Blood Pressure and Diabetic Nephropathy

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This is the fourth of a series of articles based on presentations at the American Diabetes Association Scientific Sessions held 5–9 June 2009 in New Orleans, Louisiana, pertaining to blood pressure and renal disease in diabetes.

Diabetic nephropathy and obesity

At the Clinical Update in Diabetic Nephropathy at the American Diabetes Association Scientific Sessions, Karen A. Griffin (Maywood, IL) discussed interrelationships between obesity and the kidney, noting that obesity appears to be related to the increase in end-stage renal disease (ESRD), in part because of its relationship to diabetes and hypertension, but with a 1.2-to 1.6-fold increase in chronic kidney disease (CKD) risk even correcting for these associations. Reviewing CKD staging, in stages 3, 4, and 5, the glomerular filtration rate (GFR) is 30–59, 15–29, and <15 ml/min per 1.73 m^2 BSA, respectively, and Griffin pointed out that the adjustment for body surface is quite important when considering the effect of body size. In a Kaiser Permanente analysis of 1,471 subjects developing ESRD in a 8,347,955 person-year follow-up, adjusted for age, sex, race, education, cigarette use, diabetes, blood pressure, lipids, and other variables, obesity increased the likelihood of ESRD with BMI ≥35 associated with a 5-fold increase, BMI 30–34.9 associated with a 3-fold increase, and BMI 25–29.9 associated with a 1.5-fold increase in risk (1). There are a number of different forms of obesity-related CKD, with the majority of cases associated with microalbuminuria, endothelial dysfunction, and mild-to-moderate decrease in GFR, mainly associated with cardiovascular risk. Coexistent obesity and CKD lead, however, to accelerated progression of the latter (2,3). A form of glomerulopathy occurs with obesity characterized by glomerular enlargement (which is more common in obesity) and focal segmental glomerulosclerosis (4). The pathogenesis may involve hyperfiltration, leading to glomerular capillary injury and sclerosis, in a fashion similar to occurring experimentally with 5/6 nephrectomy (5). From a hemodynamic point of view, there is a high GFR in obesity (6)—a phenomenon demonstrated in comparison of body mass among a variety of different mammalian species. GFR decreases after weight loss in morbid obesity (7,8).

Griffin noted that hyperfiltration, which occurs with loss of renal mass, as in renal transplant donors, or with increased metabolic requirement, as in pregnancy, predominantly reflects increased glomerular capillary flow rather than an increase in glomerular pressure. Most patients with hypertension develop benign nephrosclerosis, other than at extremely high blood pressure levels, while those with nonproteinuric CKD and, to an even greater extent, those with diabetic nephropathy and other renal diseases develop renal damage in a fashion related to blood pressure but at much lower blood pressure levels (9); Griffin showed experimental models of this (10), supporting the recommendation that blood pressure goals in persons with diabetes or with renal disease should be lower than those for the overall population with essential hypertension.

There are protective renal autoregulatory mechanisms that reduce susceptibility to hypertensive damage (11,12) in the absence of renal disease. Obesity does not in itself result in increased susceptibility to loss of renal autoregulation, but there is an eightfold variation in number of glomeruli per kidney present at birth, with lower number in subjects with lower birth weight (a risk factor for insulin resistance), with the number not changing subsequently (13). Obese individuals who happen to have a low glomerular number may then be at greater risk of extreme increase in glomerular size and hence of developing pressure injury, with increase in glomerular size potentially increasing the susceptibility to injury by increasing glomerular capillary wall stress (14). Griffin concluded by proposing a multihit concept of the pathogenesis of progressive glomerulosclerosis in obesity, based on the combination of decreased nephron number and/or other underlying CKD increasing likelihood of deterioration in the face of the glomerular hyperfiltration and increase in glomerular size developing from the obesity itself (15).

Diabetic nephropathy and vitamin D

Rajiv Agarwal (Indianapolis, IN) discussed effects of vitamin D on diabetic nephropathy and on the progression of CKD. A small but rather influential study carried out 3 decades ago randomized subjects with GFR <35 ml/min to 1,25-dihydroxyvitamin D (1,25-D) (1 μg daily) or to vitamin D3 (4,000 units daily), finding increased progression of loss of GFR with the former (16). Agarwal observed, however, that high dosages were used, with the majority of those receiving calcitriol developing hypercalcemia, and that the duration of treatment was overly short. Nevertheless, the concept that vitamin D should not be given in CKD was put forward, hampering development of the field. 25-hydroxyvitamin D [25(OH)D] is taken up by a specific proximal tubular receptor, then 1α-hydroxylated to 1,25-D, which then circulates to act in other tissues. There are, however, extra-renal 1α-hydroxylation systems in tissues such as the monocyte, leading to intracellular or paracrine effects, with subsequent intracellular inactivation. Vitamin D has a number of potentially beneficial renal effects, including renin-angiotensin system (RAS) inhibition by an action of the vitamin D/vitamin D receptor/RXR heterodimer to downregulate renin gene transcription, effects on insulin resistance, effects on vascular smooth muscle and endothelium, and activation of antibacterial action in monocytes and macrophages. Vitamin D also downregulates transforming growth factor (TGF)-β, decreasing tubular interstitial fibrosis, and has an effect on the mesangial cell to decrease glomerulosclerosis. Studies are beginning to emerge in man. The prevalence of vitamin D deficiency increases, and parathyroid hormone (PTH) increases with decreasing GFR, but not only is there the expected

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low level of 1,25-D but also a low level of 25(OH)D. Proteinuria levels also are inversely proportional to the 25(OH)D level, well below nephritic proteinuria levels. Agarwal noted that there is a lower prevalence of hypertension in latitudes closer to the equator with greater sun exposure (17), suggesting that this might be related to vitamin D status. 1,25(OH)D may act directly to decrease vascular smooth muscle proliferation, and 25(OH)D deficiency is associated with vascular stiffness and endothelial dysfunction, with no evidence that subjects with ESRD and higher vitamin D levels have greater degrees of arterial calcification (18). There is a sixfold higher incidence of hypertension in persons with 25(OH)D <15 ng/ml compared with those with levels >30 ng/ml (19), and the 1,25(OH)D quartile also is associated with both systolic and diastolic blood pressure (20). In a study comparing calcium supplementation alone or in combination with vitamin D, not only were PTH levels reduced, but blood pressure was lower in the latter group, suggesting that deficiency may contribute to the development of hypertension (21). Agarwal also reviewed his study of 220 subjects with stages 3 and 4 CKD showing an antiproteinuric effects of the vitamin D receptor agonist paricalcitol, with 14% of those receiving placebo versus 31% of those receiving paricalcitol having reduction in dipstick proteinuria. Improvement was seen regardless of use of ACE inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), suggesting an upstream effect on insulin resistance, on the TGF-β pathway, or on inflammation (22). Parenthetically, he noted that dipstick proteinuria shows considerably better correlation than usually recognized with the protein-to-creatinine ratio (23,24); we have shown similar correlation in assessment of microalbuminuria (25). In Agarwal's 24-person pilot study of placebo versus paricalcitol treatment of patients with 25(OH)D deficiency, albuminuria and measures of inflammation decreased; a larger trial is ongoing.

Treatment for diabetes with renal disease: what works?

Alan Go (San Francisco, CA) reviewed studies of diabetic nephropathy including clinical cardiovascular and renal end points rather than proteinuria per se, pointing out what appear to be more or less useful treatment approaches. The Steno-2 trial of 160 type 2 diabetic patients with microalbuminuria showed that an 8-year multifactorial intervention with glycemic control, RAS blockers, aspirin, and lipid lowering led to a 46% reduction in all-cause mortality after an additional 5-year period of observation (26). Improvement in nephropathy was seen at 4 and 8 years, with a 56% reduction in new and worsening nephropathy and an absolute 6% decrease in the need for dialysis. Another somewhat encouraging intervention that Go described used an electronic registry, visit reminders, and patient-specific physician alerts in 69,965 visits from 8,405 adult patients with type 2 diabetes at 238 health care providers in 24 practices from 17 health systems to achieve systolic blood pressure <130 mmHg, A1C <7%, and LDL cholesterol <100 mg/day; 12.6% of intervention vs. 8.5% of control patients achieved these goals—certainly important outcomes, although considerably less than the improvement found in process measures (27). In a trial of the direct renin inhibitor aliskiren, 599 type 2 diabetic patients with albuminuria, all treated with losartan (100 mg daily), were randomized to a placebo versus addition of 150 mg then 300 mg aliskiren. Proteinuria decreased by 18–20% with a trend to less reduction in GFR although with no significant impact on systolic blood pressure; the study was not powered to examine clinical events (28).

Other approaches do not appear to be as useful. A study comparing the ARB telmisartan with the ACEI ramipril with the combination of both included more than 9,600 diabetic patients with 4.7-year follow-up, showing noninferiority of the two individual treatments (29). Disappointingly, however, there was no additional benefit of combined treatment. Telmisartan treatment showed a trend to reduced GFR, and combined treatment showed significantly lower GFR, despite lower levels of albuminuria with these treatments than with ramipril (30), arguing against the hypothesis that albuminuria can be used as a marker of nephroprotection. Furthermore, a study of 5,927 ACEI-intolerant high-risk patients with end-organ damage followed for 56 months showed no significant benefit of telmisartan versus placebo, with particularly little evidence of benefit in patients with diabetes and with a trend to faster rate of decline in GFR with telmisartan, despite the agent being associated with lesser increase in albuminuria; elimination of patients followed for shorter periods, and of heart failure hospitalization as an end point, did give a suggestion of benefit (31). Similarly, treatment with telmisartan beginning soon after an ischemic stroke and continued for 2.5 years did not significantly lower recurrent stroke, major cardiovascular event rate, or diabetes (32).

Go reviewed several studies of statin treatment in subjects with CKD. Post hoc analysis of a trial comparing atorvastatin 10 mg with 80 mg daily in 1,501 diabetic patients showed that among the 546 patients with stage 3–4 CKD the higher dose of atorvastatin was associated with more substantial evidence of reduction in cardiovascular outcomes than was seen in those with normal GFR, as well as with greater increase in GFR (33). In a study of 2,776 patients with ESRD undergoing hemodialysis including 535 subjects with diabetes, however, administration of rosuvastatin 10 mg versus placebo did not reduce nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death—a finding similar to that of an earlier study with atorvastatin (34)—suggesting that there may be a point after which lipid lowering is not beneficial. Similarly, Go reviewed the Veterans Affairs Diabetes Trial (VADT), concluding that intensive glycemic treatment does not appear to be associated with reduction in adverse outcome, although causing a fourfold increase in hypoglycemia (35). Go's assessment may, however, be somewhat harsh, as reassessment of the VADT findings led to a correction to the effect that intensive glycemic control was associated with improvement in all albuminuria outcomes (36), and a fascinating new VADT analysis shows that glucose lowering reduced cardiovascular events in those with less coronary artery calcification (37), suggesting that glycemic treatment may play an important role early in the natural history of diabetes.

Combination RAS blockade

Lawrence Krakoff (New York, NY) discussed the question of combined blockade of the RAS at the Mount Sinai Diabetes conference on 7 January 2010, asking the question, benefit or harm? He reviewed the components of the system. Renin exists in activated and inactivated forms, but with interesting questions raised whether the latter actually have biological activity. Angiotensinogen is synthesized in the liver, influenced by a number of factors, with renin leading to generation of the decapeptide angiotensin

I and with ACE (as well as another system involving the enzyme chymase) leading to generation of the octapeptide angiotensin II (AII), which has multiple roles, including proinflammatory effects, as do other components of the system. Aldosterone secretion is stimulated by AII as well as by other factors, in particular elevations in circulating potassium levels.

The majority of antihypertensive agents have effects on some of the components of the system: β-blockers decreasing and diuretics and vasodilators increasing renal renin release, ACEI reducing AII formation, ARB acting (although only partially) at the AII type 1 receptor, and direct renin inhibitors blocking angiotensin I formation; only the calcium channel blockers are neutral. Given the importance of the RAS as an approach to blood pressure management and the complexity of the system (38), it is important to review the limitations of the existing classes of agents. ACEI will incompletely decrease AII generation and have effects on kinin and substance P, while ARBs are incomplete in their effect on the AII type 1 receptor and have no effect on the type 2 receptor. Both ACEI and ARB lead to feedback increase in active renin generation. The direct renin inhibitors also are incomplete in their action, and because of their feedback effect in increasing inactive renin levels, Krakoff raised the possibility of adverse effect if inactive renin has biologic actions.

The question, then, is whether there might be value to combining inhibitors of the RAS acting at multiple levels. A number of end points could be envisaged, including blood pressure and albuminuria reduction; adverse effects such as hyperkalemia, hypotension, and worsening renal function; and outcome benefits including cardiovascular disease events, renal disease progression, and, particularly in congestive heart failure (CHF) studies, prevention of hospitalization. One potential combination, that of β-blockers with ACEI or ARB, shows little evidence of additive blood pressure–lowering effect, although formal studies are lacking.

The first area to be investigated was the combination of ACEI with ARB treatment; a widely cited positive study (39), however, was recently retracted after investigation suggested the possibility of data fabrication (40). In a study of 405 type 2 diabetic subjects with microalbuminuria comparing the ACEI ramipril alone with the combination of ramipril plus the ARB irbesartan, no additive effect was observed on either albuminuria or blood pressure (41), and in a study of subjects with decreased cardiac function following myocardial infarction randomized to the ARB valsartan, the ACEI captopril, or both, either agent was found to be effective, but the combination led to a higher 18% rate of adverse effects in comparison with the 12–15% rates with either agent alone (42). Krakoff discussed the study Go had mentioned of 25,620 high-risk hypertensive individuals, with either diabetes or existing vascular disease, randomized to the ARB telmisartan, ramipril, or both, and noted the remarkable achievement of 99.8% follow-up over a median of 56 months. There was, he pointed out, somewhat greater blood pressure lowering with the combination but a greater likelihood of hypotension and of renal dysfunction and no difference in CV mortality, myocardial infarction, stroke, or hospitalization for CHF (29). Only in a study of 5,010 participants with CHF randomized to usual care (typically including an ACEI) alone or with addition of valsartan was there a 24% reduction in hospitalization (43), and a recent subset analysis showed that the benefit extended to subjects with renal insufficiency, although the ARB did increase the likelihood of hyperkalemia in these patients from 4.5 to 8.5% (44). Krakoff concluded that there is little benefit of combined ACEI/ARB in blood pressure and little difference in cardiovascular outcome, with a suggestion that outcome is worse with the combination in subjects studied after myocardial infarction.

The topic of combination treatment addressing RAS components has received new impetus with the direct renin inhibitor aliskiren. A study of ~2,000 hypertensive patients showed somewhat greater blood pressure lowering with aliskiren in combination with valsartan than with either agent alone, although with a greater likelihood of hyperkalemia (45); Krakoff reviewed another study Go had described of type 2 diabetic subjects with hypertension and nephropathy receiving aliskiren plus losartan or losartan alone and noted that blood pressure differences may have been lessened by use of other agents, although pointing out that there was again a trend to more frequent hyperkalemia (28). Similar findings were reported in a crossover trial of 26 type 2 diabetic subjects with albuminuria, subjects receiving aliskiren or irbesartan alone or the combination, the latter leading to significantly greater reduction in urinary albumin excretion. In the study, both agents individually reduced GFR and there was greater such effect after combined treatment (46). In a study of patients with CHF receiving either an ACEI or an ARB, aliskiren reduced basic natriuretic peptide and urine aldosterone with some evidence of improvement in left ventricular function (47); as yet there is no evidence of improvement in clinical outcome in such patients. The combination of direct renin inhibition with ARB or ACEI may, then, offer benefit, but Krakoff termed the evidence for this as not being strong and pointed out that from a financial perspective the ~30-fold greater cost of such agents than ACEI makes it somewhat difficult to strongly recommend their use.

Additional studies

A number of studies presented at the American Diabetes Association Scientific Sessions shed further light on these topics. Ou et al. (abstract 175) found mean serum 25(OH)D levels of 26 vs. 23 ng/ml in 168 diabetic vs. 85 control subjects. Among diabetic patients, 25(OH)D correlated with weight, blood pressure, fasting glucose, and A1C and negatively with age and HDL cholesterol, suggesting potential benefit of supplementation. Naik et al. (abstract 92) studied 375 subjects and found that vitamin D deficiency was associated with an increased likelihood of development of coronary artery calcification over 3-year follow-up. Philippe et al. (abstract 667) reported decreased fecal elastase and/or chymotrypsin in 92 of 458 diabetic patients; those with deficiency of both enzymes had lower vitamins E, D, and A levels and a greater likelihood of insulin deficiency, suggesting that pancreatic exocrine as well as endocrine deficiency states may not be uncommon in diabetes and giving a potential mechanism for the association of diabetes with vitamin D deficiency.

Konoshita et al. (abstract 31) screened polymorphisms in the RAS and found that the response to the ARB valsartan was greater in subjects with higher blood pressure and in those with diabetes, but also was greater in CC homozygotes of the renin C-5312T gene. Chatterjee et al. (abstract 282) followed 13,398 participants in the Atherosclerosis Risk in Communities (ARIC) Study for 9 years, with 1,484 subjects developing diabetes. Serum potassium was inversely associated with se-

rum insulin, and compared with those who had potassium ≥5 mEq/l, those with levels 4.5–4.99 had 1.4-fold and those with levels <4.5 had 1.7-fold increase in risk of diabetes, respectively, controlling for use of ACEIs, β-blockers, and diuretics. Perhaps related to this association of higher potassium with less diabetes, Muhlestein et al. (abstract 99) found that among 357 diabetic subjects with angiographically diagnosed CHD plasma renin activity <0.6 $ng \cdot ml^{-1} \cdot h^{-1}$ was associated with more than a twofold reduction in mortality.

Bountouvis et al. (abstract 796) treated 20 type 2 diabetic individuals with mean GFR 51 ml/min per 1.73 m^2 with spironolactone (25 mg daily) and found at 3 months an 8-mmHg reduction in 24-h ambulatory diastolic blood pressure but a 0.5 $mmol \cdot l^{-1} \cdot l^{-1}$ increase in potassium, without change in brachial artery flow–mediated dilation, A1C, or GFR. At 12 months, however, there was a trend to worsening GFR and loss of the effect on blood pressure, suggesting that benefits from aldosterone blockade might be outweighed by risks.

Other studies reported interesting associations of diabetes with albuminuria. De Cosmo et al. (abstract 826) reported proline-12-alanine polymorphism genotype findings among 1,119 hypertensive, initially normoalbuminuric type 2 diabetic subjects and showed that those with the alanine genotype, which is associated with lower weight, were 45% as likely to develop microalbuminuria as those homozygous for the proline polymorphism, but, interestingly, that those in the latter group receiving ACEI treatment were less likely to develop albuminuria. Voulgari et al. (abstract 819) enrolled 193 newly diagnosed type 2 diabetic cigarette smokers with microalbuminuria in a smoking cessation lifestyle program. Among the 95 who quit, albuminuria at 1 year decreased by 38%, whereas those continuing to smoke had a 16% reduction during this period. Brix et al. (abstract 28) reported that YKL-40, a marker of plaque rupture, was increased by 22 and 78% in subjects with micro-and macroalbuminuria over levels in normoalbuminuric type 2 diabetic subjects, as well as being associated with serum creatinine and age. Mohammedi et al. (abstract 30) studied polymorphisms in the enzyme superoxide dismutase 1 in 1,278 type 1 diabetic patients from three cohorts, finding associations of specific alleles with microalbuminuria and hypertension.

Kim et al. (abstract 790) found urate levels of 4.5, 5.0, and 5.6 mg/dl among 320, 94, and 41 type 2 diabetic subjects with normo-, micro-, and macroalbuminuria, respectively, independent of age, sex, creatinine clearance, A1C, lipids, diabetes duration, blood pressure, plasminogen, fibrinogen, or C-reactive protein levels. In multivariate regression analysis, other significant determinants of albuminuria were fibrinogen, total cholesterol, and systolic blood pressure. Uric acid levels are associated with reduction in insulin sensitivity, perhaps because of change in tubular urate handling, and a number of studies also suggested association with the development of diabetes. Kodama et al. (abstract 1002) found that a 1 mg/dl increase in uric acid was associated with an 8% increase in diabetes risk in a meta-analysis of 11 studies adjusting for BMI and blood pressure. Kramer et al. (abstracts 660 and 1044) reported that 2,342 subjects undergoing glucose tolerance testing and followed for a mean of 13.2 years showed, for every 2 mg/dl increase in serum uric acid, 25, 20, and 20% increases in all-cause mortality adjusted for age, smoking, BMI, alcohol, exercise, diuretic use, and estimated GFR among subjects with normal and impaired glucose tolerance and with diabetes, respectively, suggesting that the association of urate with mortality may be independent of its association with abnormal glucose metabolism. Of 566 subjects having follow-up glucose tolerance testing, 55 developed type 2 diabetes; for each 1 mg/dl increase in urate, the risk increased 50%, adjusting for age, sex, BMI, diuretic use, and GFR, with risk only significant among those with impaired fasting glucose at baseline. Shankar et al. (abstract 1048) confirmed an association of uric acid with diabetes risk in 2,868 subjects followed over 15 years, independent of age, sex, education, cigarette and alcohol use, blood pressure, lipids, and A1C, with the likelihood of diabetes 1.2-, 1.7-, and 1.9-fold increased in the 2nd, 3rd, and 4th tertiles of serum uric acid level, respectively.

Other aspects of hypertension and renal disease in diabetes were addressed as well. Schwartz et al. (abstract 112) studied 57 type 2 diabetic subjects with chronic kidney disease, finding that creatinine levels decreased 8, 21, and 19% and estimated glomerular filtration rate increased 9, 29, and 27%, respectively, at 25, 75, and 150 mg daily doses of the antioxidant inflammation modulator Bardoxolone methyl. Watanabe et al. (abstract 809) reported that levels of insulin-like growth factor binding protein-related protein 1, a member of the IGFBP family with low affinity for IGF but a high and specific affinity for insulin, are increased in human renal proximal epithelial cells incubated with transforming growth factor-β1, with levels of the protein increased in urine of persons with diabetes, suggesting it to be a marker of tubular injury. Ghanim et al. (abstract 807) reported that a 4-h insulin infusion reduced transforming growth factor β, plasminogen activator inhibitor-1 and intercellular adhesion molecule-1 in ten type 2 diabetic patients, suggesting potential benefit. Khalil et al. (abstract 26) found significantly greater amino acid infusion-induced increase in glomerular filtration rate and renal plasma flow, and decrease in renal vascular resistance, in children of type 1 diabetic mothers than of type 1 diabetic fathers, suggesting that in utero exposure to the diabetic environment may lead to reduced renal reserve.

Leichter et al. (abstract 26-LB) found that among 284 persons undergoing eye screening the presence of arcus senilis was associated with fasting glucose and blood pressure as well as with age; there was no association with lipids or body weight. Waki and Terasaki (abstract 395) reported the outcome of simultaneous pancreas kidney transplants during the period from 1987–2007, finding that graft survival has been stable since 1995. Rayhill and Roberts (abstract 396) reported that both greater donor age and donor BMI >30 were associated with lower graft survival. Kazempour-Ardebili et al. (abstract 401) performed 48-h continuous glucose monitoring on 17 diabetic persons with end-stage renal insufficiency, finding 24-h mean glucose of 227 versus 176 mg/dl on dialysis versus nondialysis days, with nadir glucose occurring in 14 of the patients within 24 h after dialysis.

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