REFERENCES

Abbott RD, Donahue RP, MacMahon SW, Reed DM, and Yano K. Diabetes and risk of stroke. **J Am Med Assoc** 1987;257:494-952.

Alderson LM, Endemann G, Lindsey S, Pronczuk A, Hoover RL, Hayes KC. LDL enhances monocyte adhesion to endothelial cells in vitro. **Am J Pathol** 1986;123:334-342.

Atkinson MA, Maclaren NK. The pathogenesis of insulin dependent diabetes mellitus. **N Eng J Med** 1994;331:1428-1436

Babiy AV. Gebicki JM, Sullivan DR, Willey K. Increased oxidize ability of plasma lipoproteins in diabetic patients can be decreased by probucol therapy and is not due to glycation. **Biochem Pharmacol** 1992;43:995-1000.

Banhegyi G, Braun L, Csala M, Puskas F,and Mandl J. Ascorbate metabolism and its regulation in animals. **Free Radical Biol Med** 1997;23(5):793-803.

Barnett AH. Pathogenesis of diabetic microangiopathy : an overview. **Am J Med** 1991;90 (Suppl 6a):6A-67S

Bassaller C, Habib GB, Yamamoto H, Williams C, Wells S, Henry PD. Impaired muscarinic endothelium-dependent relaxation and cyclic guanosine 5'-monophosphate formation in atherosclerotic human coronary artery and rabbit aorta. **J Clin Invest** 1987;79:170-174.

Baumgartner-Parzer SM, Wagner L, Gessl A, Waldhäusl W. Modulation by high glucose of adhesion molecule expression in endothelial cells. **Diabetologia** 1995;38:1367-1370.

Baynes JW. Role of oxidative stress in development of complications in diabetes. **Diabetes** 1992;40:405-412.

Baynes JW. Role of oxidative stress in the development of complications in diabetes. **Diabetes** 1991;40:405-412.

Bell DSH. Stroke in diabetic patient. **Diabetes Care** 1994;17:213-219.

Bendich A, Machlin LJ, Scandurra O, Burton GW Wayner DM. The antioxidant role of vitamin C. **Adv Free Radic Biol Med** 1986;2:419-444.

Bjor kheim I and Kallner A. **J Lipid & Res** 1976;17:360.

Bendich A: Antioxidant nutrients and immune functions : introduction. **Adv Exp Med Biol** 1990;262:1-12.

Block G, and Levine M. Vitamin C : a new look. **Ann Intern Med** 1991;114:909-910.

Boyd RB, Burke JP, Atkin J, Thompson VW, and Nugint JF. Significance of capillary basement membrane changes in diabetes mellitus. **J Am Pod Med Assoc.** 1990;6:307.

Brett J. Schmidt AM, Zou XY-S, Weidman YE, Pinsky D Neeper M et al. Tissue distribution of RAGE : expression in smooth muscle, cardiac monocytes, and neural tissue in addition to the vasculature. **Am J Pathol** 1994;143:1699-1712.

Brolin SE, Naeser P. Sorbitol in aortic endothelium of diabetic rats. **Diabetes Res.** 1988;8:59-61.

Brownlee M, Vlassara H, Cerami A. Non-enzymatic glycosylation products on collagen covalently trap low density lipoprotein. **Diabetes** 1985;34:938-941.

Brunzell JD, Porte D, and Bierman EL. Abnormal lipoprotein-lipase mediated plasma triglyceride removal in diabetes mellitus associated with hypertriglyceridemia. **Metabolism.** 1979;28:901-907.

Bucala R, Makita Z, Koschinsky T. Lipid advanced glycosylation pathway for lipid oxidation in vivo. **Proc Natl Acad Sci USA** 1993;90:6434-6438.

Bucala R, Mokita Z, Koshinsky T, Cerami A, Vlassara H. Lipid advanced glycosylation: pathway for lipid oxidation in vivo. **Proc Natl Acad Sci USA** 1993;90:6434-6438.

Bucala R, Tracey KJ,and Cermi Aadvanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilation in experimental diabetes. **J Clin Invest** 1991;87:432-438

Bucala R, Tracey KS, Cerami A. Advanced glycosylation and products quench nitric oxide and mediate defective endothelium-dependent vasodilation in experimental diabetes. **J Clin Invest** 1991;87:432-438.

Cagliero E, Maiello M, Boeri D, Roy S, Lorenzi M. Increased expression of basement membrane components in human endothelial cells cultured in high glucose. **J Clin Invest** 1988;82:735.

Calver A, Collier J, Vallance P. Inhibition and Stimulation of nitric oxide synthesis in the human forearm arterial bed of patients-with insulin-dependent diabetes. **J Clin Invest** 1992;90:2548-2554.

Cameron NE, Dines KC ,Cotter MA. The potential contribution of endothelin-1 to neurovascular abnormalities in streptozotocin-diabettic rats. **Diabetologia** 1994;37:1209-1215

Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in human. **Am J Clin Nutr** 1999;69:1086-1107.

Ceriello A, Dello Russo P, Amstad P, Cerutti P. High glucose-induces antioxidant enzymes in human endothelial cells in culture: evidence linking hyperglycemia and oxidative stress. **Diabetes** 1996;45:471-477.

Ceriello A. Acute hyperglycemia and oxidative stress generation. **Diabetes Med** 1997;14 (Suppl 1) : S45-S49.

Ceriello A. Borto lotti N. Crescentini A, et al. Antioxidant defenses are

Cester N, Rabini RA, Salvolini E. Activation of endothelial cells during insulin-dependent diabetes mellitus a biochemical and morphological study. **Eur J Clin Invest** 1996;20:569-573.

Chang KC, Chung SY, Chong WS, Suh JS. Possible superoxide radical-induced alteration of vascularreactivity in aortas from streptozotocin-treated rats. **J Pharmacol Exp Ther** 1993;266:992-1000.

Chang KC, Chung SY, Chong WS, Suh JS, Kim SH, Noh HK, Seong BW,

Chatterjee SN, Chatterjee IB. Ascorbic acid metabolism in diabetes mellitus. **Metabolism** 1981;30:572-577.

Cohen RA. Dysfunction of vascular endothelium diabetes mellitus. **Circulation** 1993;87(suppl V):V67-V76.

Cotter MA, Love A, Watt MJ, Cameron NE, and Dines KC. Effects of natural free radical scavengers on peripheral nerve and neurovascular function in diabetic rats. **Diabetologia** 1995;38:1285-1294.

Davies MJ, Gordon JL, Gearing AJ, Pigott R, Woolf N, Katz D, Kyriakopoulos A. The expression of the adhesion molecules

ICAM-1, VCAM-1, PECAM, and E-selectin in human altherosclerosis. **J Pathol** 1993;171:223-229.

Dennis KY, Mclennan S, Fisher E, Heffernan S, capogrecoc, Glynis RR, and Turtle JR. Ascorbic acid metabolism and polyol pathway in **Diabetes** 1989;38:257-261.

Diplock AT. Safety of antioxidant vitamins and β-carotene. **Am J Clin Nutr** 1995;62 (Suppl 1) : 1510S-15106S.

Dosquet C, Weill D, Wautier JL. Molecular mechanism of blood monocyte adhesion to vascular endothelial cells. **Nouv Rev Fr Haematol** 1999;34:S55-S59.

EK A, Strom K, Cotgreave IA. The uptake of ascorbic acid into human umbilical vein endothelial cells and its effect on oxidant insult. **Biochem Pharmacol** 1995;50:1339-1346.

Esposito C, Gerlach H, Brett J. Endothelial receptor-mediated binding of glucose-modified albumin is associated with-increased monolayer permeability and modulation of cell surface coagulant properties. **J Exp Med** 1989;170:1387-1407.

Evans RM, Currie L, Campbell A. The distribution of ascorbic acid between various cellular components of blood, in normal individuals, and its relation to the plasma concentration. **Br J Nutr** 1982;47:473-482.

Fasching P, Waldhäusl W, Wagner OF. Elevated circulating adhesion molecules in NIDDM potential mediators in diabetic macroangiopathy (letter). **Diabetologia** 1996;39:1242-1244.

Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. **Proc Natl Acad Sci USA.** 1989;86:6377-6381.

Frei B. On the role of vitamin C and other antioxidants in atherogenesis and vascular dysfunction. **Society for Exp Biol Med**. 1999;222:196-204.

Frei B. Reactive oxygen species and antioxidant vitamins : mechanism of action. **Am J Med** 1994;97 (suppl 3A):3S-5A.

Freyschuss A, Xiu RJ, Zhang J, Ying X, Diczfalusy U, Jogestrand T et al. Vitamin C reduces cholesterol-induced microcirculatory changes in rabbits. **Arterioscler Thromb Vasc Biol** 1997;17:1178-1184.

Furchgott RF. The discovery of endothelium-derived relaxing factor and its importance in the identification of nitric oxide. **JAMA** 1996;276:1186-1188.

Gary UC, Hassid A. Nitric oxide-generating vasodilators and 8-bromo-cyclin guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. **J Clin Invest** 1989;83:1774-1777.

Gibbons GE. Hyperlipidemia of diabetes. **Clin Sci** 1986l71L477-486.

Ginsberg HN. Lipoprotein physiology in nondiabetic and diabetic states relationship to atherosclerosis. **Diabetes Care** 1991;14:839-855.

Ginter E, Zdichynec B,Holzerova O, Ticha E, Kobza R, Koziakova M, Cerna O,et al. Hypocholesterolemic effect of ascorbic acid in maturity onset diabetes mellitus. **Int J Vit Nutr Res** 1978;48:368-373

Ginter E. Cholesterol-vitamin C control its transformation to bile acids. **Science** 1973;179:702-704

Giugliano D, Ceriello A and Passio. Diabetes mellitus, Hypertension, and Cardiovascular Disease: which role for oxidative stress? **Metabolism** 1995;44(3):363-368.

Giugliano D, Ceriello A, and Paolisso G. Paolisso G. Diabetes mellitus, hypertension, and Cardiovascular disease which role for oxidative stress. **Metabolism** 1995;44(3):363-368.

Giuseppe P, D'Amore A, Balbi V, Volpe C, Galzerano D, Giugliano D Glidazide. **Am J Med** 1991; 90 (supply) 505-545

Gonzalez AM, Sochor M, Hothersall JS, McLean P. Effect of aldose reductase inhibitor (sorbinil) on integration of polyol pathway, pentose phosphate pathway, and glycolytic route in diabetic rat lens. **Diabetes** 1986;35:1200-1205.

Gonzalez RG, Barnett P, Aguayo J, Cheng HM, Chylack LT. Direct measurement of polyol pathway activity in the ocular lens. **Diabetes** 1984;33:196-199.

Gotoh N, and Niki E. Rates of interactions of superoxide with-vitamin E, vitamin C, and related compounds as measured by chemi Suminescence. **Biochem Biophys Acta** 1992;1115:201-207.

Gryglewski RJ, Palmer RMJ, and Moncada S. Superoxide anion is involved **in the breakdown of endothelium-derived vascular relaxing factor. Nature (Lond)** 1986;320:454-456.

Gryglewski RJ, Palmer RM, Moncada S. Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor. **Nature.** 1986;320:454-456.

Guigkiano D, Ceriello A, and Paolisso G. Oxidative stress and diabetic vascular complications. **Diabetes Care** 1996;V19(3):257-267.

Hadcock S, Richardson M, Winocour PD, Hatton MW. Intimal alterations in rabbit aortas during the first 6 months of alloxan-induced diabetes. **Arterioscler Thromb** 1991;11:517-529.

Hadcock S, Richardson M, Winocour PH, Hatton MW. Intimal alterations in rabbit aortas during the first 6 months of alloxan-induced diabetes. **Arteriosclerosis Thrombosis** 1991;11:517-529.

Hadcocks S, Richardson M, Wincour P, and Hatton MWC. Intimal alterations in the first six months of alloxan-induced diabetes. **Arterioscler Thromb** 1991;11:517-529.

Harris MI. Hypercholesterolemia in diabetes and glucose intolerance in the US population. **Diabetes Care** 1991;14:366-374.

Hattori Y, Kawasaki H. Superoxide dismutase recovers altered endothelium dependent relaxation in diabetic rat aorta. **Am J Physiol** 1991;261:H1086-H1094.

Heim K, Thomas FGj, Ramwell PW. Superoxide production in the isolatied rabbit aorta and the effect of alloxan, indomethacin and nitrovasodilators. **J Pharmacol Exp Ther** 1991;256:537-541

Heitzer T, Just H, Munzel T. Antioxidant vitamin C improves endothelial dysfunction in chronic smokers. **Circulation** 1996;94:6-9.

Helmke BP, Bremner SN, Zweifach BW, Shalak R, and Schmid-Schonbein GW. Mechanisms for increased blood flow resistance due to leukocytes. **Am J Physiol** 1997;273:H2884-H2890.

Hoogerbrugge N, Verkerk A, Jacobs ML, Postema PTE, and Jongkind JF. Hypertriglyceridemia enhances monocyte binding to endothelial cells in NIDDM. **Diabetes Care** 1996;19:10:1122-1125.

Horning B, Arakawa N, Kohler C, Drexler H. Vitamin C improves endothelial function of conduit arteries in patients with chronic heart failure. **Circulation** 1998;97:363-368.

Hunt JV, Smith CCT, Wolff SP. Autoxidative glycoSylation and possible involvement of peroxides and free radicals in LDL modification by glucose **Diabetes** 1990;39:1420-1424.

Ishii H, Koya D, King GL. Protein Kinuse C activats and its role in the development of vascular complicates in diabetes. **J Mol Med** 1998;790:21-31.

Jacobs M, Plane F, Bruckdorfor KR. Native and oxidised low density lipoproteins have different inhibitory effects on endothelium-derived relaxing factor in the rabbit aorta **Br J Pharmacol** 1990;100:21-26.

Jackson TS, Xu AM, Via JA. Ascorbate prevents the interaction of superoxide and nitric oxide only at very high physiological concentrations. **Circ Res** 1998;83:916-922.

Jariyapongshul A, Niimi H, Patumraj S. Cerebral microcirculation response to hemorrhagic hypotension in spontaneously diabetic rats:an intravital fluorescence microscopic analysis. **Proceeding 6th World Congress for Microcirculation,** Munich(Germany) 1996 August :977-981.

Jariyapongshul A, Niimi H, Kasantikul V, Maneesri S, Patumraj S. Morphological changes of cerebral microcirculation in streptozotocin-induced diabetic rats: a pilot studies of in vivo fluorescence and electron microscopy **Proceeding of the third Asian Congress for Microcirculation,** Bangkok(Thailand) 1997 October :239-245.August :977-981.

Jia L, Bonaventura J Stamler JS. S-Nitrosohemoglobin; a dynamic activity of blood ivolved in vascular control. **Nature** 1996;380:221-226.

Johnson PC, Brendel K, and Meezan E. Thickened cerebral-cortical capillary basement membranes in diabetes. **Arch Patho Lab Med** 1982;106:214-217.

Joris I, Zand T, Nunnari JJ, Krolikowski FJ, Mano G. Studies-on the pathogenesis of atherosclerosis I. Adhesion and emigration of mononuclear cells in the aorta of hypercholesterolemic rats. **AM J Patho** 1983;113:341-358.

Kannel WB, and McGEE DL. Diabetes and Cardiovascular disease. **J Am Med Hsso** 1979;241:2035-2038.

Karpen CW, Pritchard KA, Arnold JH. Restoration of the prostacyclin / thromboxane A_2 balance in the diabetic rat in fluence of vitamin E. **Diabetes** 1982;31:947-951.

Kashiwagi A, Asahina T, Ikebuchi M, Tanaka Y, Takagi Y, Nishio Y, Kikkawa R, Shigita Y. Abnormal glutathione metabolism-and increased cytotoxicity caused by H_2O_2 in human umbilical vein endothelial cells cultured in high glucose medium. **Diabetologia** 1994;37:264-269.

Kashiwagi A, Asahina T, Nishio Y, Ikebuchi M, Tanaka Y Kikkawa R et al. Glycation, Oxidative Stress, and Scavenger activity : Glucose metabolism and Radical scavenger dysfunction in endothelial cells . **Diabetologia** 1996;45 (Suppl 3) S84-S86.

Keegan A, Walbank H, Cotter MA, Cameron NE. Chronic vitamin E treatment prevents defective endothelium dependent relaxation in diabetic rat aorta. **Diabetologia** 1995;38:1475-1478.

Khan BV, Parthasaranthy SS, Alexander RW, Medford RM. Modified low density lipoprotein and its constituents augment cytokine-activated vascular cell adhesion molecule-1 gene expression in human vascular endothelial cells. **J Clin Invest** 1995;95:1267-1270.

Kimi JA, Berlinen JA, Natarajan RD, Nadler TL. Evidence that glucose increases monocyte binding to human aortic endothelial cells. **Diabetes** 1994;43:1103-1107

King GL, Kumisaki M, Nishio Y, Inoguchi T, Shiba T, Xia P. Biochemical and molecular mechanisms in the development of diabetic vascular complications. **Diabetes** 1996;45:S105-S108.

King GL, Shiba T, Oliver J, Inoguchi T, and Bursell S-E. Cellular and molecular abnormalities in the vascular endothelium of diabetes mellitus. **Annu. Rev. Med.** 1994;45:179-188.

Kirs tein M, Brett J, Radoff S. Advanced protein glycosylation induces transendothelial human monocyte chemotaxis and secretion of platelet-derived growth factor role in vascular disease of diabetes and aging. **Proc Natl Acad Sci USA** 1990;87:9010-9014.

Ko HJ, Chun KW. Possible superoxide radical-induced alteration of vascular reactivity in aortas from streptozotocin-treated rats. **J Pharmacol Exp Thes** 1993;266:992-1000.

Lehr HA, Frei B, Arfors KE. Vitamin C prevents cigarette smoke-induced leukocyte aggregation and adhesion to endothelium in vivo. **Proc Natl Acad Sci USA.** 1994:91:7688-7692.

Lehr HA, Frei B, Olofsson M, Carew TE, Arfors KE. Protection from oxidized LDL-induced leukocyte adhesion to microvascular and

macrovascular endothelium in vivo by vitamin C but not by vitamin E. **Circulation** 1995;91:1525-1532.

Lehr HA, Hübner C, Finckh B, Angermüller S, Nolte D, Beisiegel U, Kohlschütter A. Role of leukotrienes in leukocyte adhesion following systemic administration of oxidatively modified human low density lipoproteins in hamster. **J Clin Invest** 1991;88:9-14.

Lein YH, Stern R, and FU JCC. Inhibition of collagen fibril formation in vitro and subsequent cross-linking by glucose. **Science** 1984;225:1489.

Levine GN, Frei B, Koulouris SN, Gerhard MD, Keaney JF,Vita JA. Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease. **Circulation** 1996;93:1107-1113

Levine M. New concept in the biology and biochemistry of ascorbic acid. **N Eng J Med** 1986;314:892-902.

Like AA. Streptozotocin-induced pancreatic insulitis;Newmodel of diabetes mellitus. Science 1976;193:415-417.

Lin SJ, Hong CY, Chang MS, Chiang BN, Chieu S. Increased aortic endothelial death and enhanced transport in streptozotocin-diabetic rats. **Diabetologia** 1993;36:923-930.

Lindsay RM, Peet RS, Wilkie GS, Rossiter SP, Smith W, Baird JD, Williams BC. In vivo and in vitro evidence of altered nitric oxide metabolism in the spontaneously diabetic, insulin-dependent BB/Edinburgh rat. **Br J Pharmacol.** 1997;120:1-6.

Lüscher TF, Raij L, Vanhoutte PM. Endothelium-dependent responses in-normotensive and hypertensive Dahl rats. **Hypertension** 1987;9:157-163.

Malik RA, Newrick PG, Sharma AK. Microangiopathy in human diabetic neuropathy. **Diabetologia** 1989;32:92-102.

Malik RA, Tesfaye S, Thompson SD, Veves A, Sharma AK, Boulton AJ, Ward JD. Endoneurial localisation of microvascular damage in human diabetic neuropathy. **Diabetologia** 1993;36:454-459.

Martin. Recovery by ascorbate of impaired nitric oxide-dependent relaxation resulting from oxidant stress in rat aorta. **Br J Pharmacol** 1998;125: 782-786.

Maxfield EK, Cameron NE, Cotter MA, Dines KC. Angiotensin II receptor blockade improves nerve function ,modulates nerve blood flow and stimulates endoneurial angiogenesis in streptozotocin-diabetic rats. **Diabetologia** 1994;36:1230-1237.

May JM, Cobb CE, Mendiratta S, Hill KE, Bark RF. Reduction of the ascorbate free radical to ascorbate by thioredoxin reductase. **J Biol Chem** 1998;273:23039-23045.

Mayhan W, Simsons LK, Sharpe QM. Mechanism of impaired responses of cerebral arterioles during diabetes mellitus. **Am J Physiol** 1991;260:H319-H326.

Mayhan WG, Simmons LK, Sharp GM. Mechanism of impaired responses of cerebral arterioles during diabetes mellitus. **Am J Physiol** 1991;260:H319-H326.

Mayhan WG. Impairment of endothelium-dependent dilation of cerebral arterioles during diabetes mellitus. **Am J Physiol** 1989;256:H621-H625.

McLennan SV, Heffernen S, Wright L. Changes in hepatic glutathione metabolism in diabetes. **Diabetes** 1991;40:344-348.

McLeod DS, Lefer DJ, Merges C, Lutty GA. Enhanced expression of intercellular adhesion molecule-1 and P-selectin in diabetic human retina and choroid. **Am J Pathol** 1995;147:662-653.

Meister A. Glutathione-ascorbic acid antioxidants system in animals. **J Biol Chem** 1994;269:9397-9400.

Mellors AJ, Nahrwold DL, Rose RC. Ascorbic acid flux across mucosal border of guinea pig and human ileum. **Am J Physiol** 1977;233:E374-E379.

Melord JM, and Herman D. Oxygen radicals and human diseases **Ann Intern Med** 1987;107:526-545.

Mendiratta S, Qu Z-C, May JM. Erythrocyte ascorbate recycling : antioxidant effects in blood. **Free Radic Biol Med** 1998;24:789-797.

Miyata N, Tsuchida K, Okuyama S, Otomok, Kamatak, Kasuya Y. Age-related changes in endothelium-dependent relaxation in aorta from-genetically diabetic WBN/kob rats. **Am J Physiol**. 1992;262:H1104-H1109.

Moncada S, Gryglewski R, Bunting S. An enzyme isolated from-arteries transforms prostaglandin endoperoxides to an unstable-substance that inhibits platelet aggregation. **Nature** 1976;263:663-665.

Moncada S, Palmer RM, Higgs EA. Nitric oxide : physiology, pathophysiology and pharmacology. **Pharmcol Rev** 1991;43:109-142.

Moncada S. Biological importance of prostacyclin. **Br J Pharmacol** 1982;76:3-31.

Moore SA, Bohlen HG, Miller BG, Evan AP. Cellular and vessel wall morphology of cerebral cortical arterioles after short-term diabetes in adult rats. **Blood Vessels** 1985;22:265-277.

Morel DW, Di Corleto PE, Chisolm GM. Endothelial and smooth muscle cells alter low density lipoprotein in vitro by free radical oxidation. **Arteriosclerosis** 1984;4:357-364.

Morigi M, Angioletti S, Imberti B, Donadelli R, Micheletti G, Figliuzzi M, Remuzzi A, Zoja C, and Remuzzi G. Leukocyte-endothelial Interaction is augmented by high glucose concentrations and hyperglycemia in a NF-kB-dependent Fashion. **J. Clin. Invest** 1998;101:9:1905-1915.

Mullarkey CJ, Edelstein D, Brownlee M. Free radical generation by early glycation products: a mechanism for accelerated atherogenesis in diabetes. **Biochem Biophys Res Commun.** 1990;173:932-939.

Newrick PG, Wilson AJ Jakubowski J, Boulton AJM, Ward JD. Sural nerve oxygen tension in diabetes. **BMJ** 1986, 293:1053-1054.

Ng LL, Ng Keekwong FC, Quinn PA, and Davies JE. Uptake mechanisms for ascorbate and dehydroascorbate in lymphoblasts from diabetic nephropathy and hypertensive patients. **Diabetologia** 1998;41:435-442

Ng Keek Wong FC, Ng LL. Two distinct uptake mechanisms for ascorbate and dehydroascorbate in human lymphoblasts and their interaction with glucose. **Biochem J** 1997;324:225-230.

Nikkila EA. Plasma triglycerides in human diabetes. Proc. R. Soc. Med. 1974;67:18-21.

Nishikimi N. Oxidation of ascorbic acid with superoxide anion-generated by the xanthine-xanthine oxidase system. **Biochem Biophys Res. Commun** 1975,63:463-468.

Oberlet LW. Free radicals and diabetes. **Free Radic Biol Med** 1988;5:112-124.

Oyama Y, Kawasaki H, Hattoriy, Kanno M. Attenuation of endothelium-dependent relaxation in aorta from diabetic rats. **J Pharmacol**. 1986;131:75-78.

Palmer RMJ, Ferrige AG, Moncada & Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. **Nature** 1987;327:524-526.

Paolisso G, Amore AD, Balbi V, Volpec, Galzerano D, Giugliano D, et al.

Park JB, Levine M. Purification, cloning and expression of dehydro ascorbic-acid reducing activity from human neutrophils, identification as glutaredoxin. **Biochem J** 1996;315:931-938.

Paving H-H, Viberti GC, Keen H, Christansen JS, Lassen NA: Hemodynamic factors in the genesis of diabetic microangiopathy. **Metabolism** 1983;32:943-949.

Pecoraro RE and Chen MS. Ascorbic acid metabolism in Diabetes mellitus.

Ann NY Acad Sci 1989;86:248-258.

Pecoraro RE and Chen MS. Ascorbic acid metabolism in Diabetes mellitus. **Ann NY Acad Sci** 1989;86:248-258.

Pieper GM, Gross G. Oxygen free radicals abolish endothelium-dependent relaxation in diabetic rat aorta. **Am J Physiol** 1988;255:H825-H833.

Pigott R, Dillon LP, themingway IH, Gearing AJH. Soluble forms of E-selectin, ICAm-1, and VCAM-1 are present in the supernatants of cytokine activated cultured endothelial cells. **Biochem Biophys Res Commu** 1992;187:584-589.

Porta M, La Selva M, Molinatti P, Molinatti GM. Endothelial cell function in diabetic microangiopathy. **Diabetologia** 1987;30:601-609.

Poston RN, Johnson-Tidey RR. Localized adhesion of monocytes to human atherosclerotic plaques demonstrated in vitro : impkications for atherogenesis. **Am J Pathol** 1996;149:73-80.

Rankin SM, Parthasarathy S, Steinberg D. Evidence for a dominant role of lipoxygenase (s) in the oxidation of LDL by mouse peritoneal macrophages. **J Lipid Res** 1991;32:449-456.

Reilly PM, Schiller HJ, Bulkley GB. Pharmacologic approach to tissue injury mediated by free radicals and other reactive oxygen species. **Am J Surg** 1991;61:488-503.

Retsky KL, Freemom MW, and Frei B. Ascorbic acid oxidation products protect human low density lipoprotein against atherogenic modification. **J Biol Chem** 1989;268:1304-1309.

Ruderman NB, Williamson JR, and Brownlee M. Glucose and diabetic vascular disease. **FASEB J** 1992;6:2905-2914.

Salonen JT, Salonen R, Ihanainen M. et al. Vitamin C deficiency and low linolenate intake associated with elevated blood pressure the kuopio ischemic heart disease risk factor study. **J hypertension** 1987;5 (suppl) : S521-S524.

Salonen JT, Salonen R, Ihanainen M, et al. Blood pressure, dietary fats, and antioxidants. **Am J Clin Nutr** 1988;48:1226-1232.

Schmidt AM, Crandall J, Hori O, Cao R, Lakatta E. Elevated plasma levels of vascular cell adhesion molecule-1 (VCAM-1) in diabetic patients with microalbuminuria: a marker of vascular dysfunction and progressive vascular disease. **Br J Haematol** 1996;92:747-750.

Schmidt AM, Hori O, Chen JX, Li JF, Crandall J Zhang R et al. AGEs interacting with their endothelial receptor induce expression of VCAM-1 in cultured human endothelial cells and in mice. **J Clin Invest** 1995;96:1395-1403.

Schneider SK and Kohn RR. Effects of age and diabetes mellitus on the solubility and nonenzymatic glycosylation of human skin collagen. **J Clin Invest** 1985;67:1630-1636.

Schroder S, Palinski W, Schmid-Schonbein G. Activated monocytes and granulocytes, capillary non reperfusion and neovascularization in diabetic retinopathy. **Ann J Pathol** 1991;139:81-100.

Seip RL, Anglopoulos TJ, Semenkovich CF. Exercise induces human lipoprotein lipase gene expression in skeleton muscle but not adipose tissue. **Am J Physiol** 1995;268:E229-E236.

Sgambato S, Varsichio M, and D'Onofrio F. Plasma vitamin C affects homeostasis in healthy subjects and in non-insulin-dependent diabetics. **Am J Physiol** 1994;266 : E261-268.

Sharma P, Pramod J, Sharma PK, Sapra M, Manorma and kothari LK. Effect of vitamin C deficiency and excess on the liver : a histopathological and biochemical study in guinea pigs fed normal on high cholesterol diet. **Indian J Pathol Microbiol** 1990;33:307-313.

Shimokawa H, Vanhoutte PM. Impaired endothelium-dependent relaxation to aggregating platelets and related vasoactive substances in

porcine coronary arteries in hypercholesterolemia and atherosclerosis. **Circ Res** 1989;64:900-914.

Som S, Basu S, Mukherjee D. Ascorbic acid metabolism in diabetes mellitus. **Matabolism** 1981;30: 572-577.

Som S, Raha C, and Chatterjee IB. Ascorbic acid : a scavenger of superoxide radical. **Acta Vitaminol Enzymol** 1983;5:243-250.

Spiro RG. Biochemistry of the renal glomerular basement membrane and its alterations in diabetes mellitus. **N Eng J Med** 1973;288:1337.

Spiro RG. Search for a biochemical basis of diabetic microangiopathway. **Diabetologia**;1976:12:1.

Srikanta S, Ganda OP, Jackson RA. Type I diabetes mellitus in monozygote twins : chronic progressive beta cell dysfunction. **Ann Intern Med** 1983;93:320.

Stahl W, and Sies H. Antioxidant defense: Vitamin E and C and Carotenoids. **Dibaetes** 1997;46 (Suppl 2): S14-S18.

Stamler JS, Jaraki O, Osborne J, Simon DI, Keaney J, Vita J , Singel D, Valeri CR, Loscalza J. Nitric oxide circulates in mamalian plasma primarily as an S-nitroso adduct of serum albumin. **Proc. Natl. Acad. Sci. USA** 1992;89:7674-7677.

Stankola L, Riddle M, Larned J et al. Plasma ascorbate concentrations and blood cell dehydroascorbate transport in patients with diabetes mellitus. **Metabolism** 1984;33:347-353

Stauber WT, Ong S-H, and McCusky RS. Selective extravascular escape of albumin into cerebral cortex of the diabetic rat. **Diabetes** 1981;30:500.

Steinbrecher UP. Role of superoxide anion in endothelial-cell modification of low-density lipoproteins. **Biochim Biophys Acta** 1988;959:20-30.

Strain JJ. Disturbances of micronutriment and antioxidant status in diabetes. **Proc Nutr Soc** 1991;50:591-604.

Takata K, Horiuchi S, Araki N. Endocytic uptake of nonenzymatically glycosylated proteins is mediated by a scavenger receptor for aldehyde-modified proteins. **J Biol Chem** 1988;263: 14819-14825.

Tarsio JF, Reger LA, Furcht LT. Dearcased interaction of fibronectin, type IV collagen and heparin, due to non-enzymatic glycosylation. Implications for diabetes mellitus. **Biochemistry** 1987;26:1014-1020.

Teafarnariam B, Jakubowski JA, Cohen RA. Contraction of diabetic rabbit aorta due to endothelium-derived PGH_2/TXA_2. **Am J Physiol** 1989;257:H1327...-H1333.

Tesfamariam B, Brown ML, Deykin D, Cohen RA. Elevated glucose promotes generation of endothelium-derived vasoconstrictor prostanoids in rabbit aorta. **J Clin Invest** 1990;85:929-932.

Tesfamariam B, Cohen RA. Role of superoxide anion and endothelium in vasoconstrictor action of prostaglandin endoperoxide. **Am J Physiol** 1992;31:H1915-H1919.

Tesfamariam B, Jakubowski JA, Cohen RA. Contraction of diabetic rabbit aorta due to endothelium-derived PGH_2/TXA_2. **Am J Physiol** 1989;257:H13272-H1333.

Tesfamarin B .Free radicals in diabetic endothelial cell dysfunction. Free **Radical Biol Med** 1994;16:383-391

Tesfamarin B, and Cohen RA. Free radicals mediate endothelial cell dysfunction caused by elevated glucose. **Am J Physiol** 1992;263:H321-H326.

Tesfaye S, Malik R, Ward JD. Vascular factors in diabetic neuropathy. **Diabetologia** 1994;37:847-854.

Thomas SR, Neuzil J, Mohr D, Stocker R. Co-antioxidants make α-tocopherol an efficient antioxidant for low-density lipoprotein. **Am J Clin Nutr** 1995;62:1357S-1364S.

Ting HH, Timimi FK, Haley EA, Roddy MA Gang P, Creager MA. Vitamin C improves endothelium-dependent vasodilation in forearm resistance vessels of humans with hypercholesterolemia. **Circulation** 1997;95:2617-2622

Ting HH,Timimi FK, Boles KS, Creager SJ, Ganz P, and Creager MA. Vitamin C improves endothelium-dependent vasodilation in patients with non-insulin-dependent diabetes mellitus. **J Clin Invest** 1996;97(1):22-28.

Tominson KC, Gardiner SM, Hebden AR, Bennett T. Functional consequences of streptozotocin-induced diabetes mellitus, with particular reference of the cardiovascular system. **Pharmacol Rev** 1992;44:103-150.

Tooke JE. Microcirculation and diabetes. **Br Med Bull** 1989;45:206-212.

Tsilibary EC, Charonis AS, Reger LA, Wohlhueter RM, Furcht LT. The effect of non enzymatic glycosylation on the binding of the main non-collagenous NC1 domain to type IV collagen. **J Biol Chem** 1988;263 (Suppl 9):4302-4308.

Tucker BJ. Early onset of increased transcapillary albumin escape in awake diabetic rats. **Diabetes** 1990;39:919-923.

Tuomilehto J, Rastenytes D, Jousilahti P, Sarti C, Vastiainen E. Diabetes Mellitus as a risk factor for death from stroke 1996;27:210-215.

Ulrich S, Burkhard H, Michael J,and Hanjorg J. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. **Circulation** 1997;96:1513-1519

Upston JM, Karjalainen A, Bygrave FL, Stocker R. Efflux of hepatic ascorbate a potential contributor to the maintenance of plasma vitamin C. **Biochem J** 1999;342:49-56.

Vatassery GT. Oxidation of vitamin E, vitamin C and thiols in rat brain synaptosomes by peroxynitrite. **Biochem Pharmacol** 1996;52:579-586.

Vlassara H. Receptor-mediated interactions of advanced glycosylation and product with cellular components within diabetic tissues. **Diabetes** 1992;41 (Suppl 2):52-56.

Ward KK, Low PA, Schmelzer JD, Zochodne DW. Prostacyclin and noradrenaline in peripheral nerve of chronic experimental diabetes in rats . **Brain** 1989;112:197-208

Washko P, Rotrosen D, Levine M. Ascorbic acid-transport and accumulation in human neutrophils. **J Biol Chem** 1989;264:18996-19002.

Washko PW, Welch RW, Dhariwal KR, Wang Y, Levine M. Ascorbic acid and dehydroascorbic acid analysis in biological samples. **Anal Biochem** 1992;204:1-57.

Weiss SJ, Young J, Lo Bunglio A F et al. Role of hydrogen peroxide in neutrophil-mediated destruction of cultured endothelial cells. **J Clin Invest** 1981;68:712-714.

Weiss, SJ, King GW, and Lo Buglio AF. Superoxide generation by human monocytes and macrophages. **Am J Hematol**: 1978;4:1-8.

Welch RV, Wang Y, Crossman Ajr, Park JB, Kirk KL, Levine M. Accumulation of vitamin C , ascorbate, and its oxidized metabolism dehydroascorbic acid occurs by separate mechanisms. **J Biol Chem** 1995;270:12584-12592.

Wikstrom TM, Braide U, Bagge, and B Risberg. Erythrocyte-leukocyte interactions in the vascular bed of isolated perfused rat lungs. **Int. J. Microcirc. Clin Exp** 1987;12:17-32.

Wolff SP, Dean RT. Glucose autoxidation and protein modification. The potential role of oxidative glycosylation in diabetes. **Biochem J** 1987;245:243-250.

Yan SD, Schmidt AM, Anderson GM. Enhanced cellular oxidant stress by the interaction of advanced glycation and products with their receptors / bindind proteins. **J Biol Chem** 1994;269:9889-9897.

Yang IS, Torney JJ, Trimble ER. The effect of ascorbate supplementation on oxidation stress in the streptozotocin diabetic rats. **Free Rad Biol Med** 1992;13:41-46.

Yang X-D, Michie SA, Mebius RE, Tisch R, Weissman I, and MC Devitt HO. The role of cell adhesion molecules in the development of IDDM: implications for pathogenesis and therapy. **Diabetes** 1996;45:705-710.

Yew MS. Effect of streptozotocin diabetes on tissue ascorbic acid and dehydroascorbic acid. **Horm Metab Res** 1983;15:158.

Young IS, Torney JJ, Trimble ER. The effect of ascorbate supplementation on oxidative stress in the streptozotocin diabetic rat. **Free Raol Biol Med** 1992;13:41-46.

Yue DK, McLennan S, McGill M. Abnormalities of ascorbic acid metabolism and diabetic control differences between diabetic patients and diabetic rats. **Diabetes Res Clin Pract** 1990;9:239-244.

Yue DK, Mclennon KS. Fisher E, Hefferman S, Capogreco C, Ross RF, and Turtle JR. Ascorbic acid status and polyol pathway in diabetes. **Diabetes** 1989;38:257-261.

Yuichi O, Timothy E, harrison P, and Harison DG. Hypercholesterolemia increased endothelial superoxide anion production. **J Clin Invest** 1993;91:2546-2551.

APPENDIX

APPENDIX

I Ascorbic Acid (Vitamin C) Chemistry and Biochemistry

Ascorbic acid ($C_6H_6O_8$) is a water soluble,hexonic sugar acid, with a molecular weight of 176.13. Ascorbic acid is synthesized from glucose in most animals.

Vitamin C refers to all compounds that exhibit the biological activity of ascorbic acid , including both ascorbic acid and its oxidized form, dehydroascorbic acid. Removal of one electron from ascorbic acid yields semidehydroascorbic acid (ascorbate radical). This form of the vitamin is a free radical, it contains an unpaired electron. The removal of a second electron yields dehydroascorbic acid. Semidehydroascorbate is an intermediate in this conversion pathway. Dehydroascorbate reductase requires glutathione (GSH) as a source of reducing power. Both ascorbic acid and dehydroascorbic acid have biologicalactivity. The latter compound may break down to form diketogulonic acid. Diketogulonic acid has no biological activity (Levine M, 1986).

II. Plasma ascorbic acid determination

In the present study, a specific enzymatic spectrophotometric method for ascorbic acid in plasma was used. Samples were analyzed indirectly by measuring the absorbance at 593 nm of a reaction product, a complex of ferrous ion and 2,4,6-tris (2-puridyl)-s-triazine (Fe^{+}- TPTZ). Ascorbic acid is specifically quantified by pretreating one of a pair of replicate samples

with ascorbate oxidase, to oxidize the ascorbic acid , then reacting both samples with Fe^{3+}-TPTZ and measuring the difference between the asorbances at 593 nm of the treated and untreated samples (Liu TZ et al., 1982).

Table 14. Procedure for Enzymatic-assisted plasma ascorbic acid determination.

Material	AA oxidase	AA oxidase
	Treated tube	Free tube
Unknown plasma or (standard and controls (ml)	0.1	0.1
AA oxidase working solution (ml)	0.05	-----
H_2O (ml)	------	0.05
Vertex-mix gently and incubate at 37°C in a waterbath for 15 minutes		
Acetate buffer, pH 3.6 (ml)	1.25	1.25
TPTZ Solution (ml)	0.15	0.15
$FeCl_3$-$6H_2O$ Solution (ml)	0.1	0.1
Gently mix the contents of every tube after additions. Allow to stand at room tenperature for exactly 5 min. Meosure absorbance at 593 nm.		

Plasma ascorbic acid concentration can obtained from a standard curve (LIU TZ et al., 1982).

III. Streptozotocin-Induced Diabetic Rats Model

The animal model of insulin-dependent diabetes mellitus (IDDM) that is used in this study is induced by a single intravenous injection with the dose of 55 mg/kg BW streptozotocin (STZ) (Jariyapongskul A et al., 1996).

In this study, we used STZ-treated rat model as an insulin-dependent diabetes mellitus, because this model closely resemble to IDDM in human. The dose of 55 mg/Kg/BW STZ is used by a single intravenous injection. With this dose, the rats become hyperglycemia and hypoinsulinemia within 24-48 hours after induction.

Streptozotocin induce beta-cell damage by initiating biochemical events which cause DNA strand breaks . STZ is able to cause beta-cell specific damage via its ability to interact with the glucose sensing mechanism of the beta-cells and cause beta-cells specific damage (Like AA, 1976)

IV. Fluorescence Microscopic Technique

Intravital fluorescence microscopy has been used to observe the microvascular of parenchymatous organ, such as brain, heart, lung, liver, pancreas, gut, kidney.

Microscopic viewing may be performed by trans-illumination or by epi-illumination using a modified Leitz Orthoplan microscope (75 W, XBO,

xenon lamp or 100 W, HBO, mercury lamp which attached to a Ploemo-Pak illuminator with different fillter blocks for epi-illumination).

In this study the microscopic pictures are recorded by means of low-light level SIT (Silicon-intensified target) video camera-assisted image analysis system . The availability of different fluorescent markers for in vivo study are fluorescein isothiocyanate (FITC)-labeled Red blood cells (RBCs) and Rhodamine-B isothiocyanate (RITC)-labeled dextran, and their fluorescence emissions are detected separately by using two sets of filters (FITC: χem-520 nm; RITC:χem=595 nm). FITC-labeled RBCs flowing in single microveels used to measure the RBC velocity in arterioles, venules and capillaries while fluorescence images of the RITC-labeld dextran dissolved in plasma used to measure the diameter of various microvessels.

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