REFERENCES

Adam DH and Shaw S. Leukocyte-endothelial interactions and regulation of Spriger TA. Traffic signals for lymphocyte recirculation and leukocyte emigration : the multistep paradigm. **Cell** 76 (1994) : 301-314.

Adams MK, Jessup W and Celermajer DS. Cigarette smoking is associated with increased human monocyte adhesion to endothelial cells : reversibility with oral L-arginine but not vitamin C. **J Am Coll Cardiol** 29 (1997) : 491-497.

Almer LO, Pandolphi M and Nilsson IM. Diabetic retinopathy and the fibrinolytic system. **Diabetes** 24 (1976) : 529-34.

Alum A. Oculation. Adler's Physiology of the eye. Mosby, St. Louis (1992) : 198-227.

Alum A and Bill A. Ocular and optic nerve blood flow at normal and increased intraocular pressure in monkey : a study with radioactively labelled microspheres including flow detor minations in brain and some other tissue. **Exp Eye Res** 15 (1973) : 15-29.

Arend O, Wolf S, Jung F, et al. Retinal microcirculation in patients with diabetes mellitus : dynamic and morphological analysis of perifoveal capillary network. **Br J Ophthalmol** 75 (1991) : 514-518.

Ashton N. Studies of the retinal capillaries is relation to diabetic and other retinopathies. **Br J Ophthalmol** 49 (1963) : 521-538.

Atalay M and Laaksonen DE. Diabetes, oxidative stress and physical excrcise. **Journal of Sports Science and Medicine** 1 (2002) : 1-14.

Aydin A, Orhan H, Sayal A, et al. Oxidative stress and nitric oxide related parameters in type II diabetes mellitus : effects of glycemic control. **Clin Biochem** 34 (2001) : 65 – 70.

Azar DT, Spurr-Michaud SJ, Tisdale As, et al. Altered epithelialbasement membrane interactions in diabetic corneas. **Arch Ophthalmol** 110 (1992) : 537-540.

Bandello F,Brancato R, Lattanzio Ret al. Relation between iridopathy and retinopathy in diabetes. **Br J Ophth** 78 (1994) : 542-545.

Barnett AH. Pathogenesis of Diabetic Microangiopathy. **Am J Med** 24; 90 (1991) : S67-S73.

Baumgartner-Parzer SM, Wagner L, Pettermann M, et al. Modulation by high glucose of adhesion molecule expression in cultured endothelial cells. **Diabetologia** 38 (1995) : 1367-1370.

Bayer RE. The role of axcorbate in antioidant protection of biomembranes: interaction witn vitamin E and Coenzyme Q. **J Bioenerg Biomembr** 26 (1994) : 349-258.

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

Bethesda. National diabetes data group. Diabetes in america. 20 ed : National institutes of health; National institutes of diabetes and digestive and kidney diseases, NIH publication no 95 (1995) : 1450-1468.

Biegelsen ES and Loscalso J. Endothelial function and atherosclerosis. **Coro Artery Dis** 10 (1999) : 241-256.

Blair NP, Feke GT, Morales – Stoppello J, et al. Prolongation of the retinal mean circulation time in diabetes. **Arch Ophthalmol** 100 (1982) : 764-768.

Bravi MC, Pietrangeli P, Laurenti O, et al. Polyol pathway activation and glutathione redox status in non-insulin-dependent diabetic patients. **Metabolism** 46 (1997) : 1194-1198.

Bresnick GH , De Venecia G , Myers FL , et al. Retinal ischemia in diabetic retinopathy. **Arch Ophthamol** 93 (1975) : 1300-1310.

Brody T. Nutitional Bilchemistry. 1st ed. Academic press: California, (1994).

Brune B, Knethen AV and Sandan KB. Nitric oxide and it's role in apoptosis. **Eur J. Pharmacol** 357 (1998) : 261-272.

Bursell SE, Clermont AC, Kinsley B, et al. Retinal blood flow changes in patients with IDDM. Diabetes mellitus with no diabetic retinopathy : a video fluorescein angiography study. **Invest Ophthalmol Vis Sci** 37 (1996) : 886-897.

Calver A, Collicr J and Vallance P. Inhibition and stimulation of nitric oxide synthesis in the human forearm artcrial bed of patients with insulin-dependent diabetes. **J Clin Invest** 90 (1992) : 2548-2554.

Canas-Barouch F, Miyamoto K, Allport JR, et al. Intergrin-mediated neutrophil adhesion and retinal leustasis in diabetes. **Invest Ophthamol Vis Sci** 41 (2000) : 1153-1158.

Carr AC and Frei B. Toward a new recommended dictary allowance for vitamin C based on antioxidant andhealth effects in humans. **American Jounal of Clinical Nutrition** 69; 6 (1999) : 1086-1107.

Carr AC, McCall MR and Feri B. Oxidation of LDL by mycloperoxidase and reactive nitrogen species : reaction pathways and antioxidant protection**. Arteriosler Thromb Vase Biol** 20 (2000) : 1716-1723.

Cerami A, Stevens VJ and Monneir VM. Role of nonenzymatic glycosylation in the development of the sequelae of diabetes mellitus. **Metabolism** 28; Suppl 1 (1979) : 431-437.

Chin JH, Azhar S and Hoffman BB. Inactivation of endothelial derived relaxing factor by oxidized lipoproteins. **J Clin Invest** 89 (1992) : 10-18.

Chung TW, Liu AG and Yu JH. Increased red cell rigidity might affect retinal capillary blood flow velocity and oxygen transport efficiency in type II diabetes**. Diabetes Res** 23 (1993) : 75-82.

Clermont AC, Aiello LP, Mori F, et al. Vascular endothelial growth factor and severity of nonproliferative diabetic retinopathy mediate retinal hemodynamics in vivo: a potential role for vascular endothelial growth factor in the progression of nonproliferative diabetic retinopathy. **Am J Ophthalmol** 124 (1997) : 433-446.

Cohen RA. The role of nitric oxide and other endothelium- derived vasoactive substances in vascular disease. **Prog Cardiovasc Dis** 38; 2 (1995) : 105-128.

Cosentino F and Luscher TF. Endothelial dysfunction in diabetes mellitus. **J Cardiovas Pharmacol** 32; suppl 3 (1998) : S54-S61.

Cunha Vaz JG, Fonscera JR, de Abreu JRF, et al. Studies on retinal blood flow. **Arch Ophthalmol** 96 (1978) : 809-811.

Dai S and Mc Neill JH. Ascorbic acid supplementation prevents hyperlipidemia and improves myocardial performance in streptozotocindiabetic rats. **Diabetes Res Clin Pract** 10 (1995) : 91-97.

De Mattia G, Laurenti O, Bravi C, et al. Effect of aldose reductase inhibition on glutathione redox status in erythocytes of diabetic patients. **Metabolism** 43 (1994) : 965-968.

Elgawish A, Glomb M, Friedlander M, et al. Involvement of hydrogen peroxide In collagen cross-linking by high glucose *in vitro* and *in vivo*. **J Biolchem** 271 (1996) : 12964-12971.

Engerman RL, Kern TS and Garment MB. Capillary basement membrane in retina, kidney and muscle of diabetic dogs and its response to 5 yeass aldose reductase inhibition. **J Diabetes Coplication** 7 (1993) : 241-245.

Ernst E and Matrai A. Altered red and white blood cell rheology in type II diabetes. **Diabetes** 35 (1986) : 1412-1415.

Esterbauer H, Jurgen G, Quehenberger O, et al. Autoxidation of human low density lipoprotein : loss of poly unsaturated fatty acids and vitamin E and generation of al dehydes. **J Lipid Res**. 28 (1987) : 495-509.

Forrester JV, Shafice AF, Schroder S, et al. The role of growth factors in proliferative diabetic retinopathy. **Eye** 7 (1993) : 276-287.

Furchgott RF. Indroduction to EDRF rescarch. **J Cardiovasc Pharmacol** 22; suppl 7 (1993) : S1-S2.

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

Giugliano D, paolisso G and Ceriello A. Oxidative stress and diabetic vascular complications. **Diabetes Care** 19 (1996) : 257-267.

Gokce N, keancy JF Jr, Frei B, et al. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. **Circulation** 99 (1999) : 3234-3240.

Goldin E, Casadevall M, Mourelle M, et al. Role of prostaglandins and nitric oxide in gastrointestinal hyperemia of diabetic rats. **Am J physiol** 270 (1996) : G684-G690.

Griendling KK and Alexander RW. Endothelial control of the Cardiovascular system : recent advances. **FASEB J** 10 (1996) : 283-292.

Grunwald JE, Dupont J and Riva CE. Retinal Hemodynamics in patients with early diabetes. **Br J ophthalmol** 80 (1986) : 327-331.

Grunwald JE, Riva CE, Sinclair SH, et al. Laser Doppler velocimetry study of retinal circulation in diabetes mellitus. **Arch Ophthalmol** 104 (1996) : 991-996.

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

Gutteridge JM and Halliwell B. Ann, NY Acad. **Sci**. 899 (2000) : 136-147.

Hadcock S, Richardson M, Winocour PD, et al. Intimal alterations in rabbit aortas during the first 6 months of alloxan-induced diabetes. **Arterioscler Thromb**. May-Jun 11; 3 (1991) : 517-529.

Haefliger IO , Flammer J , Luscher TF. Nitric oxide and endothelin-1 are important regulators of human ophthalmic artery. **Invest ophthalmol Vis Sci** 33 (1992) : 2340-2343.

Halliwell B and Aruoma OI. DNA damage by oxygen-derived species : its mechanism and measurement in mammalian systems. **FEBS Lett** 281 (1991) : 9-19.

Halliwell B and Chirico S. Lipid peroxidation: its mechanism, measurement and significance. **Am J Clin Nutr** 57; suppl 2 (1993) : 7155-7255.

Halliwell B. Vitamin C: antioxidant or pro-oxidant in vivo. **Free Radic Res** 25 (1996) : 439-454.

Halliwell B. Antioxidant defense mechanisms: from the beginning to the end (of the beginning). **Free Radic Res**. 31 (1999) : 261-272.

Harlan JM. Consequence of leukocyte-vessel wall interaction in inflammatory and immune reaction. **Semin Thromb Hemost** 13; 4 (1987) : 416-434.

Hsueh WA and Anderson PW. Systemic hypertension and the rennin-angiotension system in diabetic vascular complications. Am J **Cardiol** 72 (1993) : H14-H21.

Hunt JV, Dean Rt and Woff SP. Hydroxyl radical production and autoxidation glucosylation : glucose autoxidation as the cause of protein damage in the experimental glucation model of diabetes mellitus and ageing, **Biochem J** 256 (1998) : 205-212.

Ishii H, Jirousek MR, Koya D, et al. Ameliotation of vascular dysfunction in diabetic rate by an oral PKCB inhibitor. **Science** 272 (1996) : 728-731.

Jackson TS, Xu A, Vita JA, et al. Ascorbate prevents the interaction of superoxide and nitric oxide only at very high physiological concentrations. **Circ Res** 83 (1998) : 916-922.

Jakus V, Radikalov UV and Bratisl Lek Listy. The role of free radicals, oxidative stress and antioxidant systems in diabetic vascular disease. **Bratisl Lek Listy**. 101 (2000) : 541-551.

Jariyapongskul A, Nimi H and Patumraj S. Cerebral imcrocirculation respone to hemorrhagic hypotension in spontaneously diabetic rats: an intravital fluorescence microscopic analysis. **Proceeding 6th world Congress for Microcirculation**, Munich (Germany) August (1996) : 977-981.

Jariyapongskul A, Patumraj S, Yamaguchi S and Niimi H. The effect of long-term supplementation of vitamin C on leukocyte adhesion to the cerebral endothelium in STZ-induced diabetic rats. **Clin Hemorheol Microcirc**. 27; 1 (2002) : 67-76.

Jones AF, Winkles JW, Thornalley PJ, et al. Inhibitory effect of superoxide dismutase on fructosamine assay. **Clin Chem**. Jan 33; 1 (1987) : 147-149.

Joussen AM, Poulaki V, Qin W, et al. Retinal vascular endothelial growth factor induces intercellular adhesion molecular – 1 and endothelial nitric oxide synthase expression and inifiafes early diabetic retinal leukocyte adhesion *in vivo*. **Am J Pathol** 160 (2002) : 501-509.

Juhan I, Vague P, Buonocore M, et al. Abnormalities of erythrocyte deformability and platelet aggregation in insulin-dependent diabetic corrected by insulin in vivo and *in vitro*. **Lancet I** (1982) : 535-537.

Kalia N, Bardhan M, Reed S, et al. Effects of chronic administration of helicobacterpylori extracts on rat gastric mucosal microcirculation *in vivo*. **Digestive Diseases and Sciences** 45; 7 (2000) : 1343-1351.

Kantar A, Giorgi P Curatola G, et al. Alterations in membrane fluidity of diabetic polymorphonuclear leukocytes. Biochem Med Metab Biol 46 (1991) :422-426.

Kashiba M, Oka J, Ichikawa R, et al. Impaired reductive regeneration of ascorbic acid in the Goto-Kakizaki diabetic rat. **Biochem J** 351 (2000) : 313-318.

Kashiba M, Oka J, Ichikawa R, et al. Impaired ascorbic acid metabolism in streptozotocin – induced diabetic rats. **Free radical biology & medicine** 33 (2002) : 1221-1230.

Kashiwagi A. Complications of diabetes mellitus and oxidative stress. **JMAJ** 44; 12 (2001) : 521-528.

Kawagishi T, Nishizawa Y, Emoto M, et al. Impaired retinal artery blood flow in IDDM patient before clinical manifestation of diabetic retinopathy. **Diabetes Care**; 18 (1995) : 1544-1549.

Keancy JF and Vita JA. Atherosclerosis, oxidative stress and antioxidant protection in endothelium- derived relaxing factor action. **Prog Cardiovasc Dis** 38 (1995) : 129-154.

Kim JA, Berliner JA, Natajaran RD, et al. Evidence that glucose increases monocyte binding to aortic endothelial cells. **Diabetes** 43 (1995) : 1103-1107.

Kinoshita JH. Aldose reductase in the diabetic eye. XLIII Endward Jachson Memorial Lecture. **Am J Ophthalmol** 102 (1986) : 685-692.

Klann E, Roberson ED, Knapp LT et al. A role for super oxide in protein kinase C activation and induction of long-term potentiation. **J Biol Chen** 273 (1998) : 4516-4522.

Klein R, Klein BE and Moss SE. Visual impairment in diabetes. **Ophthalmology** 91 (1984) : 1-8.

Kohner EM, Patel V and Rassam SMB. Role of bloodflow and impair autoregulation in the pathogenesis of diabetic retinopathy. **Diabetes** 44 (1995) : 603-607.

Koya D and King GL. Protein kinase C activation and the development of diabetic complications. **Diabetes** 47 (1998) : 857-866.

Kubes P, Suzuki M and Granger DN. Nitric oxide and endogenous modulateor of leukocyte adhesion. **Proc Nati Acad Sci USA** 88 (1991) : 4651-4555.

Kugiyama K, Motoyama T, Hirashima O, et L. Vitamin C affenuates abnormal vasomotor reactivity in spasm coronary arteries in patients with coronary spastic angina. **J Am Coll. Cardiol** 32 (1998) : 103-109.

Kume S, Takeya M, Mori T et al. Immunohistochemical and ultrastructural detection of advanced glycation end-products in atherosclerotic lesions of human aorta with a novel specific monoclonal antibody. **Am J patho** 147 (1995) : 654-657.

Lefer DJ, Nakanishi K, Johnston WE, et al. Antineutrophil and myocardial protectingactions of a novel nitric oxide donor after acute myocardial ischemia and reperfusion in dogs. **Circulation** 88 (1993) : 2337-2350.

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

Lehr HA, Frei B, Olofsson AM, et al. Protection from oxidized LDL-induced leukocyte adhesion to microvascular and macrovascular endothelium in vivo by vitamin C but vitamin E. **Circulation** 91 (1995) : 1525-1532.

Levine GN, Frei B, Koulouris SN, et al. Ascorbic acid reverses endothelial vasomotor dysfunction inpatients with coronary artery disease. **Circulation** 93 (1996) : 1107-1113.

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

Liu TZ, Chin N, Kiser MD, et al. Specific spectrophotometry of ascorbic acid in serum or plasma by use of ascorbate oxidase. **Clin Chem** 28; 11 (1982) : 2225-2228.

Lo SK, Janakiden K, LaiL, et al. Hydrogen peroxide – induced increase in endothelial adhesiveness is dependent on ICAM-1 activation. **Am Physiol** 264 (1993) : L406-L412.

Lopez-Jaramillo P, Gonzalez MC, Palmer RM, et al. The crucial role of physiological $Ca2^{+}$ concentrations in the production of endothelial nitric oxide and the control of vascular tone. Br J Phamacol 101 (1990) : 489-493.

Losada M and Alio JL. Malondialdehyde serum concentration in type 1 diabetic with retinopathy. **Doc Ophthamol** 93; 3 (1997) : 223-229.

Lowe GDO, Ghafour IM, Belch JJF, et al. Increased blood viscosity in diabetic proliferative retinopathy. **Diabestes Res** 3 (1986) : 60-67.

Martin A and Frei B. Both intracellular and extracellular vitamin C inhibit atherogenic modification of LDL by human vascular endothelial cells. **Arterioscler Thromb Vas Biol** 17 (1997) : 1583-1590.

Masuda M, Murakami T, Egawa H, et al. Decrease fluidity of polymorphonuclear leukocyte membrane in streptozotocin – induced diabetic rats. **Diabetes** 39 (1990) : 466-470.

Matsuse T, Ohga E, Teramoto S, et al. Elevated AGE-modified Apo B in the sera of euglycemic, normolipidemic patient with atherosclerosis. **Mol Med** 3 (1998) : 617-627.

Mayfield J. Diagnosis and clasasification of diabetes mellitus: New criteria. **Am Family Physician** 15 (1996).

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

Mc Millan DE. Plasma protein change, blood viscosity and diabetic microangiopathy. **Diabetes** 25; suppl 2 (1976) : 858-864.

Mc Millan DE, Ufferback NG and LaPuma J. Reduced erythrocyte deformability in diabetes. **Diabetes** 27 (1978) : 895-901.

Mc Millan DE. The effect of diabetes on blood flow properties. **Diabetes** 32; suppl 2 (1983) : 56-63.

Miyamoto K, Khosrof S, Bursell SE, et al. Pvention of leukostasis and vascular leakaye in streptozotocin – induced diabetic retinopathy via intercellular adhesion molecule – 1 inhibition. **Proc Natl Acad Sci USA** 96 (1999) : 10836-10841.

Monnier VM and Cerami A. Nonenzymatic browing *in vivo*: possible process for aging of long – lived proteins. **Science** 211 (1981) : 491-493.

Mooradian AD. Effect of ascorbate and dehydroascorbate on tissue uptake of Glucose. **Diabetes** 36 (1987) : 1001-1004.

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

Munch G, Schinzel R, Loske C, et al. Alzheimer' disease synergistic effects of glucose deficit, oxidative stress and advance glycation end products. **J Neural Transm** 105 (1998) : 439-461.

Natarajan R, Bair W, Lanting L, et al. Effects of high glucose on vascular endothelial growth factor expression in vascular smooth muscle cells. **Am J physiol** 273 (1997) : H2224-H2231.

Neuzil J, Thomas SK and Stocker R. Requirement for, promotion or inhibition by 2-tocopherol of radical-induced initiation of plasma lipoprotein lipid peroxidation. **Free Radic Biol Med**. 22 (1997) : 57-71.

Ng LL, Ngkeekwong FC, Quinn PA, et al. Uptake mechanisms for ascorbate and dehydroascorbate in lymphoblasts from diabetic nephropathy and hypertansive patients. Diabetologia; 41 (1998) : 435-442.

Nishikawa T, Edelstein D, DU XL, et al. Normalizing mitochondial superoxide production blocks three pathway of hyperglycaemic damage. **Nature** 404 (2000) : 787-790.

Niskanen LK, Salonen JT, Nyyssonen k, et al. Plasma lipid peroxidation and hyperglycemia : a connection through hyperinsulinaemia? **Diabet Med** 12 (1995) : 802-808.

Nitenberg A, Vorleu Si P, Sachs R, et al. Impairment of coronamy vascular reserve and ach induced corotary vasodilation indiabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function: **Diabetes** 42 (1993) : 1017-1025.

Nukatsuka M, Yoshimura Y, Nishida M, et al. Importance of the concentration of ATP in rat pancreatic beta cells in the mechanism of streptozotocin-induced cytotoxicity. **J Endocrinol** 127 (1990) : 161-165.

Obrosova IG, Van HuysenC, Fathallah L, et al. An aldose reductase inhibitor reverses early diabetes-induced changes in peripheral nerve function, metabolism, and antioxidative defense. **The FASEB J** 16 (2002) : 123-125.

Ohgawa H, Ohishi N and Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. **Analytical Biochemistry** 95 (1979) : 351-358.

Panes J, Pery M and Granger DN. Leukocyte-endothelial cell adhesion : avenues for therapeutic intervention. **Br J Pharmacol**; 126 (1999) : 537-550.

Paolisso G, D'Amore A, Balbi V, et al. Plasma vitamin C affects glucose homeostasis in healthy subjects and in non-insulin-dependent diabetics. Am J Physiol. 266; 2 Pt 1 (1994) : E261-E268.

Pecsvarady Z, Fisher TC, Darwin CH, et al. Decrease polymorphonuclear leukocyte deformability in NIDDM. **Diabetes Care** 17 (1994) : 57-63.

Pickup J. and Gareth W. **Textbook of diabetes mellitus**. 2st edition; Volume 2. Mosby: st. Louis (1997).

Rayment SJ, Shaw J, Woollard KJ, et al. Vitamin C supplementation in normal subjects reduces constitutive ICAM-1. **Biochemical and Biophysical Research Communications** 308; Issue 2 (2003) : 339-345.

Rimm EB, Stampfer MJ, Ascherio A, et al. Vitamin E consumption and the risk of coronary heart disease in men. **N Eng J Med** 328 (1993) : 1450-1456.

Sannomiya P, Oliverira MA, Fortes ZB. Aminoguanidine and the prevention of leukocyte dysfunction in diabetes mellitus: a direct microscopy study. **J Pharmacol** 122 (1997) : 894-898.

Santini SA, Marra G, Giardina B et al. Defective plasma antioxidant defenses and enhanced susceptibility to lipid peroxidation in un complication IDDM. **Diabetes** 46 (1997) : 1853-1858.

Schmid-Schonbein G, Volgere H. Red cell aggregation and red cell deformability in diabetes. **Diabetes** 25; suppl 2 (1976) : 897-902.

Schroder S, Palinski W, Schmid-Schonbein G. Activated monocytes and granulocytes, capillary nonreperfusion and neovascularization in diabetic retinopathy. **Am J Pathol** 139 (1991) : 81-100.

Schwidt AM, Hori O, Chen JX, et al. Advanced glycation end products interacting with their endothelial receptor induce expression of vascular cell adhesion molecule-1 (VCAM-1) in cultured endothelial cells and in mice. **J Clin Invest** 96 (1995) : 1935-1403.

Seftel AD, Vaziri ND, Ni Z, et al. Advance glycation end products in human penis: elevation in diabetic tissue, site of deposition, and possible effect through iNOS or cNOS. **Urology** 50 (1997) : 1016-26.

Semdly LA, Tonnesen MG, Sandhaus RA, et al. Neutrophil – mediated injury to endothelial cells. **J Clin Invest** 77 (1986) : 1233-1243.

Sell DR, Lapolla A, Odetti P, et al. Pentosidine formation in skin correlates with severity of complications in individuals with long-standing IDDM. **Diabetes** 41 (1992) : 1286-1292.

Sies H (Ed). Oxidative stress; from basic research to clinical application, London. **Academic Press.** (1991) : 619.

Solzbach U, Horning B, Jeserich M, et al. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. **Circulation** 96 (1997) : 1513-1519.

Springer TA. Adhesion receptors of the immune system. **Nature** 346 (1990) : 424-434.

Sridulyakul P, Chakraphan D, Bhattarakosol P and Patumraj S. Endothelial nitric oxide synthase expression in systemic and pulmonary circulation of streptozotocin induced diabetic rats comparison using image analysis. **Clinical hemorheology and microcirculation** 29 (2003) : 423-428.

Stahl W and Sies H. Antioxidant defense : vitamin E and C and and carotenoid. **Diabetes** 46; suppl 2 (1997) : S14-S18.

Standl E, Balletshofer B, Dahl B, et al. Predictor of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. **Diabetologia** 39 (1996) : 1540-1545.

Steinberg D. Low density lipoprotein oxidationand its pathobiological significance. **J Biol Chem** 272 (1997) : 20963-20966.

Stitt AW, He C, Friedman S, et al. Elevated AGE- modified Apo B in the serum of euglycemic, normolipidemic patient with atherosclerosis. Mol Med; 3 (1997) : 617-627.

Stitt AW. Advanced glycation: an important pathological event in diabetic and age related ocular disease. **Br J Ophthalmol** 85 : (2001) : 746-753.

Takagi C, Bursell SE, Lin YW, et al. Regulation of retinal hemodynamics indiabetic rats by increase expression and action of endathelin-1. **Invest Ophthalmol Vis Sci** 37 (1996) : 2504-2518.

Takahashi K, Brooks RA, kanse SM, et al. Endothelin I is produced by cultured bovine retinal endothelial cells and endothelin receptors are present on associated pericytes. **Diabetes** 38 (1989) : 1200-1202.

Tanaka Y, Adams DH, Shaw S. Proteoglycans on endothelial cells present adhesion–inducing cytokines to leucocytes. **Immunol Today** 14 (1993) : 111-115.

Tapan KB. Vitamins in Human Heath and Diacase CAB international : Guildford CK. (1996).

Tesfamariam B, Jakubowski JA and Cohen RA. Contraction of diabetic rabbit aorta due to endothelium – derived PGH_2 I TXA_2. **Am J Physiol** 257 (1989) : H1327-H1333.

The expert committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. **Diabetes Case** 24; suppl 1 (2001) : S5-S20.

Tilton RG, Hofmann AL, Kilo C, et al. Pericyte degeneration and basement membrane thickening in skeletal muscle capillaries of human diabetic. **Diabetes** 30 (1981) : 326-334.

Tooke JE. Microvascular haemodynamics in diabetes mellitus. **Clin Sci** 70 (1986): 119-25.

Tousoulis D, Davies G and Toutouzas P. Vitamin C increases nitric oxide availability in coronary atherosclerosis. **Ann Interm Med** 131 (1999) : 156-157.

Vander Jagt DJ, Harrison JM, Ratliff M, et al. Oxidative stress indice in IDDM subjects with and without long term diabetic complications. **Clin Biochem** 34 (2000) : 265-270.

Virsaladze D and Kipiani V. Anals of biomedical research and education. endothelial dysfunction in diabetic vasculopathy. V1 (2001) : 1-3.

Wautier JL, Loukourian C, Chappey O, et al. Receptor mediated endothelial cell dysfunction in diabetic vasculopathy, solubic receptor for advanced glycation end products block hypermeability in diabetic rats. **J Clin Invest** 97 (1996) : 238-243.

Weber C, Wolfgang E, Weber K, et al. Increased adhesiveness of isolated monocytes to endothelium is prevented by vitamin C in take in smokers. **Circulation** 93 (1996) : 1492.

Welch RW, Wang Y, Crossman A Jr, et al. Accumulation of vitamin C (ascorbate) and its oxidized metabolite dehydroascorbic acid occurs by separate mechanisms. **J Biol Chem** 270 (1995) : 12584-12592.

West E, Simon OP and Morrison EY. Streptozotocin alters pancratic beta-cell responsiveness to glucose with in six hours of injection into rats. **West Indian Med J** 45 (1996) : 60-62.

Will JC and Byers T. Does diabetes mellitus increase the requirement for vitamin C. **Nutr Rev**. 54; 7 (1996) : 193-202.

Wilson DJ and Green WR. Ophthalmic pathology of diabetes. **Ophthalmic Pathology with Clinical Correlations**. (1997) : 199-210.

Wolf S, Arend O, Toonen H, et al. Retinal capillary blood flow measurement with a scanning laser ophthalmoscope. **Ophthalmology** 98 (1991) : 996-1000.

Wolff SP and Dean RT. Glucose autoxidation and protein modification. The potential role of "Autoxidation glycosylation'' in diabetes. **Biochem J** 245 (1987) : 243-250.

Yang X-D, Michie SA, Mebius RE, et al. The role of cell adhesion molecules in the development of IDDM: implications for pathogenesis and therapy. Diabetes 1996; 45 (1996) : 705-710.

Yanoff M. Ocular pathology of diabetes mellitus. **Am J ophthalmol** 67 (1969) : 21–28.

Young IS and Woodside JV. Antioxidants in health and diacase. **J Clin Pathol** 54 (2001) : 176-186 .

Zanardo RO, Oliveira MA and Fortes ZB. Endothelial-leukocyte interaction in diabetes: antioxidant treatment. **Hypertension** 33 (1998) : 1095.

APPENDIX

I. Ascorbic Acid (Vitamin C) Chemistry and Biochemistry

Ascorbic acid ($C_6H_6O_8$) is 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 asorbancesat 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
$FeCl_3$-6 H_2O Solution (ml)	0.1	0.1
Gently mix the contents of every tube after additions. Allow to stand at room temperature 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-cell 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 filter 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 dextran (MW 150,000 ; 15 mg/kg BW) (FITC-dextran)-labeled plasma and Rhodamine-6G (0.15 mg/kg BW) to stain mitochondria especially in leukocyte, and their fluorescene emissions are detected separately by using two sets of filters (FITC dextran :χem-520 nm; R6G : χem=595 nm). FITC- dextran dissolved in plasma used to measure the diameter of various microvessels.

V. Free radical by products: Malondialdehyde (MDA)

Oxidation of polyunsaturated fatty acids leads to numerous peroxidic and aldehydic compound, in particular the volatile low molecular weight aldehyde, malondialdehyde (MDA). The chemical composition of the end products of peroxidation will depend on the fatty acid composition of the lipid substrate used and upon what metal ions are present. Thus copper and iron ions give different end- product distributions as measured by the thiobarbituric acid (TBA) test. This is one of the most commonly used method for detecting and measuring lipid peroxidation. The lipid material is simply heated with TBA at low pH, and the formation of a pink chromogen is measured at or close to 532nm. The chromogen is formed by reaction of one molecule of malondialdehyde (MDA) with two molecules of TBA (Ohgawa H et al., 1979).

Reagents

1. 8.1% Sodium dodecyl sulfate (SDS)

Dissolve SDS 8.1 g in distilled water and allow to stand overnight at room temperature until it is dissolved. Then make up to 100 ml. Do not shake because this solution will product a lot of bubble and store in refrigerator.

2. 20% of acetic acid solution (pH 3.5)

Pipette 26.61 ml of 37% HCl into volumeric flask (1,000 ml) and make up to 1,000ml with distill water. 0.27 M HCl is then obtained. Add 20 ml pure acetic acid in 80 ml 0.27 m HCl. Adjust the solution to pH 3.5 with 1 N NaOH.

3. 0.8% Thiobarbituric acid (TBA)

Weight TBA 0.8 g. Then add distilled water, heat and stirr until it is dissolved. Make this solution up to 100 ml and mix.

4. 1,1,3,3- Tetramethoxypropane (TMP) or malondialdehyde bis (dimethyl acetal)

Solution is used as an external standard. The level of lipid peroxide is expressed as nmole of MDA.

Pipette 16.4 μl stock TMP and make up to 100 ml with distill water. Then pipette 0.04, 0.08, 0.12, 0.16, 0.20 ml of this stock TMP solution and distill water to 10 ml in each concentration. These will give the following concentration of standard TMP: 4, 8, 12, 16, 20 nmole/ml. Store the stock solution in refrigerator.

5. 1.15% KCl in 0.1 M KH_2PO_4 to make phosphate buffer pH 7.4 add 1.15 g of KCl to 100 ml of this 0.1 M phosphate buffer (pH7.4), mix thoroughlly.

Procedure

1. After washing the isolated muscle in ice-cold 0.9% NaCl, the eye ball homogenate are prepared by homogenizing each gram of wet tissue in 4 ml of 1.15% KCl in 0.1 M phosphate buffer, pH7.4.

2. Pipette the following solutions into a series of glass tubes with screw capped:

Solution (ml)	Blank (ml)	Standard	(ml)
Unknown			
Sample	-	-	0.5
8.1% SDS	0.2	0.2	0.2
20% Acetic acid (pH 3.5)	1.5	1.5	1.5
0.8% TBA	1.5	1.5	1.5
TMP stock standard	-	0.5	-
Distill water	0.8	0.3	0.3

3. Heated the tubes in the water-bath at 95°C for 60 min.

4. After cooling with top water, 1.0 ml of distilled water and 5.0 ml of the mixture of n-butanol and pyridine (15:1 v/v) are added and shaken vigorously (at least 1 min.).

5. After centrifugation at 4,000 rpm for 10 min, the organic layer is taken and its absorbance at 532 nm is measured.

6. The content of lipid peroxide is expressed in terms of nmole MDA/ml.

CALIBRATION CURVE

1. Prepare a series of tube containing TMP stock standard in water in the following concentrations: 2.0 nmole/0.5 ml, 4.0 nmole/0.5 ml, 6.0 nmole/0.5ml, 8.0 nmole/0.5ml and 10.0 nmole/0.5ml.

2. Perform the procedure as in step 2.

3. Determine the absorbance at 532 nm. Then plot the optical density versus nmole of MDA/ml.

BIOGRAPHY

Miss Tippawan Rungjaroen was born on April 26, 1975 in Suratanee, Thailand. She graduated Bachelor of Nursing Science from Faculty of Nusing, Mahidol University in 1998.