Cigarette Smoking and Diabetes

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Smokers are insulin resistant, exhibit several aspects of the insulin resistance syndrome, and are at an increased risk for type 2 diabetes. Prospectively, the increased risk for diabetes in smoking men and women is around 50%. Many patients with type 1 and type 2 diabetes mellitus are at risk for micro- and macrovascular complications. Cigarette smoking increases this risk for diabetic nephropathy, retinopathy, and neuropathy, probably via its metabolic effects in combination with increased inflammation and endothelial dysfunction. This association is strongest in type 1 diabetic patients. The increased risk for macrovascular complications, coronary heart disease (CHD), stroke, and peripheral vascular disease, is most pronounced in type 2 diabetic patients. The development of type 2 diabetes is another possible consequence of cigarette smoking, besides the better-known increased risk for cardiovascular disease. In diabetes care, smoking cessation is of utmost importance to facilitate glycemic control and limit the development of diabetic complications.

It is a well-known fact that cigarette smoking constitutes a significant health hazard. This does still not appear to influence smoking habits among diabetic patients, although they, as a group, are at higher risk for cardiovascular morbidity and mortality than nondiabetic individuals.[1] Recent surveys have not shown that smoking habits are different among diabetic patients than comparable nondiabetic populations.[2,3] The prevalence of smoking among diabetic patients is probably around 25% in the United States and some countries in Western Europe. In other countries the prevalence of smoking in the general population may be higher, but there can also be marked differences in smoking habits between men and women.[4] In most countries, smoking habits among diabetic patients have not been explored, and it is not yet known if smoking habits are different in type 1 diabetic patients compared with type 2 diabetic patients.

Several experimental studies have shown that smoking has negative effects on glucose and lipid metabolism in diabetic as well as in nondiabetic subjects (see later). As a consequence, cigarette smoking is associated with worsening of the metabolic control in diabetic patients,[5,6] as well as an increased risk for development of microvascular as well as macrovascular complications and mortality in diabetes.[7,8] Furthermore, it has been shown in large prospective studies that cigarette smoking increases the risk for the development of type 2 diabetes mellitus in the general population.[9] This may be mediated via direct metabolic effects, solely or in combination with a metabolically unfavorable life style. Vascular effects, or activated inflammation, also may contribute to the serious consequences of cigarette smoking in diabetic (as well as nondiabetic) subjects.

Smoking Increases the Risk for Diabetes

Several prospective studies have shown that cigarette smoking is associated with an increased risk for diabetes mellitus in men and women. Generally, these studies were large and population based. Information was collected by mailed questionnaires to the participants, but in some cases complemented with information from medical records. In most of these studies the follow-up

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period was greater than 10 years. The results generally were presented after adjustments for possible covariates.

The health professionals' follow-up study showed that the risk for diabetes among men who smoked 25 cigarettes or more per day was 1.94 (95% confidence interval, 1.25-3.03) compared with nonsmokers.[10] In a smaller British study it was shown that the risk for diabetes was 50% higher among smokers, although not independent of other risk factors, obesity and low physical activity being the strongest.[11] Another recent British study, however, showed that the risk for diabetes in smoking men is around 1.7, also after adjustment for age, body mass index, physical activity, alcohol intake, social class, undiagnosed coronary heart disease, and antihypertensive treatment. The mean follow-up period in this study was close to 17 years, and the results also showed that a lowering of the increased risk for diabetes was seen after 5 years and a normalization of the risk was seen 20 years after smoking cessation.[12] Similar results were reported from a Japanese study, which also reported a positive correlation between tobacco consumption and risk for diabetes.[13]

Almost identical results were presented recently from The Physicians Health Study.[14] During 12 years, or 255,830 person-years, of follow-up, it showed a 70% increase in the risk for diabetes in men who smoke more than 20 cigarettes per day (after multivariate adjustment). There was also a positive association between risk for diabetes and greater consumption, as well as a near to normal risk for diabetes in past smokers.[14]

There are at least 3 more studies in men confirming the main results of the reviewed articles.[15-17] In women, not as many studies have been performed, but the results of 2 major prospective surveys show similar results. The first results from The Nurses' Health Study in the United States (114,247 women, 1,277,589 person-years of follow-up) showed that the risk for diabetes in heavy smokers is 1.42 after adjustment for other risk factors.[18]

After 16 years of follow-up a new analysis of results from the same cohort was performed.[19] It was shown clearly that overweight or obesity were the strongest predictors of diabetes, although, as in men, low physical activity, a poor diet, current smoking, and abstinence from alcohol were all independently associated with risk for diabetes.[19] The adjusted risk for diabetes in the smokers was around 1.4 when compared with the nonsmokers.

Data from The Cancer Prevention Study were used to analyze the correlation between tobacco use and risk for diabetes in both men and women.[9] This prospective cohort study was performed between 1959 and 1972. The risk for diabetes was increased in men who smoked more than 1 and 2 packs per day (risk compared with nonsmokers 1.19 and 1.45, respectively). In women the risk was higher (risk 1.21 and 1.74 in women smoking more than 1 and 2 packs per day, respectively). After smoking cessation the risk for diabetes returned to normal after 5 years in women and after 10 years in men.[9]

There are only a few studies that have failed to show an association between smoking and risk for diabetes. These studies from the 1970s to 1980s were not adequately designed or powered to test this hypothesis.[20-22]

Generally, it is considered that smoking only causes an increased risk for type 2 diabetes because type 1 diabetes is relatively rare in the age groups studied. This also is consistent with the adverse metabolic effects of smoking, which are outlined in this article. Type 1 diabetes is strictly an insulin-deficiency condition, caused by autoimmune pancreatic β-cell destruction, whereas insulin resistance in combination with impaired insulin secretion are the main metabolic defects in type 2 diabetes.[23,24]

Smoking Impairs Metabolic Control in Diabetes

The effects of cigarette smoking on insulin use or metabolic control in diabetic patients have been described only in a small number of articles.

In a cross-sectional study, Madsbad et al[5] compared insulin doses and related variables in diabetic patients treated with insulin injections. In the 114 smokers insulin doses as well as serum triglyceride levels were significantly higher than in the 163 nonsmokers, in a dose-dependent manner. HbA1 or HbA1c were not measured in this study, but blood and urine glucose levels were not different in the 2 groups. This suggests that a larger insulin dose is needed to achieve similar metabolic control in smoking patients as in nonsmokers.

In another cross-sectional study in type 1 diabetic patients (n = 192), it was shown that smoking is more common in patients with higher HbA1c levels.[25] This difference existed although there were differences in attitudes toward diabetes, psychologic well-being, and similar factors between the 2 groups.

In a relatively large prospective study, in which the effects of an intensified insulin treatment and teaching program were examined, it was shown that smoking was the most consistent determinant for HbA1 levels in relatively young insulin-treated diabetic subjects.[6] In this study, in which 697 diabetic patients without debilitating late complications were followed-up for 3 years, HbA1 levels were higher throughout the study, but improved to a similar degree as in the nonsmokers as an effect of the teaching program.

To the best of our knowledge, the effects on HbA1c levels and the requirement of hypoglycemic treatment in type 2 diabetic patients have not been studied, although the metabolic effects of smoking in these patients may be even greater than in insulin-sensitive type 1 diabetic patients.

Metabolic Effects of Smoking and Nicotine

The metabolic effects of smoking have been examined mainly in nondiabetic subjects. Most often in these studies, insulin sensitivity has been determined by use of the euglycemic hyperinsulinemic clamp technique.[26] This, or slightly modified techniques, are considered to be the gold standard in metabolic studies.

In 1993, Attvall et al[27] showed that acute smoking impaired insulin sensitivity in healthy young men. In cross-sectional studies, Eliasson et al[28] and Facchini et al[29] compared the degree of insulin-mediated glucose uptake (insulin sensitivity) in smoking and nonsmoking men. It was shown that the measures of insulin sensitivity were significantly lower (10% to 40%) in the smokers. The degree of insulin resistance also was correlated positively to tobacco consumption, and, in long-term users of nicotine gum, to serum cotinine levels (cotinine is a metabolite from nicotine; serum or urine levels of cotinine are considered to reflect degree of nicotine use).[30,31] Interestingly, the insulin resistance in the smokers normalized 8 weeks after smoking cessation despite a 2.7-kg weight gain.[32]

The smokers also exhibited various aspects of insulin resistance syndrome. They had significantly higher serum free fatty acids and triglyceride levels, lower high-density lipoprotein cholesterol,[28,29] a higher proportion of atherogenic small dense low-density lipoprotein particles, as well as elevated fibrinogen levels and plasminogen activator inhibitor 1 activity than the nonsmoking control subjects.[28] In the long-term users of nicotine gum similar effects were seen in plasminogen activator inhibitor 1 activity but the effects on lipids were not as pronounced as in smokers.[31]

One aspect of insulin resistance syndrome that has attracted attention recently is postprandial hypertriglyceridemia. Postprandial dyslipidemia has been shown to be associated with cardiovascular disease and insulin resistance.[33,34] Interestingly, this phenomenon also was seen in the smokers.[28,35] The cause for this abnormality, however, is not yet known. One possible explanation may be a defective clearance of triglyceride-rich chylomicrons and their remnants in smokers.[36]

Other studies, not using exact measurements of insulin sensitivity, also have shown that smokers exhibit changes in glucose metabolism when compared with nonsmokers. Tobacco users are hyperinsulinemic and relatively glucose intolerant when compared with nonsmokers.[37-40] In a recent, large cross-sectional analysis, smoking habits also were correlated clearly with HbA1c levels in nondiabetic individuals after adjustments for confounding factors.[41] The role of HbA1c in nondiabetic individuals have been under debate, although the results from this study add support for the concept that tobacco use does have adverse effects on glucose homeostasis.

A small number of studies did not find the same effects. Godsland and Walton[42] were not able to show differences in insulin sensitivity in smoking and nonsmoking women. This may have been caused by lower tobacco consumption. Furthermore, these results were actually a subanalysis of data from a study testing a different hypothesis.[43] Similarly, in a study of metabolic differences between hypertensive and nonhypertensive patients, a substudy was not able to detect a difference in insulin sensitivity between smokers and nonsmokers.[44] Most likely, the design of that study did not allow discrimination of the meta-

bolic changes caused by hypertension from the ones caused by smoking.

In type 1 diabetic patients, Helve et al[45] examined cross-sectional and acute effects of smoking on insulin sensitivity. Despite elevated levels of circulating epinephrine, cortisol, growth hormone, and glucagon levels after smoking, no effect on insulin sensitivity was seen. It is possible that fluctuations in blood glucose and metabolic control may have disguised the influence of smoking in these diabetic patients.

In type 2 diabetic smokers (n = 28) and nonsmokers (n = 12), insulin sensitivity was measured by using euglycemic clamps.[46] The smokers were clearly more insulin resistant, as well as glucose intolerant, than the nonsmokers. Thus, it was concluded that smoking markedly, and in a dose-dependent manner, aggravated the insulin resistance seen in the diabetic patients.[46]

Similarly, we recently reported that nicotine administered intravenously caused a marked reduction (circa 30%) in insulin sensitivity in type 2 diabetic but not in healthy control subjects who did not smoke.[47] These results suggest that nicotine, and possibly also tobacco use or other environmental factors, may be particularly disadvantageous in susceptible individuals but not in healthy (insulin sensitive) subjects.

Smoking and Microvascular Diabetes Complications

Microvascular complications in diabetes mellitus (ie, retinopathy, nephropathy, and neuropathy) are linked to metabolic control in type 1 and type 2 diabetes.[48,49] The mechanisms for the development of microvascular complications are not fully understood, although several pathogenetic pathways have been suggested.[50-52] Hyperglycemia has a central role as a trigger for subsequent events, such as conversion of glucose to sorbitol by aldose reductase, nonenzymatic glycosylation of proteins and receptors in susceptible tissues, increased exposure to oxidative stress, as well as the activation of protein kinase C and mitogen-activated protein kinases. These pathogenetic pathways have been suggested to lead to the disturbances in morphology and function seen in diabetic retinopathy, nephropathy, and neuropathy.[50-52]

Nephropathy

Although the associations between tobacco use and these events have not been studied in detail, there have been several studies showing that smoking increases the risk for some microvascular complications in diabetes. Several studies in type 1 diabetic patients clearly have shown the negative effects of tobacco use on albuminuria and renal function. Chase et al,[7] for example, showed that the albumin excretion rate was 2.8 times higher in smokers than nonsmokers, also after statistical correction for glycemic control, duration of diabetes, age, sex, and blood pressure. The progression rate of albuminuria in the smoking patients also was greater than in the nonsmokers.

Recently, it was also shown that smoking promotes the progression of renal disease in type 2 diabetic subjects.[53-55] The number of patients in the study by Biesenbach et al[53] was small (n = 36) but the follow-up period was 13 years. At inclusion the 2 groups (smokers and nonsmokers) had similar clinical and laboratory data, but the progression of nephropathy, as well as the development of atherosclerotic disease, was clearly increased in the smokers. Only tobacco use and blood pressure levels were associated independently with the impairment in renal function in a multiple regression analysis, emphasizing the possible roles of smoking and vascular disease in these susceptible individuals.[53]

In 2 prospective studies by Chuahirun et al,[54,55] the negative effects on nephropathy in type 2 diabetes were confirmed, even in patients with optimal antihypertensive therapy. Recently, additional evidence for functional and structural changes in the glomeruli of type 2 diabetic smoking patients were presented.[56] Ninety-six patients underwent kidney biopsy examination, which, by use of electron and light microscopic techniques, clearly showed significant changes in glomeruli and basal membranes, corresponding to impairments in glomerular filtration rates in the smokers.

Retinopathy

Generally, smoking has not been considered a strong risk factor for retinopathy.[57] Fairly large studies in mixed populations have not given strong support for such an association, except in a

subgroup of elderly patients.[58,59] A couple of studies in type 1 diabetic patients, however, suggest that smoking does predispose for retinopathy.[60,61] In the study by Chase et al,[7] it also was shown that retinopathy was more common among type 1 diabetic smokers than nonsmokers, although not after statistical adjustment for covariates. In that study it also was shown that the progression of retinopathy was accelerated in the smoking patients. To conclude, it is possible that smoking is a risk factor for diabetic retinopathy in certain subgroups.

Neuropathy

The role of tobacco use for the development of diabetic neuropathy is relatively difficult to examine because of methodologic problems and the frequent occurrence of confounding factors.[62] Diabetic neuropathy may take a long time to develop and may affect the different sensory, motor, and autonomic nerve fibers to varying degrees in different individuals. This will in turn make it difficult to standardize study methods.

These are probably the causes for the limited number of studies that have set out to resolve this question. In a case-control study, however, it was shown that the risk for neuropathy was 3 times higher in smoking type 1 diabetic patients than in nonsmokers.[63] Smoking was not related to neuropathy in type 2 diabetic patients in that study. In another study, in young insulin-treated diabetic subjects, it was shown that, apart from glycemic control, cigarette smoking as well as height, and female gender may be independent risk factors for progression of distal sensory neuropathy.[64] Other studies, also in type 1 diabetic patients, have confirmed the roles of glycemic control as well as smoking habits for the development of clinical neuropathy.[65,66]

Smoking and Macrovascular Diabetes Complications

The multiple effects of smoking on the vascular and hemostatic systems as well as inflammation are reviewed elsewhere in this issue. Some of these effects have been established for several years. However, it as if that diabetic patients are particularly susceptible to some of these effects because the risk for cardiovascular morbidity and mortality is elevated in this group.[8,67,68]

In the London cohort of the prospective (8-year follow-up) World Health Organization Multinational Study of Vascular Disease in Diabetics, it was shown that smoking is significantly associated with an increased risk for coronary heart disease (CHD), but not for stroke, in type 1 and type 2 diabetic patients.[8] In the Diabetes Control and Complications Trial, which originally was designed to study the role of intensive insulin treatment and optimized glycemic control in type 1 diabetes, smoking was not a significant risk factor for macrovascular complications.[69] The subjects participating in this study were relatively young and, thus, this trial was not optimally designed to study the role of tobacco use in macrovascular complications. Other studies in slightly older type 1 diabetic subjects have shown that smoking does increase the risk for CHD.[70,71]

In type 2 diabetic subjects, the United Kingdom Prospective Diabetes Study clearly showed that cigarette smoking is a significant and independent risk factor for CHD,[72] stroke,[73] as well as peripheral vascular disease.[74] In a recent analysis from the Nurses' Health Study, a dose-effect relationship between smoking habits and mortality was shown.[75] Thus, the risk for mortality from all causes is 1.64 in diabetic women who smoke 15 to 34 cigarettes per day, and 2.19 in women who smoke more than 34 cigarettes per day. Ten years after having stopped smoking the risk for mortality has normalized when compared with nonsmoking diabetic women. Similar data regarding smoking and risk for CHD in the same cohort also have been published recently.[76]

A relatively large prospective study analyzed the effects of smoking cessation on cardiovascular risk in diabetic patients.[77] Mortality risks in exsmokers with diabetes were compared with risks for subjects who have never smoked. All-cause mortality risks were around 50% higher for patients who stopped smoking during the past 1 to 9 years and 25% higher in individuals who quit smoking before that, when compared with subjects who have never smoked. The results from this study show that stopping smoking reduce mortality risk in diabetes, "but risks remain high several years after quitting and are highly dependent on the duration of smoking."[77]

Aspects of the Pathophysiologic Mechanisms

Patients with type 1 and type 2 diabetes seem to be particularly susceptible to the adverse effects of tobacco use and possibly also other forms of nicotine. Other reviews in this symposium have dealt with pathophysiologic mechanisms leading to the increased risk for cardiovascular diseases. Generally, the diabetic condition per se, even in nonsmokers, is associated with long-term exposure to oxidative stress, impaired endothelial function, and dyslipidemia.[50,52,72,78,79] Obviously, there is reason to believe that smoking, added to such a high-risk disposition, may well explain the additional risk for cardiovascular disease and other morbidity seen in diabetes.

The causes for type 2 diabetes are still unknown, although the main metabolic aberrations have been well characterized. As pointed out earlier, insulin resistance in combination with a relative impairment in insulin secretion are the major metabolic defects in type 2 diabetes.[23,24]

Studies published during recent years have not been able to show any significant aberrations in insulin secretion as an effect of cigarette smoking.[29,80,81] Contrary to this, a negative effect of smoking on insulin sensitivity has been documented in several studies.[28,29] Cigarette smoking and nicotine administration increase the circulating levels of insulin-antagonistic hormones (ie, catecholamines, cortisol, and growth hormone).[82-85] Smoking also has been shown to affect the autonomic nervous system.[86,87] It is possible that nicotine, via these (and possibly also other) mechanisms impairs insulin sensitivity, directly or indirectly. An additional negative factor for the insulin-mediated glucose uptake is high circulating levels of free fatty acids, indicating increased lipolysis.[88] It has been well known for many years that smoking acutely elevates circulating free fatty acid levels.[83]

The potential role of endothelial dysfunction or inflammation for the development of insulin resistance and type 2 diabetes has not yet been elucidated fully, although these have been found to be associated with insulin-resistant states such as prediabetes.[89-91] Thus, it is possible that some, or all, of these factors jointly may play important roles, mediating some of the effects of tobacco use on glucose metabolism, causing diabetes in susceptible individuals.

Conclusions

A high number of clinical and experimental studies and surveys give strong support for significant associations between tobacco use, the development of diabetes, glycemic control, and diabetic complications (micro- and macrovascular). It is probable that most of these effects are exerted by nicotine, possibly in conjunction with other substances in the cigarette smoke. A different lifestyle in the smokers compared with nonsmokers also may play a role,[92] although most of the reviewed studies have tried to adjust for confounding factors, or were designed to examine acute effects of tobacco and nicotine.

Thus, there is evidence that the development of type 2 diabetes is another consequence of cigarette smoking, besides the better-known risk for cardiovascular and other disease. In diabetes care, smoking cessation is of utmost importance to facilitate glycemic control and limit the development of diabetic complications.

References

1. Haffner SM, Lehto S, Ronnemaa T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229-234, 1998
2. Ford ES, Malarcher AM, Herman WH, et al: Diabetes mellitus and cigarette smoking. Findings from the 1989 National Health Interview Survey. Diabetes Care 17:688-692, 1994
3. Gill GV, Rolfe M, MacFarlane IA, et al: Smoking habits of black South African patients with diabetes mellitus. Diabet Med 13:996-999, 1996
4. Mackay J, Eriksen M: The Tobacco Atlas. World Health Organization, 2002
5. Madsbad S, McNair P, Christensen MS, et al: Influence of smoking on insulin requirement and metabolic status in diabetes mellitus. Diabetes Care 3:41-43, 1980
6. Bott U, Jorgens V, Grusser M, et al: Predictors of glycaemic control in type 1 diabetic patients after participation in an intensified treatment and teaching programme. Diabet Med 11:362-371, 1994
7. Chase HP, Garg SK, Marshall G, et al: Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. JAMA 265:614-617, 1991
8. Morrish NJ, Stevens LK, Fuller JH, et al: Risk factors for macrovascular disease in diabetes mellitus: The

London follow-up to the WHO Multinational Study of Vascular Disease in Diabetics. Diabetologia 34:590-594, 1991
9. Will JC, Galuska DA, Ford ES, et al: Cigarette smoking and diabetes mellitus: Evidence of a positive association from a large prospective cohort study. Int J Epidemiol 30:540-546, 2001
10. Rimm EB, Chan J, Stampfer MJ, et al: Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 310:555-559, 1995
11. Perry IJ, Wannamethee SG, Walker MK, et al: Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. BMJ 310:560-564, 1995
12. Wannamethee SG, Shaper AG, Perry IJ: Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care 24:1590-1595, 2001
13. Uchimoto S, Tsumura K, Hayashi T, et al: Impact of cigarette smoking on the incidence of type 2 diabetes mellitus in middle-aged Japanese men: The Osaka Health Survey. Diabet Med 16:951-955, 1999
14. Manson JE, Ajani UA, Liu S, et al: A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. Am J Med 109: 538-542, 2000
15. Feskens EJ, Kromhout D: Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. Am J Epidemiol 130:1101-1108, 1989
16. Kawakami N, Takatsuka N, Shimizu H, et al: Effects of smoking on the incidence of non-insulin-dependent diabetes mellitus. Replication and extension in a Japanese cohort of male employees. Am J Epidemiol 145:103-109, 1997
17. Ko GT, Chan JC, Tsang LW, et al: Smoking and diabetes in Chinese men. Postgrad Med J 77:240-243, 2001
18. Rimm EB, Manson JE, Stampfer MJ, et al: Cigarette smoking and the risk of diabetes in women. Am J Public Health 83:211-214, 1993
19. Hu FB, Manson JE, Stampfer MJ, et al: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345:790-797, 2001
20. Keen H, Jarrett RJ, McCartney P: The ten-year follow-up of the Bedford survey (1962-1972): Glucose tolerance and diabetes. Diabetologia 22:73-78, 1982
21. Medalie JH, Papier CM, Goldbourt U, et al: Major factors in the development of diabetes mellitus in 10,000 men. Arch Intern Med 135:811-817, 1975
22. Wilson PW, Anderson KM, Kannel WB: Epidemiology of diabetes mellitus in the elderly. The Framingham Study. Am J Med 80:3-9, 1986
23. Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988
24. Kahn SE: Beta cell failure: Causes and consequences. Int J Clin Pract 13-18, 2001 (suppl)
25. Lundman BM, Asplund K, Norberg A: Smoking and metabolic control in patients with insulin-dependent diabetes mellitus. J Intern Med 227:101-106, 1990
26. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 237:E214-E223, 1979
27. Attvall S, Fowelin J, Lager I, et al: Smoking induces insulin resistance—a potential link with the insulin resistance syndrome. J Intern Med 233:327-332, 1993
28. Eliasson B, Mero N, Taskinen MR, et al: The insulin resistance syndrome and postprandial lipid intolerance in smokers. Atherosclerosis 129:79-88, 1997
29. Facchini FS, Hollenbeck CB, Jeppesen J, et al: Insulin resistance and cigarette smoking. Lancet 339: 1128-1130, 1992
30. Eliasson B, Attvall S, Taskinen MR, et al: The insulin resistance syndrome in smokers is related to smoking habits. Arterioscler Thromb 14:1946-1950, 1994
31. Eliasson B, Taskinen MR, Smith U: Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. Circulation 94:878-881, 1996
32. Eliasson B, Attvall S, Taskinen MR, et al: Smoking cessation improves insulin sensitivity in healthy middle-aged men. Eur J Clin Invest 27:450-456, 1997
33. Patsch JR, Miesenbock G, Hopferwieser T, et al: Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. Arterioscler Thromb 12:1336-1345, 1992
34. Jeppesen J, Hollenbeck CB, Zhou MY, et al: Relation between insulin resistance, hyperinsulinemia, postheparin plasma lipoprotein lipase activity, and postprandial lipemia. Arterioscler Thromb Vasc Biol 15: 320-324, 1995
35. Axelsen M, Eliasson B, Joheim E, et al: Lipid intolerance in smokers. J Intern Med 237:449-455, 1995
36. Mero N, Syvanne M, Eliasson B, et al: Postprandial elevation of ApoB-48-containing triglyceride-rich particles and retinyl esters in normolipemic males who smoke. Arterioscler Thromb Vasc Biol 17:2096-2102 1997
37. Zavaroni I, Bonini L, Gasparini P, et al: Cigarette smokers are relatively glucose intolerant, hyperinsulinemic and dyslipidemic. Am J Cardiol 73:904-905, 1994
38. Ronnemaa T, Ronnemaa EM, Puukka P, et al: Smoking is independently associated with high plasma insulin levels in nondiabetic men. Diabetes Care 19: 1229-1232, 1996
39. Eliasson M, Lundblad D, Hagg E: Cardiovascular risk factors in young snuff-users and cigarette smokers. J Intern Med 230:17-22, 1991
40. Frati AC, Iniestra F, Ariza CR: Acute effect of cigarette smoking on glucose tolerance and other cardiovascular risk factors. Diabetes Care 19:112-118, 1996
41. Sargeant LA, Khaw K-T, Bingham S, et al: Cigarette smoking and glycemia: The EPIC-Norfolk Study. Int J Epidemiol 30:547-554, 2001
42. Godsland IF, Walton C: Insulin resistance and cigarette smoking. Lancet 340:607, 1992
43. Godsland IF, Walton C, Felton C, et al: Insulin resistance, secretion, and metabolism in users of oral contraceptives. J Clin Endocrinol Metab 74:64-70, 1992
44. Nilsson PM, Lind L, Pollare T, et al: Increased level of

hemoglobin A1c, but not impaired insulin sensitivity, found in hypertensive and normotensive smokers. Metabolism 44:557-561, 1995
45. Helve E, Yki-Jarvinen H, Koivisto VA: Smoking and insulin sensitivity in type I diabetic patients. Metabolism 35:874-877, 1986
46. Targher G, Alberiche M, Zenere MB, et al: Cigarette smoking and insulin resistance in patients with non-insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 82:3619-3624, 1997
47. Axelsson T, Jansson PA, Smith U, et al: Nicotine infusion acutely impairs insulin sensitivity in type 2 diabetic patients but not in healthy subjects. J Intern Med 249:539-544, 2001
48. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 329:977-986, 1993
49. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352:837-853, 1998
50. Brownlee M, Vlassara H, Cerami A: Nonenzymatic glycosylation and the pathogenesis of diabetic complications. Ann Intern Med 101:527-537, 1984
51. Tomlinson DR: Mitogen-activated protein kinases as glucose transducers for diabetic complications. Diabetologia 42:1271-1281, 1999
52. Cai J, Boulton M: The pathogenesis of diabetic retinopathy: Old concepts and new questions. Eye 16: 242-260, 2002
53. Biesenbach G, Grafinger P, Janko O, et al: Influence of cigarette-smoking on the progression of clinical diabetic nephropathy in type 2 diabetic patients. Clin Nephrol 48:146-150, 1997
54. Chuahirun T, Wesson DE: Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. Am J Kidney Dis 39:376-382, 2002
55. Chuahirun T, Khanna A, Kimball K, et al: Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. Am J Kidney Dis 41:13-21, 2003
56. Baggio B, Budakovic A, Vestra MD, et al: Effects of cigarette smoking on glomerular structure and function in type 2 diabetic patients. J Am Soc Nephrol 13:2730-2736, 2002
57. Porta M, Bandello F: Diabetic retinopathy. A clinical update. Diabetologia 45:1617-1634, 2002
58. Moss SE, Klein R, Klein BE: Association of cigarette smoking with diabetic retinopathy. Diabetes Care 14: 119-126, 1991
59. Walker JM, Cove DH, Beevers DG, et al: Cigarette smoking, blood pressure and the control of blood glucose in the development of diabetic retinopathy. Diabetes Res 2:183-186, 1985
60. Muhlhauser I, Sawicki P, Berger M: Cigarette-smoking as a risk factor for macroproteinuria and proliferative retinopathy in type 1 (insulin-dependent) diabetes. Diabetologia 29:500-502, 1986
61. Muhlhauser I, Bender R, Bott U, et al: Cigarette smoking and progression of retinopathy and nephropathy in type 1 diabetes. Diabet Med 13:536-543, 1996
62. Westerman RA, Lindblad LE, Wajnblum D, et al: Confounding factors in non-invasive tests of neurovascular function in diabetes mellitus. Clin Exp Neurol 29: 149-160, 1992
63. Mitchell BD, Hawthorne VM, Vinik AI: Cigarette smoking and neuropathy in diabetic patients. Diabetes Care 13:434-437, 1990
64. Christen WG, Manson JE, Bubes V, et al: Risk factors for progression of distal symmetric polyneuropathy in type 1 diabetes mellitus. Sorbinil Retinopathy Trial Research Group. Am J Epidemiol 150:1142-1151, 1999
65. Maser RE, Steenkiste AR, Dorman JS, et al: Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes 38:1456-1461, 1989
66. Reichard P: Risk factors for progression of microvascular complications in the Stockholm Diabetes Intervention Study (SDIS). Diabetes Res Clin Pract 16: 151-156, 1992
67. Jarrett RJ, McCartney P, Keen H: The Bedford survey: Ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. Diabetologia 22:79-84, 1982
68. Manson JE, Colditz GA, Stampfer MJ, et al: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med 151:1141-1147, 1991
69. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 75:894-903, 1995
70. Sinha RN, Patrick AW, Richardson L, et al: A six-year follow-up study of smoking habits and microvascular complications in young adults with type 1 diabetes. Postgrad Med J 73:293-294, 1997
71. Moy CS, LaPorte RE, Dorman JS, et al: Insulin-dependent diabetes mellitus mortality. The risk of cigarette smoking. Circulation 82:37-43, 1990
72. Turner RC, Millns H, Neil HA, et al: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 316:823-828, 1998
73. Kothari V, Stevens RJ, Adler AI, et al: UKPDS 60: Risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke 33: 1776-1781, 2002
74. Adler AI, Stevens RJ, Neil A, et al: UKPDS 59: Hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care 25:894-899, 2002
75. Al-Delaimy WK, Willett WC, Manson JE, et al: Smoking and mortality among women with type 2 diabetes:

The Nurses' Health Study cohort. Diabetes Care 24: 2043-2048, 2001

76. Al-Delaimy WK, Manson JE, Solomon CG, et al: Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. Arch Intern Med 162:273-279, 2002

77. Chaturvedi N, Stevens L, Fuller JH: Which features of smoking determine mortality risk in former cigarette smokers with diabetes? The World Health Organization Multinational Study Group. Diabetes Care 20: 1266-1272, 1997

78. Komatsu M, Kawagishi T, Emoto M, et al: ecNOS gene polymorphism is associated with endothelium-dependent vasodilation in type 2 diabetes. Am J Physiol 283:H557-H561, 2002

79. Dogra G, Rich L, Stanton K, et al: Endothelium-dependent and independent vasodilation studies at normoglycaemia in type I diabetes mellitus with and without microalbuminuria. Diabetologia 44:593-601, 2001

80. Persson PG, Carlsson S, Svanstrom L, et al: Cigarette smoking, oral moist snuff use and glucose intolerance. J Intern Med 248:103-110, 2000

81. Epifano L, Di Vincenzo A, Fanelli C, et al: Effect of cigarette smoking and of a transdermal nicotine delivery system on glucoregulation in type 2 diabetes mellitus. Eur J Clin Pharmacol 43:257-263, 1992

82. Cryer PE, Haymond MW, Santiago JV, et al: Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 295:573-577, 1976

83. Kershbaum A, Bellet S: Smoking as a factor in atherosclerosis. A review of epidemiological, pathological, and experimental studies. Geriatrics 21:155-170, 1966

84. Kirschbaum C, Wust S, Strasburger CJ: 'Normal' cigarette smoking increases free cortisol in habitual smokers. Life Sci 50:435-442, 1992

85. Wilkins JN, Carlson HE, Van Vunakis H, et al: Nicotine from cigarette smoking increases circulating levels of cortisol, growth hormone, and prolactin in male chronic smokers. Psychopharmacology (Berl) 78: 305-308, 1982

86. Lucini D, Bertocchi F, Malliani A, et al: A controlled study of the autonomic changes produced by habitual cigarette smoking in healthy subjects. Cardiovasc Res 31:633-639, 1996

87. Niedermaier ON, Smith ML, Beightol LA, et al: Influence of cigarette smoking on human autonomic function. Circulation 88:562-571, 1993

88. Bergman RN, Ader M: Free fatty acids and pathogenesis of type 2 diabetes mellitus. Trends Endocrinol Metab 11:351-356, 2000

89. Tan KC, Chow WS, Ai VH, et al: Advanced glycation end products and endothelial dysfunction in type 2 diabetes. Diabetes Care 25:1055-1059, 2002

90. Stehouwer CD, Gall MA, Twisk JW, et al: Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: Progressive, interrelated, and independently associated with risk of death. Diabetes 51:1157-1165, 2002

91. Schmidt MI, Duncan BB, Sharrett AR, et al: Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): A cohort study. Lancet 353:1649-1652, 1999

92. Thompson DH, Warburton DM: Lifestyle differences between smokers, ex-smokers and non-smokers, and implications for their health. Psychol Health 7:311-321, 1992