

Prevention of Diabetic Nephropathy

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1

Significance of the Clinical Problem: Diabetic Nephropathy

- Progressive proteinuria (albuminuria)
- Progressive decline in GFR (glomerular filtration rate)
- USA: nearly half of patients entering ESRD (end-stage renal disease) programs have diabetes.
 - Most have T2DM, due to the higher prevalence of T2 vs. T1DM
- Nephropathy develops in 15-35% of T1DM patients; peak incidence around 15-20 yrs of diabetes duration.
- Nephropathy rates are same or higher in T2DM (not lower); about 40% in US diabetes population overall.

2

Diabetic Nephropathy: Significance of the Clinical Problem

- After adjusting for population growth, ESRD incidence in USA is 35% higher than 10 yrs ago. Reasons unclear.
- Rising cost of dialysis! Prevention or delay of dialysis has been identified as a critical goal in addressing rapidly rising health care cost.
- The medical cost of diabetic nephropathy is now over \$10 billion annually.

3

Diabetic Nephropathy: Significance of the Clinical Problem

- Once overt nephropathy (albuminuria) and low GFR are present, further progression toward ESRD may be virtually unavoidable.
- But slowing the rate of decline is important!
- There is a marked increase in CVD (cardiovascular disease) risk with nephropathy and CKD (chronic kidney disease). Among diabetes/CKD patients, CVD mortality is a higher risk than dialysis itself. Address CVD risk factors in diabetes/nephropathy/CKD patients!

4

Diabetic Nephropathy: Significance of the Clinical Problem

- With diabetes, there is value in proactive control of nephropathy risk factors both before and after the development of CKD!
 - Blood glucose
 - Blood pressure
 - Lipids
 - Tobacco use
 - Obesity
- And these are the same risk factors to address in regard to CVD!

5

Diabetic Nephropathy: Significance of the Clinical Problem

- There is a long silent period of gradual development of serious underlying kidney lesions, which is asymptomatic.
- The risk of nephropathy and CKD in diabetes tends to be underestimated:
 - By patients
 - By providers
- We have an important role as educators and guides for our patients regarding this issue.

6

Case 1: Mike M.

- 26 y/o Caucasian man, T₁DM for 18 yrs.
- Glargine/Lantus BID; aspart/Novolog before meals.
 - He estimates premeal aspart doses without counting carbs. He was taught carb counting, but doesn't like to do it.
 - For correction: aspart 1 unit for every 50 mg/dl of BG over 150 mg/dl.
 - Works in AM; attends classes in afternoon.
- Previous diagnosis HTN (hypertension). Took lisinopril; stopped 1 yr ago (cough). No other BP med.

7

Mike M.:

- No other meds. No allergies.
- Last dilated eye exam 1 yr ago, normal.
- No numbness or tingling of hands or feet.
- No chest pain or dyspnea on exertion. No claudication symptoms.
- BG meter had incorrect date and time; downloaded results difficult to interpret.
- BG values written in logbook for past week only. Insulin doses not recorded. Low BGs in afternoon; erratic and variable BGs, highs as well as lows.
- A_{1c} 7.6% today; previous 8.0%.

8

Mike M.:

- Fam. Hx: Mother with T2DM, hypothyroidism.
- Soc. Hx: Married, 2 children ages 5-1/2, 4 y/o.
Plumber by training, laid off 1 yr ago, working with his Dad. No tobacco use; no 2nd hand tobacco in home.

9

Mike M.: Physical Exam

- BP 121/75, HR 93, weight 230 lb., BMI 35. (Obesity is not restricted to T2DM!)
- HEENT: normal fundoscopic exam.
- Chest: normal.
- CV: normal heart and carotid pulses.
- Extremities: normal pulses in upper and lower extrem.
- Neuro: normal 10 gm monofilament exam of feet.
- Skin: no acanthosis; no necrobiosis or xanthomas.

10

Mike M.: Lab

- Lipid panel: TC 161, TG 214, HDL 50, LDL 69 mg/dl.
- Microalbumin:
 - Urine microalbumin <2 mg/L
 - Urine creatinine 59 mg/dl
 - UACR (urine albumin/creatinine ratio) "unable to calculate" (undetectable)
- Thyroid:
 - free T4 1.15 ng/dl (0.93 - 1.7)
 - TSH 3.27 uU/ml (0.3 - 4.5)
 - TPO-Ab (thyroid peroxidase) <10 IU/ml (<35)
 - Thyroglobulin Ab 68 IU/ml (<40)

11

Microalbuminuria: Urine Microalbumin/Creatinine Ratio (UACR):

- Normal: <30 mg/24 hr; <30 mg/gm (or mcg/mg).
- Incipient diabetic nephropathy: 30 - 300 mg/24 hr; 30 - 300 mg/gm.
- Overt diabetic nephropathy: >300 mg/24 hr; >300 mg/gm.
- Ask your lab to process a random urine sample for creatinine as well as microalbumin, and print the ratio result!
- UACR: $\frac{\text{alb. (mg/L)}}{\text{creat. (mg/dl)}} \times 100 = [\text{ratio result}] \text{ mg/gm}$
- Mike: $< 2/59 \times 100 = < 3.4 \text{ mg/gm}$.

12

Mike: Assessment

- Is Mike at risk for diabetic nephropathy?

13

Mike:

- 18 yrs duration of diabetes. In peak incidence range for nephropathy. The incidence of nephropathy in T1DM levels off after ~ 20 yrs duration.
- No evidence of any microvascular or macrovascular complications so far, including no abnormal microalbuminuria (GFR unknown at present).
- Accumulating data show patients with normal microalbumin may already have decreased GFR:
 - In T2DM: HTN, age, obesity (other causes of CKD).
 - In T1DM, too! In 1 study, decreased GFR with n'l microalbumin was assoc. with more serious glomerular lesions.
- Monitor both GFR (S. creat.) and microalbumin annually!

14

Mike: BP

- Had previous diagnosis of HTN; not on medication.
- HYPERTENSION is a major independent risk factor for diabetic nephropathy, and needs to be treated!
- Goal BP 130/80 or under.
 - ACCORD results notwithstanding. In the group with "goal BP 140/90," the avg. systolic BP was 133.
 - Renal outcomes weren't measured as primary outcome.
 - Other studies have shown benefit for BP control with nephropathy: UKPDS, DCCT-EDIC. Strong data support aggressive BP control to prevent/delay nephropathy in T1 and T2DM pts with HTN.

15

Mike: BP

- ACEI/ARB therapy may have additional beneficial effect.
- But ultimately, which drug you use is less important than whether you get the pressure down.
- BUT: BP medications have not shown benefit for primary prevention of diabetic nephropathy (n'l BP AND n'l microalbumin).
 - Possible benefit of ACEI/ARB therapy for prevention of retinopathy, but limited data.

16

Mike: BP

- Suggest: defer BP medication at this time.
- Monitor BP closely.
- Pt. education about the issue of nephropathy and the importance of watching BP.
- Low salt diet.
- Weight loss.
- (Tobacco cessation, if relevant!)

17

Mike: BG

- What about Mike's blood glucose control?
- A1c 7.6%, above goal. eAG ~ 170 mg/dl.
- Variable BG, high and low.
- Intensified glycemic control (goal A1c < 7.0%) has been shown in multiple studies to delay the development of microalbuminuria and overt albuminuria in both T1 and T2 DM.
- To adjust insulin doses, review pt's BG info.

18

Mike: BG logbook

	BB	AB	BL	AL	BD	AD	Bed
M	160		58	287	88	150	132
Tu	89		51	50			217
W	145		190	51	253	69	179
Th	175		103	103	94	218	230
F	130						

19

Mike: BG

- Is his Lantus dose appropriate?
- Are his aspart/Novolog doses accurate?
- What about carb counting?
- Does he adjust his insulin before physical activity?
- Consider trying again to have him use carb counting. It's a critical skill for T1DM mgmt. Your dietician/diabetes educator can help. Recommend a carb counting book (e.g., Calorie King). Consider a digital food scale.
- Or try suggesting a scheduled dose of rapid insulin before meals; he can then raise or lower that dose if his carb intake varies, and reduce that dose before physical activity.

20

Mike: Lipids

- Mike had high triglycerides 214 mg/dl. Goal < 150 mg/dl.
- High TG are associated with increased progression from normoalbuminuria to microalbuminuria.
- There is no data currently to support the use of lipid-lowering agents for primary prevention of diabetic nephropathy in T1DM pts with both normal microalbumin and normal lipids.
- Statin therapy is recommended for all pts with DM nephropathy and elevated LDL. Goal LDL < 100 mg/dl; optional goal < 70 mg/dl. No dose adjustment needed for any statin with GFR > 30 ml/min.

21

Mike: Lipids

- Fibrate therapy:
- Can be considered to lower TG in this setting.
- ACCORD lipid study: Reported no benefit of adding fibrates to statins for CVD outcomes in T2DM. But avg. TG was ~167 mg/dl for group at baseline. In those with TG > 200 mg/dl, fibrates did show benefit.
- Dose adjustment for CKD: Reduce dose of gemfibrozil when S. Creat. > 2 mg/dl. Reduce dose of fenofibrate when creat. clearance < 50 ml/min.

22

Mike: Thyroid

- Positive thyroglobulin antibody; family history of hypothyroidism; TSH in upper half of normal.
- Hypothyroidism can be a cause of elevated triglycerides.
- But there are no data to show benefit of thyroid hormone treatment for TSH in normal range, or for CV benefit when TSH 5 – 10 uU/ml.
- Suggest: He may be at increased risk for future progression to hypothyroidism. Inform pt.
- Monitor TFT's yearly.

23

Case 2: Mrs. Z

- 69 y/o Mexican woman, T2DM of 12 yrs duration since diagnosis (longer duration of undiagnosed diabetes?).
- Previously on oral agents; started insulin 2007.
- Developed statin-induced myositis; off statins.
- Asthma; required prednisone for exacerbation; worsened BG control. Now off steroids for several months.
- Insulin: detemir/Levemir BID; lispro/Humalog before meals by sliding scale, 2 units per 50 mg/dl above 150 mg/dl. Also glimepiride/Amaryl 4 mg BID.

24

Mrs. Z:

- Checks BG 3 times a day, before meals. States BG never over 120 mg/dl. Does not keep BG logbook. Did not bring BG meter with her today.
- A1c 8.3% today.
- Walks for ½ hr every Tuesday with her daughter.
- HTN: lisinopril 40 mg daily
losartan 25 mg daily
metoprolol 50 mg BID
doxazosin 4 mg qHS
furosemide 20 mg qAM

25

Mrs. Z:

- Hyperlipidemia: fish oil 2,000 mg BID
- Other meds:
 - Omeprazole 20 mg daily
 - Gabapentin 600 mg TID
 - KCl 20 mEq daily
 - Alendronate 70 mg weekly for osteoporosis
 - Vitamin D 1,000 IU daily (Int'l Units)
 - Vitamin B12 1,000 mg daily p.o.
- Allergies: fenofibrate (rash), simvastatin (myositis); lactose intolerant

26

Mrs. Z:

- Fam. Hx: F had T2DM, deceased MI age 62. M alive age 85, T2DM for 40 yrs, legally blind (retinopathy). Siblings: 2 brothers with T2DM, both deceased, 1 after bilat. lower extremity amputation. 4 sisters are healthy. 2 daughters age 40's, 1 with HTN. Granddaughter age 10, healthy, overweight.
- Soc. Hx: Widowed. Worked in a frozen food packaging plant, retired 3 yrs ago. Moved to MT to live with her daughter. No tobacco or 2nd hand smoke. No alcohol.

27

Mrs. Z: Physical Exam

- BP 136/62, HR 61; 136/65, 65. Weight 182 lb, BMI 33.
- Gen'l: obese, comfortable, pleasant.
- HEENT: 2-3 microaneurysms in fundi.
- Neck: Thyroid n'l size and texture.
- Chest: lungs clear now, no wheeze.
- CV: normal heart and carotid pulses, no bruit.
- Abd: benign.
- Ext.: No edema. Absent pedal pulses both feet. Skin of feet cool, mildly thin, slow capillary refill. No callus or foot ulcer.
- Neuro: Moderately impaired sensitivity by 10 gm monofilament.

28

Mrs. Z: Lab

- A1c 8.3%.
- Serum creatinine 0.7 mg/dl, eGFR 86 ml/min.
- Urine microalbumin 4 mg/L, urine creatinine 21 mg/dl
- UACR 19 mg/gm.
- Lipid panel: TC 186, TG 124, HDL 23, LDL 138 mg/dl.
- LFTs: AST 63 U/L (<45), ALT 25 U/L (<50); fatty liver?
- Thyroid: free T4 1.21 ng/dl (0.93 – 1.7), TSH 6.1 uU/ml.
- Summary: normal creat/GFR and microalbumin,
- BUT: Is Mrs. Z at risk for nephropathy?

29

Mrs. Z: Assessment

- 69 y/o woman, T2DM, obesity, HTN, dyslipidemia, neuropathy, early retinopathy, osteoporosis, asthma.
- Hispanic: Epidemiologic data suggest increased risk of diabetic nephropathy in this population (also in African Americans and East Asians). Also strong family history of cardiovascular disease. (FH of diabetes does not increase risk of diab nephropathy, but FH of CVD does increase nephropathy risk.) (Genetics of getting diabetes complications may be separate from genetics of getting diabetes itself.)

30

Mrs. Z: Hypertension

- Strong data support aggressive BP control in T2DM pts with HTN, whether urine albumin is elevated or not. Systolic BP “counts,” even if diastolic is normal.
- Combined use of ACEI + ARB: not advised. Risk of hyperkalemia and worsened azotemia, in 2008 study. This pt. already on KCl; monitor K level.
- Suggest: Stop losartan, cont. lisinopril. Add amlodipine (not diltiazem in view of HR 60’s, and use of metoprolol). Past reports of proteinuria with dihydropyridine CCB’s, more than with nondihydropyridine agents. But no difference if person already on an ACEI/ARB.
- Goal: Control BP, whichever drug it takes!

31

Mrs. Z: Lipids

- High LDL, low HDL. Intolerant to statins and fenofibrate. Fish oil primarily benefits TG; can raise LDL; monitor. TG currently normal.
- Suggest: Could consider bile acid-binding resin (cholestyramine), if tolerated (constipation, scheduling other meds). Resins may worsen TGs in people with hypertriglyceridemia.
- Weight loss: Proactive nutritional counseling for lipid control as well as BG and BP mgmt.
- Mrs. Z needs exercise! Consider walking more often with her daughter and granddaughter.

32

Mrs. Z: Glucose Control

- Intensified BG control has been shown to delay onset and progression of nephropathy in T2DM (UKPDS...).
- A1c 8.3% vs. "home BG never over 120"...?
- Mrs. Z tests only before meals. Postprandial hyperglycemia? Ask her to test at HS, after meals.
- Verify reported results? Consider download of meter.
- Encourage pt. to write down BG results or download meter at home, to increase her awareness of day-to-day BG results.
- Review testing technique: meter is correctly coded for strips? Cleaned? Calibration solution? Too old?

33

Mrs. Z: Glucose Control

- Not using any prandial insulin before meals! "Sliding scale" only covers elevation of premeal BG; doesn't cover food intake. She may no longer have adequate beta cell response to glimepiride for meal coverage.
- Consider teaching carb counting, and use a carb ratio.
- Or give "scheduled" dose of premeal rapid insulin, then increase (or decrease) dose if eating more (or less) carb at a given meal than her usual.
- Physiologic insulin: half the total daily dose would be basal (e.g., glargine), and half would be premeal food-related insulin. "Correction" doses of rapid insulin are added to the "food" doses, if needed.

34

Mrs. Z: Osteoporosis

- Continue alendronate.
- Continue Vit. D. Check serum 25-hydroxy-D level, as absorption of Vit. D is variable, and may be reduced in elderly.
- She's calcium deficient! Bisphosphonates not effective if adequate calcium isn't available. Need intake of 1,500 mg per day after menopause, in divided doses.
- Use calcium citrate when taking antacids, or with hypochlorhydria, common in elderly. Calcium carbonate requires gastric acid to dissolve and be absorbed. Calcium citrate much less so.

35

Mrs. Z: Osteoporosis

- Calcium citrate designed to be taken 2 pills per dose (citrate ion is bulky). 1,500 mg per day = 2 pills TID.
- Calcium can be constipating regardless of type of calcium. Try increasing dietary fiber, fluid intake (not sugared or salted beverages). Exercise!
- Walking will help for osteoporosis as well as for control of BG, BP, and lipids, and obesity!
- If GFR < 60 ml/min, check PTH (renal osteodystrophy). First give adequate calcium and "conventional" Vit. D. If still high, need Vit. D analog?

36

Mrs. Z: Thyroid

- Mildly high TSH, normal free T₄. “Subclinical hypothyroidism.”
- Consider starting levothyroxine, in view of difficult lipid situation.

37

Mrs. Z: B12 supplement

- May be warranted if person on metformin. Metformin can cause B₁₂ deficiency in some people; recent report. Consider checking B₁₂ level before starting B₁₂ supplement. Give B₁₂ if needed.
- But if not B₁₂ defic., should not give B₁₂ (or B₆, folic acid) for purpose of lowering homocysteine. 4 studies (2006-2008) showed that B-vitamin therapy lowered homocysteine, but did NOT reduce the number of cardiovascular events either in CVD or diabetes pts.

38

Mrs. Z: B12 supplement

- JAMA, April, 2010: B-vitamins (B₁₂, B₆, folic acid) given to patients with diabetic nephropathy and Stage 1-3 CKD resulted in a more rapid decline in GFR vs. pts. not given B-vits., and nearly double the rate of cardiovascular events (MI, stroke, revascularization, and all-cause mortality); CV events 23.5% vs. 14.4% over 36 months.
- Mechanism uncertain. Not recommended at this time to measure homocysteine, or to use B-vitamin therapy for any presumed CV or other vascular benefit.

39

Mrs. Z: B12 supplement

- Antioxidant vitamins not recommended either, esp. in high doses. Instead, eat healthy foods containing naturally-occurring antioxidants. The same foods have healthy fiber as well: non-starchy vegetables, legumes (dried beans), whole grains, and fruit.

40

THANK YOU !!!

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