic to compensatory hyperfiltration, which is largely achieved by increases in SNPF and $K_f$ in normotensive animals (18, 57, 130). Rather, such $P_{GC}$ increases represent the consequence of superimposed GC transmission of systemic hypertension because of the associated renal autoregulatory impairment (vide infra). These data also indicate that pathological $P_{GC}$ elevations cannot necessarily be inferred even if hyperfiltration is present, as has been frequently done in the obesity literature. In this context, despite the acknowledged limitations of such indirect modeling approaches (43), the dextran-sieving studies by Chagnac et al. (28) in severe obesity are widely cited in support of an elevated $P_{GC}$ during obesity hyperfiltration. However, the modeling analysis was consistent with only a modest increase in $ΔP$ (40 mmHg in obese vs. 35 mmHg in lean subjects) in the absence of a significant increase in $K_f$ (vide supra). Some investigators have also used an elevation in filtration fraction (FF), even in the absence of hyperfiltration, to infer the presence of efferent constriction and increased $P_{GC}$ (21, 86). However, changes in FF can also occur in the absence of such hemodynamic changes. This is particularly true when filtration pressure equilibrium is not achieved by the efferent end of the glomerular capillaries, as is true in most rat strains, dogs, and likely also in humans (6, 7, 26, 98). To illustrate, a modest, isolated decrease in SNPF (RPF) even when due to proportionate changes in afferent/efferent resistances in this instance does not result in a proportionate decrease in GFR, so FF exhibits an increase. Conversely, increases in SNPF due to proportionate changes in afferent/efferent resistances would lead to a smaller, nonproportionate increase in GFR, but a fall in the FF. Similarly, increases in GC area ($K_f$), if not accompanied by proportionately comparable increases in SNPF (RPF), have the potential to increase GFR and FF without a change in $P_{GC}$.

Is hyperfiltration per se injurious in the absence of substantial $P_{GC}$ elevations? While some injurious effects of lifelong hyperfiltration cannot be definitively excluded, particularly in rodents who tend to develop proteinuria and GS with aging, the bulk of evidence in humans suggests that even very substantial glomerular hyperfiltration and hypertrophy are largely benign in the absence of systemic and glomerular hypertension. For instance, normal pregnancy is associated with substantial hyperfiltration without untoward renal effects (13). Similarly, the vast majority of renal transplant donors who would be expected to exhibit greater increases in SNGFR than most obese individuals, except possibly for the small subset with severely reduced nephron numbers at birth, exhibit little evidence of adverse renal effects (16, 112). It is also possible that the loss of nephrons over time with aging, or other concurrent comorbidities may add to the need for further increases in SNGFR and GC stress in some obese individuals. A small minority of obese individuals do develop proteinuria and while the incidence of proteinuria, hypertension, and GS is somewhat higher after uninephrectomy performed for other indications, or in individuals with even greater loss of renal mass, the great majority of patients still do not develop clinically significant renal disease (50, 112). Even in rodent models, the existing data indicate that the term “hyperfiltration injury and/or nephropathy” that has been widely used in the literature is a misnomer for what is essentially hypertensive GC injury. Consistent with such concepts, although hyperfiltration is observed universally after severe RMR (5/6 ablation), the susceptibility to GS across species and even in different strains of rat and mice exhibits marked differences largely paralleling the differences in their genetic susceptibility to hypertension after.
such RMR (52). Indeed, the lack of elevated systemic pressures may account for the remarkably slow development of significant overt nephropathy in the rat with partially treated streptozotocin-induced diabetes, despite the presence of substantial hyperfiltration and glomerular hypertrophy as well as a very large number of other postulated pathogenic mediators (19). In this context, it is of note that some investigators have considered glomerular hypertrophy rather than hyperfiltration to be the primary maladaptation that causes GS because of increased and dysregulated activity of growth factors such as angiotensin II, PDGF, and TGF-β, etc. (46, 47, 83, 153). However, the arguments against “hyperfiltration” as a primary maladaptive response are equally applicable to the GC hypertrophy response.

**Obesity as a State of Potentially Enhanced Susceptibility to Hypertensive Renal Damage**

Although the glomerular hyperfiltration and/or hypertrophy in obesity are per se unlikely to be pathogenic, they may nevertheless be associated with an increased risk of hypertension and glomerular injury, due to a potential for an enhanced glomerular transmission of systemic pressures as well as an increase in the local glomerular capillary susceptibility to barotrauma.

**Glomerular BP transmission and obesity.** As noted earlier, mild to moderate hypertension as generally present in obesity, usually does not result in glomerular injury as increases in systemic BP within the autoregulatory range, episodic or sustained, are prevented from being transmitted to the glomerular capillaries by proportionate autoregulatory vasoconstriction of the preglomerular vasculature (15, 16, 35, 51, 52, 91). Accordingly, most hypertensive patients only exhibit slowly progressive benign nephrosclerosis (vascular hyaline arteriosclerosis with eventual glomerular ischemia). However, because PGF is not increased, glomerular injury (segmental GS) and/or proteinuria is not observed. Thus the slope of the relationship between BP and glomerular damage is essentially flat in most patients, with hypertension within the autoregulatory range. By contrast, if autoregulation is impaired, even moderate BP increases are more freely transmitted to the glomerular capillaries, resulting in barotrauma and GS. Such autoregulatory impairment was initially demonstrated in the 5/6 ablation model (20) but since then has been described in other models of enhanced susceptibility to hypertensive injury as well as in CKD patients with a significant loss of renal function (15, 16, 51, 91). The increased susceptibility to hypertensive GS in states of impaired autoregulation is demonstrated by a greatly reduced BP threshold for GS (15, 16, 51, 91), with the slope of the relationship (increase in % GS/mmHg increase in systolic BP) paralleling the severity of autoregulatory impairment (15, 16, 52, 53, 56). Although the primary data were obtained in experimental models, the clinical validity of the concept has been demonstrated by the adverse renal effects observed with even moderate hypertension in patients with CKD, leading to the lower recent targets for optimal BP control (<130 mmHg systolic) to slow the progression of CKD (74).

Although glomerular BP transmission can also potentially be enhanced by preglomerular vasodilation per se, if (15–17, 39, 52) the autoregulatory ability to respond to BP elevations is preserved (such as after uninephrectomy), only a modest increase in susceptibility to hypertensive GS is observed (15, 16, 100, 112). While autoregulation has not been formally evaluated in obesity, a recent study from our laboratory has shown preserved renal autoregulation in an obese diabetic rodent model, although interpretations are somewhat complicated by the fact that this model apparently develops BP-independent GS (51). Nevertheless, most obese patients are expected to exhibit modest preglomerular dilation which is unlikely per se to lead to autoregulatory impairment. On the other hand, such preglomerular dilation may be much greater in the subset of individuals who are born with a substantially reduced complement of nephrons and who then develop severe obesity (100, 114, 154). A parallel situation would be expected in individuals with both obesity and coexistent CKD. In such individuals a substantially greater glomerular transmission of systemic pressures and a higher susceptibility to GS would be expected.

In this context, it is also relevant to briefly consider some of the limitations of the presently available methods to assess glomerular BP transmission. These limitations primarily stem from the fact that BP is fundamentally labile and exhibits spontaneous rapid and often large fluctuations in the conscious state (35, 66, 88, 91). The glomerular transmission of such fluctuating pressures in states of enhanced glomerular BP transmission (55) is also expected to be a highly dynamic process, given that autoregulation is not instantaneous (15–17, 35, 52, 91). Under such conditions, PCGC in the conscious state is expected to exhibit considerable lability, paralleling BP lability. As GS is likely to reflect the aggregate chronic pressure exposure, isolated PCGC measurements, like isolated BP measurements, are unlikely to be adequate for definitive assessment (15, 16, 52, 53, 88), besides being potentially compromised by surgery and anesthesia-induced renin release and relative efferent constriction, as noted earlier (16, 53). Similarly, conventional step autoregulatory studies, although they have provided important insights, only assess the potential magnitude of the steady-state response to BP steps, but not its kinetic aspects (2, 17, 35, 91). An enhanced glomerular BP transmission and injury could occur due to either a diminished magnitude of the response or due to a slower rate of response, as both together are expected to determine how much of a given BP fluctuation is transmitted to the glomerular capillaries and for how long (2, 15–17, 91). Therefore, alternative methods have been proposed to assess dynamic BP transmission, although at least as currently performed and interpreted they too have significant limitations (2, 17, 35). Hopefully, better quantitative methodologies will be developed that will allow an adequate assessment of dynamic BP transmission in both obese and nonobese states.

**Obesity and glomerular capillary susceptibility to barotrauma.** While there is evidence that glomerular hypertrophy per se may not be pathogenic, it may nevertheless enhance the susceptibility to hypertensive GS (15, 16, 52, 96, 146). For instance, it has been postulated that glomerular hypertrophy may lead to an increase in GC wall tension at any given PCGC through the Laplace law effects (tension = pressure × radius) as illustrated in Fig. 1 (18). However, such effects would only be expected if the enlargement of GC area was at least in part due to an increase in GC radii. However, substantial enlargement in GC surface area can be achieved as after uninephrectomy by an increase in the GC length and branching without a significant increase in GC radii (103, 105, 128). Only with
hypertension and therefore to the development of GS in obesity (36, 41, 59–61). However, as for other forms of CKD, particularly proteinuric nephropathies, angiotensin II has also been postulated to directly contribute to proteinuria and GS in obesity and RAAS blockade to provide BP-independent, specific renoprotection (21, 65, 86, 110, 111). These deleterious effects of angiotensin II are believed to be mediated by both hemodynamic (efferent constriction) and nonhemodynamic (direct tissue damage-promoting) pathways. The evidence for the preferential efferent vasoconstriction is based on the filtration fraction data, which as noted earlier, have likely been overinterpreted. Moreover, the selective efferent vasoconstrictive effects of angiotensin II are primarily observed in states of reduced renal perfusion pressure, where enhanced prostaglandin and possibly nitric oxide release from the macula densa counteract the afferent responses to angiotensin II (91, 126). By contrast, there is little evidence of such preferential efferent effects in most hypertensive states. It is of note that in the high-fat diet-fed, conscious, hyperfiltering obese dog, filtration fraction and proteinuria are not increased significantly despite increased plasma renin activity (59). With respect to the other BP-independent and GS-promoting effects of angiotensin II in obesity, most such postulates are largely derived from observations in other nonobese experimental and/or clinical contexts, rather than in obesity per se. While the ability of angiotensin II to produce deleterious effects in in vitro systems has been extensively documented, the primary in vivo evidence for such postulates is based on the claims of BP-independent superior renoprotection provided by RAAS blockade. As reviewed in greater detail elsewhere, the evidence for these claims is less than definitive and is based on inadequate BP measurements in animal models and potentially flawed interpretations of the clinical trial data that have not excluded alternative explanations (14, 15, 53, 60). In any event, RAAS blockade in combination with diuretics is very effective in reducing BP, and effective BP reduction, regardless of therapeutic regimen, remains the mainstay for preventing adverse outcomes in all patients, including those with obesity and CKD (15, 16, 53, 74).

Hyperlipidemia. Evidence of renal and glomerular/mesangial lipid deposition (foam cells) in FSGS has long led to analogies with atherosclerosis and to the postulation of a pathogenic role for hyperlipidemia (58, 82). However, while there is epidemiological, clinical, and experimental evidence to suggest that hyperlipidemia and/or lipotoxicity may serve to amplify renal damage and the progression of CKD, its role in the initiation of obesity GS is largely based on observations in the OZR (34, 80–82) and the more recently described DIO model in the mouse (73). The OZR exhibits marked and early hyperlipidemia, and therapy with lipid-lowering agents substantially ameliorates the development of proteinuria and GS without reducing glomerular hypertrophy (34, 80–82). The precise mechanisms by which GS is potentiated have not been completely defined, but both early podocyte injury (34), and, based on the mouse model, glomerular cell lipotoxicity due to an upregulation of the renal expression of sterol-regulatory element-binding proteins (SREBP-1 and 2) have been postulated (73). Additionally, the lipotoxicity to the proximal tubular epithelial cells as a consequence of proteinuria and enhanced uptake of albumin-bound free fatty acids is thought to lead to tubulointerstitial inflammation, fibrosis, and accelerated pro-
type II collagen staining (75). However, severe hyperlipidemia is not a prominent feature of patients with obesity GS, and little correlation has been observed between lipid levels and renal disease progression in such patients (3, 111–114). Moreover, in patients with reduced renal mass at baseline, obesity but not differences in lipid levels distinguished those who developed progressive proteinuria and loss of function (50, 112). Of potential relevance, there are also experimental data that the adverse effects of hyperlipidemia may be exacerbated in reduced renal mass states (75).

Increased leptin levels. Wolf and coworkers (149, 150) have postulated that the increased leptin levels that are present in obesity may also contribute to proteinuria and GS. While there is substantial evidence that leptin may play a significant role in obesity hypertension, the evidence for a role in GS is more limited. Although significant effects are seen in cell culture systems, the primary in vivo evidence comes from the observed effects of 3 wk of exogenous leptin infusion in normal rats (149, 150). Modest increases in proteinuria (~2-fold) and type II collagen staining (~3-fold) were observed (data for overt histological GS were not provided) and were thought to be mediated by increased TGF-β1 and collagen production by endothelial and/or mesangial cells. However, it is of note that concentrations of leptin used were an order of magnitude higher than those found in obese individuals, but no increases in tail-cuff BP were observed. In any event, as noted by Ballermann (10), the OZR strain, in which all leptin receptors (including Ob-Ra and Ob-Rb) are defective, is extremely susceptible to develop GS. Therefore, it is likely that if leptin plays a role in obesity GS, it is probably a secondary, facilitative role.

Summary of Proposed Pathogenesis of Obesity-Related Glomerulopathy

Figure 2 schematically illustrates and summarizes the proposed construct for the pathogenesis of obesity GS discussed in the preceding pages. While it is consistent with the “multi-hit” concept for the development and progression of GS in obesity with the reduced nephron number at birth being the initial hit (100), it emphasizes an enhanced glomerular BP transmission instead of hyperfiltration per se as the determinative hit. We believe that the “hyperfiltration theory” is based on an erroneous interpretation of the importance of $P_G$ as a major determinant of SNGFR increases rather than being a secondary consequence of the enhanced glomerular transmission of co-existent hypertension. It is hypothesized that the latter occurs in a small subset of obese individuals who additionally have a reduced number of functional nephrons either because of a deficit at birth or later acquisition due to disease or surgery. Additionally, it is proposed that the substantial glomerular hypertrophy that is required in such instances to achieve the needed increases in SNGFR may further contribute to GS by magnifying the deleterious effects of enhanced BP transmission by reducing the capacity of enlarged glomerular capillaries to withstand mechanical stress (reduced podocyte density and/or increases in wall tension).

Conclusions/Perspectives

There is increasing evidence of the adverse impact of obesity on the development and progression of CKD even in the absence of diabetes. It is widely postulated that the glomerular hyperfiltration/hypertrophy in response to the increased metabolic needs of obesity leads to the development of GS in a manner analogous to that in reduced renal mass states, possibly facilitated by the other metabolic/hormonal risk factors present in obesity. Nevertheless, only a very small minority of obese individuals develop obesity-related glomerulopathy (heavy proteinuria and GS), despite a high prevalence of most of these factors in the obese population. The reasons remain unclear. We suggest that the explanation may reside in the fact that these mechanisms, including glomerular hyperfiltration/hypertrophy per se, have a very limited pathogenic potential for GS in the absence of enhanced glomerular BP transmission. Experimental and clinical data suggest that in the absence of impaired autoregulatory responses, the increase in glomerular pressure transmission is relatively modest, even with significant preglomerular vasodilation that might be expected in the vast majority of obese individuals, and despite their greatly increased prevalence of hypertension. However, recent autopsy data have indicated a much larger variability in nephron endowment (several-fold) at birth than had been suspected. We suggest that the risk of enhanced glomerular BP transmission and hypertensive injury may be significantly greater in obese individuals who are also born with severely reduced nephron numbers due to a much greater need for preglomerular vasodilation and hypertrophy at the single-nephron level. Accordingly, it is not surprising that obesity is a major risk factor for the development of GS and progressive renal disease in individuals with a substantial and additional reduction in renal mass either at birth (unilateral renal agenesis) or later in life (nephrectomy or CKD). Such individuals with a congenital or acquired nephron deficit are also more likely to exhibit salt sensitivity and possibly develop more severe hypertension, further magnifying their risk (1, 9, 11, 22, 23, 89, 92, 95, 100, 106). Therefore, the observed large impact of obesity on the risk of developing ESRD is consistent with these concepts. It is
probably also worth emphasizing that although the individual risk of obesity-related glomerulopathy and CKD is quite low, the sheer and increasing prevalence of obesity in the general population makes it likely for obesity, even in the absence of diabetes, to become an increasingly important contributor to the public health burden of CKD and ESRD. Given the limited success of current regimens in achieving sustained weight loss, the primary emphasis may need to be targeted, at least for now, to preventive public health strategies.

REFERENCES


