

Smoking and the progression of diabetic nephropathy

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GUIDELINES

No recommendations are possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **Smoking accelerates the development and progression of diabetic nephropathy. (Level III evidence - large retrospective cohort studies; clinically relevant outcomes; consistent strong effects)**
- **Cessation of smoking retards progression of diabetic nephropathy. (Level III evidence - small volume, several small cohort studies; clinically relevant outcomes; consistent strong effects)**
- **Current smoking confers a greater risk than former smoking.**
- **All patients with Type 1 or Type 2 diabetes should be strongly advised against commencement/continuation of smoking, to reduce the risk of developing and accelerating diabetic nephropathy as well as for vascular health.**

Background

Smoking has been associated with increased risks of developing diabetic kidney disease, and of accelerating its progression. The objective of this guideline is to evaluate the available clinical evidence of the impact of smoking on diabetic kidney disease.

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A II receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.

Date of search: 16 December 2003.

What is the evidence?

There are no randomised controlled trials (RCTs). Evidence is limited to retrospective analysis, and may therefore be subject to recall and selection bias. It is not absolutely established that smoking is a true independent risk factor independent of possible associated confounders such as non-compliance, accelerated vascular disease, and hypertension.

Type 1 diabetes

In Type 1 Diabetes, smoking increases the risks of:

- Developing microalbuminuria
- Chase et al (1991) – 359 young Type 1 diabetics were studied. The authors found abnormal albumin excretion ratio (AER) risk to be increased 2.8 times in smokers. Rossing et al (2002) – median 9-year follow up of a cohort of 537 Type 1 normotensive, normoalbuminuric diabetics at the Steno centre. The study identified RR of smoking in progression to microalbuminuria or macroalbuminuria as 1.61 (95%CI: 1.11–2.33)
- Progression from microalbuminuria to overt proteinuria (Rossing et al 2002).
- Decreasing the time over which these developments occur, and end-stage kidney disease (ESKD) develops (Stegmayr et al 1990, Stegmayr and Lithner 1987).

Sawicki et al (1994) calculated that the adjusted odds ratios for a 20% increase in proteinuria/year, and/or a > 20%/year reduction in GFR increased by 2.7 for every 10 pack years smoked.

One prospective observational cohort study at the Steno Diabetes Centre (Hovind et al 2003) reported conflicting results. A total of 301 albuminuric Type 1 diabetics followed for at least 3 years, the study was unable to demonstrate statistically significant differences in GFR decline between non-smokers, former smokers or current smokers. These negative results may reflect a type 2 statistical error, or may be influenced by the stringent definition of 'smoking' as > 1 cigarette/day for part or all of the study.

Cessation of smoking has been associated with reduction in AER (Chase et al 1991) and in progression of kidney failure (Sawicki et al 1994).

Type 2 diabetes

In Type 2 diabetes, smoking increases the risks of developing microalbuminuria (Biesenbach et al 1997). Gambaro et al (2001) followed 273 Type 2 diabetics for 3 years, identifying smoking as an important and graded risk factor for development and progression of microalbuminuria.

Chuahirun and Wesson (2002) prospectively sought predictors of kidney function decline in 33 Type 2 diabetic patients, successfully targeting a mean blood pressure goal of 92 mmHg (about 125/75 mmHg) with antihypertensives, including ACE inhibitors. Initial plasma creatinine was < 1.4 mg/dL follow-up 64.0 ± 1.1 months.

Regression analysis showed that smoking was the only examined parameter that significantly predicted renal function decline. In the 13 smokers, serum creatinine

increased from 1.05 ± 0.08 mg/dL to 1.78 ± 0.20 mg/dL although mean arterial pressure was the same. The 20 non-smokers had a lesser creatinine rise at 1.08 ± 0.03 mg/dL to 1.32 ± 0.04 mg/dL.

The effect of smoking appears to counteract the protective effects of improved blood pressure control and angiotensin converting enzyme inhibition in diabetic nephropathy (Chuahirun et al 2003). In this study of 84 hypertensive Type 2 diabetics, smoking and albuminuria were interrelated risk factors for renal function deterioration over 64 months, mean follow-up.

The same group (Chuahirun et al 2004) reported a 6-month study in 157 Type 2 diabetic smokers and nonsmokers along a spectrum of normo-, micro- and macroalbuminuria, and an additional 80 Type 2 diabetic quitters. Urinary transforming growth factor-beta-1 excretion was measured as a surrogate for progression, and was higher in smokers than non-smokers in each albuminuria group, and returned to non-smokers' levels in quitting smokers.

Baggio et al (2002) evaluated GFR, metabolic profile, and quantitative renal biopsy findings in 96 patients with Type 2 diabetes and increased AER, 48 of whom smoked.

Compared with non-smokers, smokers had higher HbA_{1c} (P = 0.002), AER (P = 0.026), GFR (P = 0.004), and glomerular basement membrane (GBM) width (P = 0.002). GFR was higher in current smokers than in former smokers (P = 0.001) and GBM width was related to heavy smoking (F = 5.4; P = 0.006).

What is the Evidence in children?

Couper et al (1994) documented increased risk of microalbuminuria in adolescent diabetics who smoke.

Summary of the evidence

There are no randomised clinical trials, but the consensus from multiple large cohort studies is that smoking accelerates both the development and progression of nephropathy in both Type 1 and Type 2 diabetics, and that the size of this effect is clinically important. Cessation of smoking is associated with improvement in the rate of progression in smaller cohort studies.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative (2004): "...the large sample sizes and adequate methodological quality and applicability of the studies supporting the association of smoking with faster rate of GFR decline provide reasonable evidence that there may be a deleterious effect of smoking on rate of progression."

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

American Association of Clinical Endocrinologists (2002): These guidelines advise “cessation of smoking”.

American Diabetes Association (2004): Advise all patients not to smoke. (A), include smoking cessation counselling and other forms of treatment as routine components of diabetes care. (B).

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

Out of Date

References

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Out of Date