Clinical Relevance of the Oxidative Stress Concept

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Subjects with type 2 diabetes have markedly increased rates of coronary heart disease (CHD) that are only partly explained by the increased levels of conventional cardiovascular risk factors such as total cholesterol, hypertension, and smoking. Although an increasing number of studies have suggested a role for glycemia in cardiovascular disease, considerable controversy remains. This issue may be resolved when the results of the UK Prospective Diabetes Study (UKPDS) are presented. One possible promising relatively new risk factor that may explain high levels of CHD in diabetic subjects is increased oxidative stress. Type 2 diabetic subjects have an increased preponderance of small dense low-density lipoprotein (LDL), which predisposes to the oxidation of LDL. Almost all studies show that diabetic subjects have increased oxidative stress. In addition, they may have lower levels of α-tocopherol. In most studies, increased oxidative stress has been associated with cardiovascular disease, although prospective data are lacking. If levels of oxidative stress are increased, what are the best levels to reduce it to? Improved glycemic control has been associated with decreased oxidative stress. Antioxidant replacement such as α-tocopherol may also be beneficial. Interestingly, some special properties of hypoglycemic agents have been described. Gliclazide has been reported to favorably affect both free radicals and platelet reactivity. Gliclazide may have a more favorable effect on tissue plasminogen activator (tPA) than tolbutamide. In conclusion, increased levels of oxidative stress may underlie some of the increased risk of cardiovascular disease in diabetic subjects. Interventions to decrease levels of oxidative stress by methods such as improved glycemic control, antioxidant therapy (ie, α-tocopherol), and gliclazide are indicated.

SUBJECTS WITH TYPE 2 diabetes have increased rates of microvascular complications (retinopathy, renal disease, and neuropathy) and macrovascular disease (coronary heart disease [CHD], cerebrovascular disease, and peripheral vascular disease). However, macrovascular disease (especially CHD) is by far the leading cause of morbidity and mortality in subjects with type 2 diabetes. Type 2 diabetes is associated with a 2- to 4-fold increased risk of CHD.[1-3] Recent data from Finland on 1,059 diabetic subjects and in 1,373 nondiabetic subjects reinforce the magnitude of the excess risk of CHD in type 2 diabetic subjects[4] (Table 1). The 7-year incidence rates of myocardial infarction (MI) in nondiabetic subjects with and without prior MI were 18.8% and 3.5%, respectively ($P < .001$). The 7-year incidence rates of MI in diabetic subjects with and without prior MI are 45.0% and 20.2%, respectively ($P < .001$). These Finnish data suggest that diabetic patients without previous MI have as high a rate of MI as nondiabetic subjects with previous MI, and thus, provide a rationale for treating cardiovascular risk factors as aggressively as in nondiabetic subjects with a prior MI. Diabetic subjects with a prior MI also have a worse prognosis than nondiabetic subjects with a prior MI.[5-7] Given that the incidence of CHD in type 2 diabetic subjects is high and the prognosis very poor, can improved glycemic control correct this excess risk?

GLYCEMIC CONTROL AND CHD IN DIABETIC SUBJECTS

The Wisconsin Epidemiologic Study on Diabetic Retinopathy (WESDR) directly compared the predictive power of glycated hemoglobin to the incidence of various complications of diabetes.[8] In older-onset diabetic subjects (who were likely to be type 2 diabetic subjects) of the WESDR cohort, a 1% increase in glycated hemoglobin at baseline was associated with a 50% increase in retinopathy and 20% increase in proteinuria, but only a 10% increase in the incidence of ischemic heart disease mortality. All of these associations (including ischemic heart disease mortality) were statistically significant. However, it is clear that the association between hyperglycemia and ischemic heart disease mortality was much weaker than that for retinopathy, although this could partly be because of the greater precision of assessing the incidence of retinopathy (particularly in the WESDR). Interestingly, the relation of glycated hemoglobin to ischemic heart disease mortality was stronger in younger-onset diabetic subjects (hazards ratio = 1.20) than in older-onset diabetic subjects (hazards ratio = 1.10), suggesting that glycemia may be relatively more important in relation to CHD in type 1 diabetes than in type 2 diabetes.

Recently, the United Kingdom Prospective Diabetes Study (UKPDS)[9] evaluated the effect of improved glycemic control and diabetic complications. Improved glycemic control (median HbA_{1c} reduced from 7.9% to 7.0%) over 10 years reduced (1) diabetes-related end points by 12% ($P = .029$); (2) diabetes-related deaths by 10% (P = NS); (3) MI by 16% ($P = .052$); (4) increased stroke by 11% (P = NS); and (5) reduced microvascular end points by 25% ($P < .01$) (Table 2). These results reinforce the data from the WESDR study[8] of a modest but beneficial effect on CHD of improved glycemic control. One reason why the relation between glycemia in the clinical diabetic period and the development of CHD is weak is that there may be atherogenic abnormalities (dyslipidemia, hyperlipidemia, etc) before the onset of clinical diabetes at a time when glucose concentrations are still relatively normal.[10]

DO SULFONYLUREA AGENTS INCREASE CHD?

The University Group Diabetes Program (UGDP)[11] reported a significant increase in fatal MI with tolbutamide (a sulfonylurea) in a randomized controlled trial. This report, now over 20 years old, has suggested that sulfonylureas are cardiotoxic. The UKPDS,[9] in contrast, is a much larger study with a longer

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Table 1. Incidence of Cardiovascular Events During a 7-Year Follow-up in Relation to History of MI in Subjects With Type 2 Diabetes and in Nondiabetic Subjects*

Event	Nondiabetic Subjects			Subjects With Type 2 Diabetes			All Subjects	
	Prior MI (n = 69)	No Prior MI (n = 1,304)	*P* Value	Prior MI (n = 169)	No Prior MI (n = 890)	*P* Value	*P* Value for Prior MI *v* No Prior MI	*P* Value for Diabetes *v* No Diabetes
Fatal or nonfatal MI								
Incidence during follow-up	18.8	3.5	<.001	45.0	20.2	<.001	<.001	<.001
Events/100 person-yr	3.0	0.5		7.8	3.2			
Fatal or nonfatal stroke								
Incidence during follow-up	7.2	1.9	<.01	19.5	10.3	<.001	<.001	<.001
Events/100 person-yr	1.2	0.3		3.4	1.6			
Deaths from cardiovascular causes								
Incidence during follow-up	15.9	2.1	<.001	42.0	15.4	<.001	<.001	<.001
Events/100 person-yr	2.6	0.3		7.3	2.5			

*P values were calculated with Cox proportional hazards model. The Cox models were adjusted for age and gender.
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duration of follow-up (see Table 3) that suggests sulfonylureas are associated with modestly *decreased* CHD events in comparison to a conventional therapy arm, thus settling the issue of the "supposed" cardiotoxicity of sulfonylureas.

INTERVENTIONS FOR CHD IN DIABETIC SUBJECTS

Because the relation of glycemic control to CHD is modest, a number of strategies have been suggested to reduce CHD (Table 4). In this review, we will touch on 2 of these interventions: aggressive control of cardiovascular risk factors (especially lowering of low-density lipoprotein [LDL] cholesterol) and approaches to reduction of oxidative stress.

LDL LOWERING IN DIABETIC SUBJECTS

The Scandinavian Simvastatin Survival Study (4S) studied subjects with a prior MI and high LDL levels (~186 mg/dL) and randomized them to simvastatin 20 to 40 mg/d versus placebo.[12] In a subset of 202 diabetic subjects, simvastatin was associated with a 55% reduction in CHD.[13] In another secondary prevention trial (Cholesterol And Recurrent Events [CARE]), 40 mg of pravastatin was associated with a 25% reduction in CHD.[14] Clearly, lipid lowering in diabetic subjects is indicated.[15,16] However, even in the small 4S diabetic subgroup[13] where the results are very dramatic, one half of the cases of CHD were not prevented. One might argue that the even greater LDL reduction achieved in the 4S study (36%) might do even better. This hypothesis, however, has not been tested in clinical trials. Another hypothesis to be considered is the possible role of oxidative stress.

Table 2. UKPDS Results: Intensive Blood Glucose Control (UKPDS #33)

Intensive Blood Glucose Control	Reduction (%)	*P* Value
Any diabetes-related end point	12	.029
Deaths related to diabetes	10	NS
MI	16	.052
Stroke	11↑	NS
Microvascular disease	25	.0099

↑ = Increase in the risk.
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Table 3. Comparison of Sulfonylureas and Exogenous Insulin With Conventional Glucose Control (UKPDS #33)

Intensive Blood Glucose Control	Reduction (%)	*P* Value
Primary End Points		
Any diabetes-related end point		
Chlorpropamide	7	NS
Glibenclamide	18	.018
Insulin	13	.064
Deaths related to diabetes		
Chlorpropamide	8	NS
Glibenclamide	8	NS
Insulin	10	NS
Secondary End Points		
MI		
Chlorpropamide	13	NS
Glibenclamide	22	.056
Insulin	13	NS
Stroke		
Chlorpropamide	1↑	NS
Glibenclamide	38↑	NS
Insulin	14↑	NS
Microvascular disease		
Chlorpropamide	14	NS
Glibenclamide	34	.017
Insulin	30	.015

↑ = Increase in risk.
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OXIDATIVE STRESS—GENERAL CONCEPTS

Oxidized LDL is more atherogenic than native LDL and accumulates in the carotid wall whereas native LDL[17] does not. Oxidized LDL is found in atherosclerotic lesions in experimental animals,[18,19] and antibodies to oxidized LDL have been found to correlate with the progression of atherosclerosis in experimental animals.[20] Furthermore, antioxidant therapy with

Table 4. Strategies to Reduce CHD

1. Glycemia control (? magnitude)
2. Prevention of diabetes
3. Aggressive treatment of cardiovascular risk factors
4. Diabetic agents with special effects
5. Investigational approaches (AGE, aspirin, antioxidants)

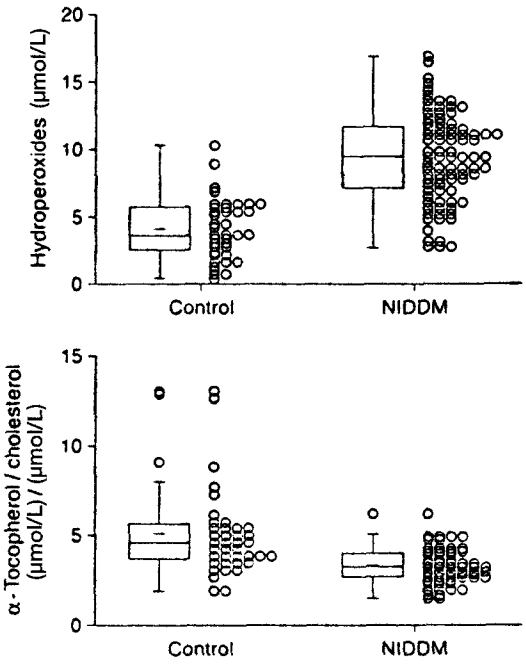

Fig 1. Data spread for lipid hydroperoxides (ROOHs) (A) and cholesterol standardized α-tocopherol (B) in control and NIDDM subjects. Adapted and reprinted with permission.[23]

vitamin E is associated with a lower risk of CHD in both men and women.[21,22]

OXIDATIVE STRESS IN DIABETIC SUBJECTS

Many studies have shown that increased lipid peroxides and/or oxidative stress is present in diabetic subjects.[23-27] In a British study of 41 healthy controls and 87 subjects with type 2 diabetes[23] (Fig 1), subjects with diabetes had lower hydroperoxides and α-tocopherol/total cholesterol levels (Fig 1). Additionally, the fasting glucose correlated with the level of hydroperoxides/total cholesterol levels (Fig 2). Haffner et al[24] showed that

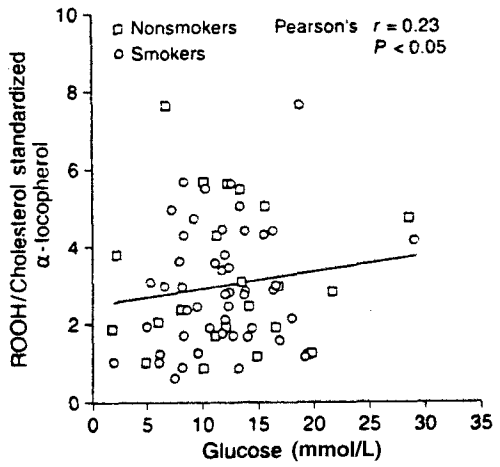

Fig 2. Correlation between ROOH/cholesterol standardized ratio and fasting blood glucose levels in non-insulin-dependent diabetes mellitus subjects. Adapted and reprinted with permission.[23]

Table 5. Selected Studies of Increased Oxidative Stress and/or Oxidative LDL in Diabetic Subjects

Author	Journal	Reference
Noorouz-Zadeh J, et al	Diabetologia	40:657-653, 1997
Haffner SM, et al	Diabetes Care	18:646-651, 1995
Jennings PG, et al	Diabet Med	4:452-456, 1987
McRury JM, et al	Diabet Med	10:331-335, 1993
Sato Y, et al	Biochem Med	21:104-107, 1979

the level of lipid peroxides was high in type 2 diabetic subjects but not in subjects with impaired glucose tolerance, suggesting that the level of glycemia may be an important determinant of lipid oxidation.

RELATION OF GLYCATION TO OXIDATION

A number of studies have summarized the relation between glycation and oxidation.[28,29] Ceriello et al[30] showed that acutely after a meal, plasma malondialdehyde and vitamin C increased, while uric acid and total plasma radical trapping measures decreased in type 2 diabetic subjects, suggesting that in the absorptive phase, free radicals are produced. Hyperglycemia may be involved in the long-term complications of diabetes through glycosylation of proteins. Advanced glycation end products (AGEs) induce crosslinking of collagen and other extracellular matrix proteins in many tissues including the arterial vessel wall.[31,32] AGEs have been associated with both microvascular[33,34] and macrovascular[35,36] complications of diabetes. In addition, apolipoprotein B, a component of LDL, can itself be modified by AGEs.[37] AGE-modified LDL has been shown to have a prolonged half-life as a result of its reduced affinity for hepatic receptors.[37] Thus, it is more likely to be taken up by scavenger receptors on macrophages in the vascular wall[38] leading to foam cell formation. The prolonged half-life of LDL and its trapping in vascular walls could lead to increased oxidation of LDL.

SMALL DENSE LDL, TYPE 2 DIABETES, AND OXIDATIVE STRESS

A number of studies suggest that small dense LDL is increased in type 2 diabetes[39,40] (Table 5), and this association is only partially dependent on the higher triglyceride levels in diabetic subjects. Small dense LDL is more susceptible to oxidation.[41,42]

METHODS TO REDUCE OXIDATIVE STRESS IN DIABETIC SUBJECTS

A number of methods are available to reduce oxidative stress in type 2 diabetic subjects (Table 6). Several studies have shown that nutritional antioxidant therapy (especially vitamin

Table 6. Methods to Reduce Oxidative Stress in Type 2 Diabetes

1. Improved glycemia
2. Antioxidant therapy
3. Hypoglycemic medicines
   (a) Gliclazide
   (b) Troglitazone (vitamin E moiety)?

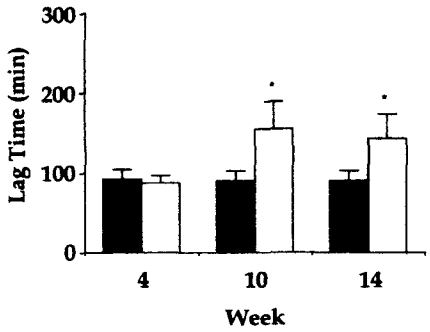

Fig 3. Measurement of lag time to initiation of rapid conjugated diene formation in LDL during Cu^{2+}-induced oxidation. LDL (100 μg/mL) samples from subjects receiving placebo (■) or vitamin E (□) supplementation were incubated in phosphate-buffered saline containing 5 mmol/L Cu^{2+} at 30°C, and absorbance at 234 nm was measured at 10-minute intervals in a Uvikon 810 spectrophotometer. Mean values ± SD measured on LDL samples isolated at 4, 10, and 14 weeks are shown. *Significant difference compared with values for the placebo group at $P < .05$. Adapted and reprinted with permission.[45]

E) reduces oxidative stress.[43-45] The report of Reaven et al[45] (Fig 3) is an example of a study in type 2 diabetic subjects.

Gliclazide has been shown to reduce susceptibility to oxidation whereas glibenclamide did not, even though there was a similar improvement in glycemic control[46] (Table 7). Additionally, gliclazide was also shown to reduce platelet aggregation whereas glibenclamide had no effect. This study suggests there may be differences between sulfonylureas in their ability to affect factors that may be related to atherosclerosis independently of glycemic control. Troglitazone has also been shown to modestly reduce oxidative stress,[47] but there is some uncertainty about the relevance to clinical practice because the dose used (400 mg orally twice daily) is greater than that approved for clinical use. In addition, because troglitazone includes a vitamin E moiety (400 mg of troglitazone is equivalent to 200 U of vitamin E), it may be that the antioxidant effects are due to the vitamin E rather than a unique property of "glitazones."

Table 8. Guidelines for Efficacy of Combination Therapy Regimens

1. Sulfonylureas
   (a) Insulin
   (b) Metformin
   (c) Acarbose
   (d) Troglitazone
2. Metformin
   (a) Sulfonylurea
   (b) Acarbose
   (c) Insulin (±)
   (d) Troglitazone (±)
3. Troglitazone
   (a) Sulfonylurea
   (b) Insulin
   (c) Metformin (±)

COMBINATION THERAPY

With the data that have accumulated from the UKPDS study,[9] it is clear that monotherapy (whether oral hypoglycemic agents or exogenous insulin) is inadequate to control type 2 diabetes adequately over time. Increased attention has been given to combination therapy. Table 8 summarizes available oral agent combinations. Because of the time that sulfonylureas have been on the market (>40 years), more data are available on this class in combination with other agents. Important, also, is the observation from the UKPDS[9] that sulfonylureas are not cardiotoxic and may reduce diabetes-related end points.

CONCLUSION

We have shown in this review that type 2 diabetic subjects have high rates of CHD and that glycemic control is therefore unlikely to eliminate the excess risk of CHD. This symposium has shown that oxidative stress is increased in diabetes and related to CHD and that there are a variety of methods to reduce oxidative stress. In addition, gliclazide may have a number of actions beyond its effects on glycemia, which include reduction of oxidative stress and platelet aggregation.

Table 7. Gliclazide (n = 15) Versus Glibenclamide (n = 14)

	Baseline			3 Mo		
	GLICL	GLIB	*P* Value	GLICL	GLIB	*P* Value
Glucose (mmol/L)	8.2	9.1	.23	8.1	9.2	.21
Lipid peroxides (μmol/L)	8.3	9.0	.11	7.0	8.3	.0002
SOD (μg/mL)	136	132	.75	152	123	.016
Platelet aggregation (%)	65%	70%	.97	51%	72%	.006

Abbreviations: GLICL, gliclazide; GLIB, glibenclamide; SOD, superoxide dismutase.
Adapted and reprinted with permission.[46]

REFERENCES

1. Kannel WB, McGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: The Framingham Study. Diabetes Care 2:120-126, 1979

2. Wingard DL, Barrett-Connor E: Heart disease and diabetes, in Harris MI (ed): Diabetes in America (ed 2). Washington, DC, US Govt Printing Office, 1995, pp 429-448

3. Stamler J, Vaccaro O, Neaton JD, et al: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 16:434-444, 1993

4. Haffner SM, Haffner SM, Lehto S, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229-234, 1998

5. Abbot RD, Donohue RP, Kannel WB, et al: The impact of diabetes on survival following myocardial infarction in men vs women: The Framingham Study. JAMA 260:3456-3460, 1988

6. Herliz J, Karlson BW, Edvardsson N, et al: Prognosis in diabetics with chest pain or other symptoms suggestive of acute myocardial infarction. Cardiology 80:237-245, 1992

7. Miettinen H, Lehto S, Salomaa VV, et al: Impact of diabetes on mortality after the first myocardial infarction. Diabetes Care 21:69-75, 1998

8. Klein R. Kelly West Lecture 1994: Hyperglycemia and microvascular and macrovascular disease in diabetics. Diabetes Care 18:258-268, 1995

9. UK Prospective Diabetes (UKPDS) Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. (UKPDS 33). Lancet 352:837-853, 1998

10. Haffner SM, Stern MP, Hazuda HP, et al: Cardiovascular risk factors in confirmed prediabetic individuals: Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 263:2893-2898, 1990

11. University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Diabetes 25:1129-1153, 1976

12. Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Study (4S). Lancet 344:1383-1389, 1994

13. Pyörälä K, Pedersen TR, Kjeksus J, et al: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: A subgroup analyses of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 20:614-620, 1997

14. Sacks FM, Pfeffer MA, Moye LA, et al: for the Cholesterol and Recurrent Events Trial Investigators: The effect of pravastatin on coronary events after myocardial infarction inpatients with average cholesterol levels: Cholesterol and Recurrent Events Trial Investigators. N Engl J Med 335:1001-1009, 1996

15. Haffner SM: Management of dyslipidemia in adults with diabetes (technical review). Diabetes Care 21:160-178, 1998

16. American Diabetes Association: Management of dyslipidemia in adults with diabetes (position paper). Diabetes Care 21:179-182, 1998

17. Witztum JL, Steinberg D: Role of oxidized low density lipoprotein in atherogenesis. J Clin Invest 88:1785-1792, 1991

18. Yla-Herttuala S, Palinski W, Rosenfeld ME, et al: Evidence for the presence of oxidatively modified LDL in atherosclerotic lesions of rabbit and man. J Clin Invest 84:1086-1095, 1989

19. Kita T, Nagano Y, Yokode M, et al: Probucol prevents the progression of atherosclerosis in Watanabe heritable hyperlipidemic rabbit, an animal model for familial hypercholesterolemia. Proc Natl Acad Sci USA 84:5928-5931, 1987

20. Salonen JF, Yla-Herttuala S, Yamamoto R, et al: Autoantibodies against oxidized low density lipoprotein and progression of carotid atherosclerosis. Lancet 339:883-887, 1992

21. Stampfer MJ, Hennekens CH, Manson JE, et al: Vitamin E consumption and the risk of coronary heart disease in women. N Engl J Med 328:1444-1449, 1993

22. Rimm EB, Stampfer MJ, Ascherio A, et al: Vitamin E consumption and the risk of coronary heart disease in men. N Engl J Med 1450-1456, 1993

23. Noorouz-Zadeh J, Rahimi A, Tajaddini-Sarnadi J, et al: Relationships between plasma measures of oxidative stress and glycemic control in NIDDM. Diabetologia 40:647-653, 1997

24. Haffner SM, Agil A, Mykkänen L, et al: Plasma oxidizability in subjects with normal glucose tolerance, impaired glucose tolerance and NIDDM. Diabetes Care 18:646-652, 1995

25. Sato Y, Hotta N, Sakamoto N, et al: Lipid peroxide level in plasma of diabetic patients. Biochem Med 21:104-107, 1979

26. Jennings PE, Jones AF, Florkowski CM, et al: Increased diene conjugates in diabetic subjects with microangiopathy. Diabetic Med 4:452-456, 1987

27. MacRury SM, Gordon D, Wilson R, et al: A comparison of different methods of assessing free radical activity in type 2 diabetes and peripheral vascular disease. Diabetic Med 10:331-335, 1993

28. Chisolm GM, Irwin KC, Penn MS: Lipoprotein oxidation and lipoprotein-induced cell injury in diabetes. Diabetes 41:61-66, 1992 (suppl 2)

29. Lyons TJ: Glycation and oxidation: A role in the pathogenesis of atherosclerosis. Am J Cardiol 71:26B-31B, 1993

30. Ceriello A, Bortolotti N, Motz E, et al: Meal-generated oxidative stress in type 2 diabetes. Diabetes Care 21:1529-1553, 1998

31. Brownlee M: Glycation products and the pathogenesis of diabetic complications. Diabetes Care 15:1835-1843, 1992

32. Vlassara H, Bucala R: Recent progress in advanced glycation and diabetic vascular disease: Role of advanced glycation end product receptors. Diabetes 45:S65-S66, 1996

33. Makiea Z, Radoff S, Rayfield EJ, et al: Advanced glycosylation end products in patients with diabetic nephropathy. N Engl J Med 325:836-842, 1991

34. McCance DR, Dyer DG, Dunn JA, et al: Maillard reaction to products and their relation to complications in insulin-dependent diabetes mellitus. J Clin Invest 91:2470-2478, 1993

35. Nakamura Y, Horii Y, Nishino T, et al: Immunohistochemical localization of advanced glycosylation endproducts in coronary atheroma and cardiac tissue in diabetes mellitus. Am J Pathol 143:1649-1656, 1993

36. Nishimoto S, Oohara T, Sakai M, et al: Collagen-glycation in the aorta: A developmental factor of aging and atherosclerosis. Kobe J Med Sci 34:179-187, 1988

37. Bucala R, Makita Z, Koschinsky T, et al: Lipid advanced glycosylation: Pathway for lipid oxidation in vivo. Proc Natl Acad Sci USA 90:6434-6438, 1993

38. Bucala R, Makita Z, Vega G, et al: Modification of LDL by advanced glycosylation end products contributes to the dyslipidemia of diabetes and renal insufficiency. Proc Natl Acad Sci USA 91:9441-9445, 1994

39. Selby JV, Austin MA, Newman B, et al: LDL subclass phenotypes and the insulin resistance syndrome in women. Circulation 85:381-387, 1993

40. Haffner SM, Mykkänen L, Stern MP, et al: Greater effect of diabetes on LDL size in women than in men. Diabetes Care 17:1164-1171, 1994

41. de Graaf J, Hak-Lemmers HLM, Hectors MPC, et al: Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. Arterioscler Thromb 11:298-306, 1991

42. Reaven PD, Grasse BJ, Tribble DI: Effects of linoleate-rich and oleate-rich diets in combination with α-tocopherol on the susceptibility of low-density lipoproteins (LDL) and LDL subfractions of oxidative modification in humans. Arterioscler Thromb 14:557-566, 1994

43. Jialal I, Grundy SM: Effect of dietary supplementation with α-tocopherol on the oxidative modifications of low-density lipoprotein. J Lipid Res 33:899-906, 1992

44. Reaven PD, Khouw A, Beltz W, et al: Effect of dietary antioxidant combinations in humans: Protection of LDL by vitamin E, but not by β-carotene. Arterioscler Thromb 13:590-600, 1993

45. Reaven PD, Herold DA, Barnett J, et al: Effects of vitamin E on susceptibility of low-density lipoprotein and low-density lipoprotein subfractions to oxidation and on protein glycation in NIDDM. Diabetes Care 18:807-816, 1995

46. Jennings PE, Scott NA, Saniabadi AR, et al: Effects of gliclazide on platelet reactivity and free radicals in type II diabetic patients: Clinical assessment. Metabolism 41:36-39, 1992

47. Cominacini L, Young MMR, Capriati A, et al: Troglitazone increases the resistance of low density lipoprotein to oxidation in healthy volunteers. Diabetologia 40:1211-1218, 1997