REFERENCES

1. Tomasz S, Katarzyna K. Anti-diabetic effect of resveratrol. Ann N Y Acad 2011; 1215:34-9.

2. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; 94:311-21.

3. Genuth S, Alberti KG, Bennett P. Expert Committee on the diagnosis and classification of diabetes mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160-67.

4. International Expert Committee. International Expert Committee on the role of the A1c assay in the diagnosis of diabetes. Diabetes Care 2009; 32:1327-34.

5. Santaguida PL, Balion C, Hunt D, Morrison K. Diagnosis, prognosis and treatment of impaired glucose tolerance and impaired fasting glucose. Evid Rep Technol Assess 2005; 128:1-11.

6. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33:S62-S69.

7. Sammeth M, Bouckenooghe T, Bottu G, Sisino G. The human pancreatic islet tanscriptome: expression of candidate genes for type 1 diabetes and the impact of pro-inflammatory cytokines. Plos Genet 2012; 8:e1002552.

8. Tao B, Pietropaolo M, Atkinson M, Schatz D, Taylor D. Estimating the cost of type 1 diabetes in the U.S.: a propensity score matching method. PLoS One 2010; 5:e11501.

9. Nambam B, Aggarwal S, Jain A. Latent autoimmune diabetes in adults: A distinct but heterogeneous clinical entity. World J Diabetes 2010; 1:111-5.

10. Huang G, Wang X, Li Z, Li H, Li X, et al. Insulin autoantibody could help to screen latent autoimmune diabetes in adults in phenotypic type 2 diabetes mellitus in Chinese. Acta Diabetol 2012; 49:327-31.

11. Chiu HK, Tsai EC, Juneja R, Stoever J, Brooks-Worrell B, et al. Equivalent insulin resistance in latent autoimmune diabetes in adults (LADA) and type 2 diabetic patients. Diabetes Res Clin Pract 2007; 77:237-44.

12. Desai M, Clark A. Autoimmune diabetes in adults: lessons from the UKPDS. Diabet Med 2008; 25:30-4.

13. Imkampe AK, Gulliford MC. Trends in Type 1 diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991-2008. Diabet Med 2011; 28:811-4.

14. Seshiah V, Das AK, Balaji V, Joshi SR, Parikh MN, et al. Gestational diabetes mellitus--guidelines. J Assoc Physicians India 2006; 54:622-8.

openkanai.com

15. Paglia MJ, Coustan DR. Gestational diabetes: evolving diagnostic criteria. Curr Opin Obstet Gynecol 2011; 23:72-5.

16. Bowers K, Laughon SK, Kiely M, Brite J, Chen Z, et al. Gestational diabetes, pre-pregnancy obesity and pregnancy weight gain in relation to excess fetal growth: variations by race/ethnicity. Diabetologia 2013; 56:1263-71.

17. Pilcher H. Alzheimer's disease could be "type 3 diabetes". Lancet Neurol 2006; 5:388-9.

18. Ruan Y, Ma J, Xie X. Association of IRS-1 and IRS-2 genes polymorphisms with polycystic ovary syndrome: a meta-analysis. Endocr J 2012; 59:601-9.

19. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2014; 37:S14-S80.

20. Unger RH, Orci L. Paracrinology of islets and the paracrinopathy of diabetes. Proc Natl Acad Sci USA 2010; 107:16009-12.

21. Chamnan P, Simmons RK, Forouhi NG, Luben RN, Khaw KT, et al. Incidence of type 2 diabetes using proposed HbA1c diagnostic criteria in the European prospective investigation of cancer-Norfolk cohort: implications for preventive strategies. Diabetes Care 2011; 34:950-6.

22. Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on Type 2 diabetes prevention. Diabet Med 2007; 24:451-63.

23. Langenberg C, Sharp SJ, Franks PW, Scott RA, Deloukas P, et al. Gene-lifestyle interaction and type 2 diabetes: The EPIC InterAct Case-Cohort Study. PLoS Med 2014; 20:e1001647.

24. Yang W, Lu J, Weng J, Jia W, Ji L, et al. Prevalence of diabetes among men and women in China. N Engl J Med 2010; 362:1090-101.

25. Donath MY, Böni-Schnetzler M, Ellingsgaard H, Ehses JA. Islet inflammation impairs the pancreatic beta-cell in type 2 diabetes. Physiology (Bethesda) 2009; 24:325-31.

26. van Raalte DH, Diamant M. Glucolipotoxicity and beta cells in type 2 diabetes mellitus: target for durable therapy? Diabetes Res Clin Pract 2011; 93:S37-46.

27. Akash MS, Rehman R, Chen S. Role of inflammatory mechanisms in pathogenesis of type 2 diabetes mellitus. J Cell Biochem 2013; 114:525-31.

28. Vinagre I, Sánchez-Quesada JL, Sánchez-Hernández J, Santos D, Ordoñez-Llanos J, et al. Inflammatory biomarkers in type 2 diabetic patients: effect of glycemic control and impact of LDL subfraction phenotype. Cardiovasc Diabetol 2014; 13:34.

29. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 2011; 11:98-107.

30. Takao R, Oguro H, Yamashita E, Kuhara M, Ogawa Y, et al. Epidemiological study of the relationship between C-reactive protein and diabetes in Japanese females. J Anal Bio Sci 2012; 35:420-25.

31. Michael J, Fowler MD. Microvascular and Macrovascular Complications of Diabetes. Clinical Diabetes 2011; 29:116-22.

32. Macky TA, Khater N, Al-Zamil MA, El Fishawy H, Soliman MM. Epidemiology of diabetic retinopathy in Egypt: a hospital-based study. Ophthalmic Res 2011; 45:73-8.

33. Abcouwer SF, Gardner TW. Diabetic retinopathy: loss of neuroretinal adaptation to the diabetic metabolic environment. Ann N Y Acad Sci 2014; 1311:174-90.

34. Al-Rubeaan K, Youssef AM, Subhani SN, Ahmad NA, Al-Sharqawi AH, et al. Diabetic Nephropathy and its risk factors in a Society with a Type 2 Diabetes Epidemic: A Saudi National Diabetes Registry-Based Study. PLoS ONE 2014; 9:e88956.

35. Magee GM, Hunter SJ, Cardwell CR, Savage G, Kee F, et al. Identifying additional patients with diabetic nephropathy using the UK primary care initiative. Diabet Med 2010; 27:1372-8.

36. Pathania M, Rathaur VK, Yadav N, Jayara A, Chaturvedi A. Quantitative Micro-albuminuria Assessment from 'Random Voided Urinary Albumin: Creatinine Ratio Versus 24 hours Urinary Albumin Concentration for Screening of Diabetic Nephropathy. J Clin Diagn Res 2013; 7:2828-31.

37. Byun SH, Ma SH, Jun JK, Jung KW, Park B. Screening for diabetic retinopathy and nephropathy in patients with diabetes: a nationwide survey in Korea. PLoS ONE 2013; 8:e62991.

38. Olmos PR, Niklitschek S, Olmos RI, Faúndez JI, Quezada TA. A new psychopathological classification of diabetic neuropathy. Rev Med Chil 2012; 140:1593-605.

39. Jung KH, Chu K, Lee ST, Bahn JJ, Kim JH, et al. Risk of macrovascular complications in type 2 diabetes mellitus: endothelial microparticle profiles. Cerebrovasc Dis 2011; 31:485-93.

40. Joseph JJ, Golden SH. Type 2 diabetes and cardiovascular disease: what next? Curr Opin Endocrinol Diabetes Obes 2014; 21:109-20.

41. Kim JH, Kim DJ, Jang HC, Choi SH. Epidemiology of micro- and macrovascular complications of type 2 diabetes in Korea. Diabetes Metab J 2011; 35:571-7.

42. Szuszkiewicz-Garcia MM, Davidson JA. Cardiovascular disease in diabetes mellitus: risk factors and medical therapy. Endocrinol Metab Clin North Am 2014; 43:25-40.

openkandi.com

43. Tan MC, Ng OC, Wong TW, Hejar AR, Anthony J, et al. The association of cardiovascular disease with impaired health-related quality of life among patients with type 2diabetes mellitus. Singapore Med J 2014; 55:209-16.

44. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab 2009; 5:150-9.

45. Malave H, Castro M, Burkle J, Voros S, Dayspring T, et al. Evaluation of low-density lipoprotein particle number distribution in patients with type 2 diabetes mellitus with low-density lipoprotein cholesterol <50 mg/dl and non-high-density lipoprotein cholesterol <80 mg/dl. Am J Cardiol 2012; 110:662-5.

46. Parish S, Offer A, Clarke R, Hopewell JC, Hill MR, et al. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. Circulation 2012; 125:2469-78.

47. Haas MJ, Mooradian AD. Therapeutic interventions to enhance apolipoprotein A-I-mediated cardioprotection. Drugs 2010; 70:805-21.

48. Leonova EI, Galzitskaya OV. Structure and functions of syndecans in vertebrates. Biochemistry 2013; 78:1071-85.

49. Alberts B, Johnson A, Lewis J, Raff M, Roberts K et al. Molecular Biology of the Cell, 5th Edn., (2008) Garland Science, New York.

50. Wang W, Haller CA, Wen J, Wang P, Chaikof EL. Decoupled syndecan-1 mRNA and protein expression is differentially regulated by angiotensin-II in macrophages. J Cell Physiol 2008; 214:750-6.

51. Manon-Jensen T, Itoh Y, Couchman JR. Proteoglycans in health and disease: the multiple roles of syndecan shedding. FEBS J 2010; 277:3876-89.

52. Brown NH. Extracellular matrix in development: insights from mechanisms conserved between invertebrates and vertebrates. Cold Spring Harb Perspect Biol 2011; 3: pii: a005082.

53. Barrett PJ, Song Y, van Horn WD, Hustedt EJ, Schafer JM. The amyloid precursor protein has a flexible transmembrane domain and binds cholesterol. Science 2012; 336:1168-71.

54. Dews IC, Mackenzie KR. Transmembrane domains of the syndecan family of growth factor co-receptors display a hierarchy of homotypic and heterotypic interactions. Proc Natl Acad Sci USA 2007; 104:20782-7.

55. Savery MD, Jiang JX, Park PW, Damiano ER. The endothelial glycocalyx in syndecan-1 deficient mice. Microvasc Res 2013; 87:83-91.

56. Stanford KI, Bishop JR, Foley EM, Gonzales JC, Niesman IR, et al. Syndecan-1 is the primary heparan sulfate proteoglycan mediating hepatic clearance of triglyceride-rich lipoproteins in mice. J Clin Invest 2009; 119:3236-45.

Open Access Library

57. Bełtowski J, Wójcicka G, Jamroz-Wiśniewska A. Adverse effects of statins-mechanisms and consequences. Curr Drug Saf 2009; 4:209-28.

58. Tornio A, Pasanen MK, Laitila J, Neuvonen PJ, Backman JT: Comparison of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) as inhibitors of cytochrome P450 2C8. Basic Clin Pharmacol Toxicol 2005; 97:104-8.

59. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science 2001; 292:1160-4.

60. Lilja JJ, Neuvonen M, Neuvonen PJ. Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. Br J Clin Pharmacol 2004; 58:56-60.

61. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, et al. SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res 2010; 38:D237-43.

62. Najib NM, Idkaidek N, Adel A, Admour I, Astigarraga RE, et al. Pharmacokinetics and bioequivalence evaluation of two simvastatin 40 mg tablets (Simvast and Zocor) in healthy human volunteers. Biopharm Drug Dispos 2003; 24:183-9.

63. Davignon, J, Mabile L. Mechanisms of action of statins and their pleiotropic effects. Ann Endocrinol 2001; 62:101-12.

64. Alegret M, Silvestre J. Pharmacological experimental approaches and related pleiotropic effects of statins. Timely Top Med 2007; 11: 583-97.

65. Ginter E, Simko V. Statins: the drugs for the 21st century? Bratisl Lek Listy 2009; 110:664-8.

66. Blanco-Colio L, Villa A, Ortego M. 3-Hydroxy- 3-methyl-glutaryl coenzyme A reductase inhibitors, atorvastatin and simvastatin, induce apoptosis of vascular smooth muscle cells by downregulation of Bcl-2 expression and Rho A prenylation. Atherosclerosis 2002; 161: 17–26.

67. Shyamal C, Yan X, Christopher G, Jincai L. Emerging role of PKA/eNOS pathway in therapeutic angiogenesis for ischaemic tissue diseases. Cardiovasc Res 2012; 53:8029-35.

68. Masaaki L, Douglas W. Statins and endothelium. Vascular pharmacology journal 2007; 46:1-9.

69. Murrow JR, Sher S, Ali S, Uphoff I, Patel R, et al. The differential effect of statins on oxidative stress and endothelial function: atorvastatin versus pravastatin. J Clin Lipidol 2012; 6:42-9.

70. Rigas G, Mouses E. The Role of Statins in Chronic Kidney Disease. American Journal of Nephrology 2011; 34:195-202.

71. Belalcazar LM, Haffner SM, Lang W, Hoogeveen RC, Rushing J, et al. Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: from the look AHEAD study. Obesity (Silver Spring) 2013; 21:944-50.

72. Janosi J, Sebestyen A, Bocsi J. Mevastatin-induced apoptosis and growth suppression in U266 myeloma cells. Anticancer Res 2004; 3:817-22.

73. Hu Y, Tong CS, Xu W, Pan J, Ryan K. Anti-inflammatory effects of simvastatin on adipokines in type 2 diabetic patients with carotid atherosclerosis. Diab Vas Dis Res 2009; 6:262-8.

74. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. , eds. St. Louis: Elsevier Saunders; 2006. pp. 425-437.

75. Gabbay KH, Hasty K, Breslow JL, Ellison RC, Bunn HF, Gallop PM. Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. J Clin Endocrinol Metab 1977; 44: 859-64.

76. Allain C, Poon LS, Chan CS, Richmond W. Enzymtic determination of total serum cholesterol. Clin Chem 1974; 20:470-5.

77. Warnick RG, Nauck M, Rifai N. Evolution of methods for measurement of HDL-C from ultracentrifugation to homogenous assays. Clin Chem 2001; 47:1579-96.

78. Assman G, Jabs HU, Notte W, Schriewer H. Precipitation of LDL with sulphpolyanions: a comparison of two methods for LDL cholesterol determination. J Clin Chem Clin Biochem 1984; 22:781-5.

79. Fossati P, Prencipe L. Serum triglycerides determined calorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem 1982; 28:2077-80.

80. Friedewald WT, Levy IR, Fredrikson DS. Estimation of the concentration of low density lipoprotein cholesterol and very low density lipoprotein in plasma without use of the preparative ultracentrifugation. Clin Chem 1972; 18:499-502.

81. Marcovina SM, Albers JJ, Dati F, Ledue TB, Richitie RF. International Federation of Clinical Chemistry standarization project for measurements of apolipoproteins A-I and B. Cin Chem 1991; 37:1676-82.

82. Uchida Y, Nukina N. Sandwich ELISA for the measurement of Apo-E levels in serum and the estimation of the allelic status of Apo-E isoforms. J Clin Lab Anal 2000; 14:260-4.

83. Moss DW, Henderson AR .Clinical enzymology. In: Burits CA, Ashwood ER.Tietz Textbook of Clinical Chemistry. 3rd ed. W.B Saunders Company Philadelphia 1999, pp. 617-721.

84. Rej R, Horder M. Aspartate aminotransferase. In: Berg Meyer H, ed. Methods of Enzymatic Analysis. 3rd ed. Verlag Chemie (Pub) Basel 1983, pp. 416-33.

obeikandi.com

85. Horder M. Elser RC, Gerhardt W, Mathieu M, Sampson EJ. International Federation of Clinical Chemistry, Scientific Division Committee on Enzymes: approved recommendation on IFCC methods for the measurement of catalytic concentration of enzymes. Part 7. IFCC method for creatine kinase (ATP: creatine N-phosphotransferase, EC 2.7.3.2). Eur J Clin Chem Biochem 1991; 29:435-56.

86. Price CP, Trull AK, Berry D, Gorman EG. Development and validation of a particle-enhanced turbidimetric immunoassay for C-reactive protein. J Immunol Methods 1987; 99: 205-11.

87. Leng S, McElhaney J, Walston J, Xie D, Fedarko N, Kuchel G. ELISA and multiplex technologies for cytokine measurement in inflammation and aging research. J Gerontol A Biol Sci Med Sci 2008; 63:879-84.

88. Edmund L, David J, Christopher P. Kidney Function Tests. In: Tietz Text Book of Clinical Chemistry and Molecular Diagnostics. Burtis CA, Ashwood ER, Bruns DE. (eds). 4th ed. Elsevier Saunders Company, St Louis. 2006, pp. 813-5.

89. Wanping S, Fengmeng W, Fang X. A Novel Anti-Human Syndecan-1 (CD138) Monoclonal Antibody 4B3: Characterization and Application. Cellular & Molecular Immunology 2007; 4:209-14.

90. Leslie E, Geoffrey J, James M. Statistical analysis. In: Interpretation and uses of medical statistics. 4th ed. Oxford Scientific Publications; 1991. pp. 411-6.

91. Chehade JM, Gladysz M, Mooradian AD. Dyslipidemia in type 2 diabetes: Prevalence, pathophysiology, and management. Drugs 2013; 73:327-39.

92. Ling X, Keizo K, Munehiro K, Daisuke K. Diabetic angiopathy and angiogenic defects. Fibrogenesis and Tissue Repair 2012; 5:1-9.

93. van Raalte DH, Diamant M. Glucolipotoxicity and beta cells in type 2 diabetes mellitus: target for durable therapy? Diabetes Res Clin Pract 2011; 93:S37-46.

94. Eizirik DL, Cardozo AK, Cnop M. The role for endoplasmic reticulum stress in diabetes mellitus. Endocr Rev 2008; 29:42-61.

95. Cernea S, Dobreanu M. Diabetes and beta cell function: from mechanisms to evaluation and clinical implications. Biochemia Medica 2013; 23:266-80.

96. Masato E, Toshiyuki K, Francesco C, Hana J, Thomas FL. Statin prevents tissue factor expression in human endothelial cells: role of Rho/Rho-Kinase and Akt pathways. Circulation 2002; 105:1756-59.

97. Danesh FR, Kanwar YS. Modulatory effects of HMG-CoA reductase inhibitors in diabetic microangiopathy. FASEB 2004; 18:208-15.

openthesis.com

98. Vereth W, De Jayzer D, Davey PC. Rosuvastatin rstores superoxide dismutase expression and inhibits accumulation of oxidized LDL in the aortic arch of obese dyslipidemic mice. Br J Pharmacol 2007; 151:347-55.

99. Verges B. Abnormal hepatic apolipoprotein B metabolism in type 2 diabetes. Atherosclerosis 2010; 211:353-60.

100. Haas ME, Attie AD, Biddinger SB. The regulation of ApoB metabolism by insulin. Trends Endocrinol Metab 2013; 24:391-7.

101. Baigent C, Blackwell L, Emberson J, Holland LE. Efficacy and safety of more intensive lowering LDL-C: A meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376:1670-81.

102. Adetola FO, Adeola OI. Statin therapy in the management of diabetes mellitus; How relevant? American Medical Journal 2013; 4:36-42.

103. Tonkin A, Byrnes A. Treatment of dyslipidemia. F1000 Prime Rep 2014; 3:6-17.

104. De-xiu BU, Grifflin G, Lichtman AH. Mechanisms for the anti-inflammatory effects of statins. Curr Opin Lipidol 2011; 22:165-70.

105. Quiset-Paulsen P. Statins and inflammation: an update. Curr Opin Cardiol 2010; 25:399-405.

106. Pasterkamp G, van Lammeren GW. Peliotropic effects of statins in atherosclerosis disease. Expert Rev Cardiovasc Ther 2010; 8:1235-37.

107. Triolo M, Annema W, de Boer JF, Tietge UJ. Simvastatin and bezafibrate increase cholesterol efflux in men with type 2 diabetes. Eur J Clin Invest 2014; 44:240-8.

108. Van Tits LJ, Smilde TJ, van Wissen S. Effects of atorvastatin and simvastatin on low-density lipoprotein subfraction profile, low-density lipoprotein oxidizability, and antibodies to oxidized low-density lipoprotein in relation to carotid intima media thickness in familial hypercholesterolemia. J Invetig Med 2004; 52:177-84.

109. Vermissen J, Oosterveer DM, Yazdanpanah M, Mulder M, Dehghan A, et al. A frequent variant in the ABCA1 gene is associated with increased coronary heart disease risk and a better response to statin treatment in familial hypercholesterolemia patients. Eur Heart J 2011; 32:469-75.

110. Pang J, Chan DC, Barrett PH, Watts GF. Postprandial dyslipidaemia and diabetes: mechanistic and therapeutic aspects. Current Opinion in Lipidology 2012; 23: 303-9.

111. Ting RZ, Yang X, Yu LW, Luk AO, Kong AP. Lipid control and use of lipid-regulating drugs for prevention of cardiovascular events in Chinese type 2 diabetic patients: a prospective cohort study. Cardiovasc Diabetol 2010; 22:9-77.

112. Barter PJ, Brandrup-Wognsen G, Nicholls SJ. Effects of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. J Lipid Res 2010; 51:1546-53.

obeikandl.com

113. Song G, Liu J, Zhao Z, Yu Y. Simvastatin reduces atherogenesis and promotes the expression of hepatic genes associated with reverse cholesterol transport in apoE-Knockout mice fed high-fat diet. Lipids Health Dis 2011; 18:10-8.

114. Guan JZ, Tamasawa N, Murakami H, Matsui J. HMG-CoA reductase inhibitor, simvastatin improves reverse cholesterol transport in type 2 diabetic patients with hyperlipidemia. J Atheroscler Thromb 2008; 15:20-5.

115. Isley WL, Miles JM, Patterson BW, Harris WS. The effect of high-dose simvastatin on triglyceride-rich lipoprotein metabolism in patients with type 2 diabetes mellitus. J Lipid Res 2006; 47:193-200.

116. Okeoghene OA, Alfred A. The efficacy and safety of Simvastatin in the treatment of lipid abnormalities in diabetes mellitus. Indian J Endocrinol Metab 2013; 17:105-9.

117. Schneider JG, von Eynatten M, Parhofer KG, Volkmer JE, Schiekofer S, et al. Atorvastatin improves diabetic dyslipidemia and increases lipoprotein lipase activity in vivo. Atherosclerosis 2004; 175:325-31.

118. Ohira M, Endo K, Saiki A, Miyashita Y, Terai K, et al. Atorvastatin and pitavastatin enhance lipoprotein lipase production in L6 skeletal muscle cells through activation of adenosine monophosphate-activated protein kinase. Metabolism 2012; 61:1452-60.

119. Barbagallo CM, Rizzo M, Noto D, Frasheri A, Pernice V, et al. Accumulation of apoE-enriched triglyceride-rich lipoproteins in patients with coronary artery disease. Metabolism 2006; 55:662-8.

120. Lewin AJ, Kipnes MS, Meneghini LF, Plotkin DJ, Perevozskaya IT, et al. Effects of simvastatin on the lipid profile and attainment of low-density lipoprotein cholesterol goals when added to thiazolidinedione therapy in patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther 2004; 26:379-89.

121. Ling Y, Li X, Gu Q, Gao X. Circulating ApoE level is independently associated with urinary albumin excretion in type 2 diabetic patients. Intern Med 2011; 50:2961-6.

122. Xue C, Nie W, Tang D, Yi L, Mei C. Apolipoprotein E gene variants on the risk of end stage renal disease. PLoS One 2013; 8:e83367.

123. Marques-Vidal P, Bastardot F, von Känel R, Paccaud F, Preisig M, et al. Association between circulating cytokine levels, diabetes and insulin resistance in a population-based sample. Clin Endocrinol (Oxf) 2013; 78:232-41.

124. Lowe G, Woodward M, Hillis G, Rumley A, Li Q, et al. Circulating inflammatory markers and the risk of vascular complications and mortality in people with type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. Diabetes 2014; 63:1115-23.

125. Wang X, Bao W, Liu J, Ouyang Y, Wang D, et al. Inflammatory markers and risk of type 2 diabetes. Diabetes Care 2013; 36:166-75.

126. Sindhu S, Singh HK, Salman MT, Fatima J, Verma VK, et al. Effects of atorvastatin and rosuvastatin on high-sensitivity C- reactive protein and lipid profile in obese type 2 diabetes mellitus patients. J Pharmacol Pharmacother 2011; 2:261-5.

127. Ionica FE, Mota M, Pisoschi C, Popescu F, Gofita E, et al. Statins therapy, C-Reactive protein and type 2 diabetes. J Curr Health Sci 2009; 32: no. 2.

128. Krysiak R1, Okopien B. the effect of ezetimibe and simvastatin on monocyte cytokine release in patients with isolated hypercholesterolemia. J Cardiovasc Pharmacol 2011; 57:505-12.

129. Berthold HK, Berneis K, Mantzoros CS, Krone W, Gouni-Berthold I, et al. Effects of simvastatin and ezetimibe on interleukin-6 and high-sensitivity C-reactive protein. Scand Cardiovasc J 2013; 47:20-7.

130. Jougasaki M, Ichiki T, Takenoshita Y, Setoguchi M. Statins suppress interleukin-6-induced monocyte chemoattractant protein-1 by inhibiting Janus kinase/signal transducers and activators of transcription pathways in human vascular endothelial cells. Br J Pharmacol 2010; 159:1294-303.

131. Kown Mi-Jung, Jang B, Yi JY, Han IC, Oh ES. Syndecans play dual roles as cell adhesion receptors and docking receptors. FEBS Lett 2012; 586:2207-11.

132. Chen K, Liu ML, Schaffer L, Li M, Boden G, et al. Type 2 diabetes in mice induces hepatic overexpression of sulfatase 2, a novel factor that suppresses uptake of remnant lipoproteins. Hepatology 2010; 52:1957-67.

133. Chen K, Liu ML, Schaffer L. Type 2 diabetes strongly induces hepatic overexpression of SULF2, a novel factor that suppresses uptake of remnant lipoproteins. Atheroscler 2009; 10:e280.

134. Chen K, Liu ML, Li M. Metabolic factors in type 2 diabetes augment hepatocyte expression of SULF2, a novel suppressor of remnant lipoprotein uptake. Circulation 2009; 120:S1175.

135. Williams KJ, Chen K. Recent insights into factors affecting remnant lipoprotein uptake. Curr opin Lipidol 2010; 21:1218-28.

136. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Non-fasting triglycerides and risk for myocardial infarction, ischemic heart disease and death among women and men. JAMA 2007; 298:299-308.

137. Fuki IV, Meyer ME, Williams KJ. Transmembrane and cytoplasmic domains of syndecan mediate a multistep endocytic pathway involving detergent-insoluble membrane rafts. Biochem J 2000; 351:607-12.

138. Foley EM, Gordts PL, Stanford KI, Gonzales JC, Lawrence R, et al. Hepatic remnant lipoprotein clearance by heparan-sulfate proteoglycans and low-density lipoprotein receptors depend on dietary conditions in mice. Arterioscler Thromb Vasc Biol 2013; 33:2065-74.

Obeikandl.com

139. Deng Y, Foley EM, Gonzales JC, Gordts PL, Li Y, et al. Shedding of syndecan-1 from human hepatocytes alters very low density lipoprotein clearance. Hepatology 2012; 55:277-86.

140. Gorovoy M, Gaultier A, Campana WM, Firestein GS, Gonias SL, et al. Inflammatory mediators promote production of shed LRP1/CD91, which regulates cell signaling and cytokine expression by macrophages. J Leukoc Biol 2010; 88:769-78.

141. Meyers CD, Tannock LR, Wight TN, Chait A. Statin-exposed vascular smooth muscle cells secrete proteoglycans with decreased binding affinity f or LDL. J Lipid Res 2003; 44:2152-60.

142. Little PJ, Ballinger ML, Osman N. Vascular wall proteoglycan synthesis and structure as a target for the prevention of atherosclerosis. Vasc Health Risk Manag 2007; 3:117-24.

143. Hayashida K, Parks WC. Syndecan-1 shedding facilitates the resolution of neutrophilic inflammation by removing sequestered CXC chemokines. Blood 2009; 114:3033-43.

144. Teng YH, Aquino RS, Park PW. Molecular functions of Syndecan-1 in diseases. Matrix Biol 2012; 31:3-16.

145. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis Lancet 2010; 376: 1916–22.

146. Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, Cleeman JI, et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. Circulation 2002; 106: 1024-8.

opeikandi.com

obeikandl.com

مستوى السينديكان -١ و الإنترليوكين -٦ والبروتين سى التفاعلى فى مصل الدم لمرضى السكرى نوع (٢) المعالجون بالاستاتين.

Serum levels of syndecan-1, interleukin-6 and C-reactive protein in statin-treated patients with type 2 diabetes mellitus

Protocol of a thesis submitted to the
Medical Research Institute
University of Alexandria
in partial fulfillment of the
requirements for the degree of

خطة بحث مقدمة إلى
معهد البحوث الطبية
جامعة الإسكندرية
إيفاءاً جزئيا لشروط
الحصول على درجة

Ph.D. in Biochemistry

الدكتوراه في الكيمياء الحيوية

By
Mohamed Abd Elateef Mahmoud

من
محمد عبد اللطيف محمود

B.Sc. (Biochemistry)
Faculty of Science
University of Alexandria
2001

بكالوريوس علوم (كيمياء حيوية)
كليه العلوم
جامعة الإسكندرية
٢٠٠١

Master of Science in Immunology
Medical Research Institute
University of Alexandria
2008

ماجستير العلوم فى المناعة
معهد البحوث الطبية
جامعة الإسكندرية
٢٠٠٨

Department of Biochemistry
Medical Research Institute
University of Alexandria
2011

قسم الكيمياء الحيوية
معهد البحوث الطبية
جامعة الإسكندرية
٢٠١١

obeikandl.com

Supervisors

Dr. Wafaa Mahmoud Elsayed Abdel Rehim
Assistant Professor, Department of Biochemistry
Medical Research Institute
University of Alexandria

Dr. Eman Abd Elmeneam Sharaf
Professor, Department of Biochemistry
Medical Research Institute
University of Alexandria

Dr. Eman Wagdy Gaber
Assistant Professor, Department of Internal Medicine
Medical Research Institute
University of Alexandria

الساده المشرفون

الدكتورة / وفاء محمود السيد عبد الرحيم
أستاذ مساعد بقسم الكيمياء الحيوية
معهد البحوث الطبية
جامعة الإسكندرية

الدكتورة / إيمان عبد المنعم شرف
أستاذ بقسم الكيمياء الحيوية
معهد البحوث الطبية
جامعة الإسكندرية

الدكتورة / إيمان وجدى جابر
أستاذ مساعد بقسم الأمراض الباطنة
معهد البحوث الطبية
جامعة الإسكندرية

obeikandl.com

BACKGROUND

Diabetes mellitus is a complex metabolic disease affecting about 5% of people all over the world, characterized by hyperglycemia and associated with microvascular, macrovascular and neuropathic complications. [1] The increase in prevalence of type 2 diabetes is posing a massive health problem that results from the disease and from its association with obesity and cardiovascular (CV) risk factors, particularly dyslipidemia and hypertension. [2]

The hallmarks of type 2 diabetes are hyperglycemia, insulin resistance, and insulin deficiency. Inflammation has been implicated as an important etiological factor in the development of both insulin resistance and type 2 diabetes mellitus. In addition, it is increasingly recognized that insulin resistance contributes to the characteristic dyslipidemia associated with type 2 diabetes. [3] Dyslipidemia is manifested by raised levels of triglycerides (TG) carried in very-low-density lipoprotein (VLDL) particles, low levels of high-density lipoprotein cholesterol (HDL-C) and the more atherogenic low-density lipoprotein (LDL) particles.[4]

Previous studies have shown that VLDL is highly atherogenic since excessive uptake of these lipoproteins by macrophages causes massive cholesterol accumulation and foam cell formation. Apo E-VLDL clearance occurs primarily through heparan sulfate proteoglycans (HSPG)-mediated process. Specific HSPG, like those of the syndecans participate in the endocytic clearance of dietary lipids through binding to several protein particles like apoA, apoE and lipoprotein lipase. [5] Syndecans are type 1 transmembrane domain proteins that are thought to act as coreceptors, especially for G protein-coupled

obeikandi.com

receptors. These core proteins carry three to five heparan sulfate and chondroitin sulfate chains, which allow for interaction with a large variety of ligands. [6]

Syndecans have important roles during development, wound healing and tumor progression by controlling cell proliferation, differentiation, adhesion and migration. Mammals have four syndecan family members, syndecan-1 to 4. All cells express at least one member of the syndecan family, with the exception of erythrocytes. A plethora of ***in vitro*** data on the role of syndecans as coreceptors, signaling receptors and binding partners for chemokines, cytokines, growth factors, integrins and other adhesion molecules, supports their role as integral parts of inflammatory events. [6]

Syndecan-1 is a cell surface receptor that binds to structural extracellular matrix molecules via attached heparan sulfate chains. It is implicated in the regulation of heparin-binding growth factors and in regulating integrin signaling activity. Syndecan-1 is also involved in inflammation and lipoprotein physiology, and syndecan-1 shedding showed to be a critical mechanism that facilitates the resolution of neutrophilic inflammation by aiding the clearance of pro-inflammatory chemokines in type 2 diabetes.[7]

Interleukin-6 (IL-6), a major pro-inflammatory cytokine, is produced in a variety of tissues, including activated leukocytes, adipocytes, and endothelial cells, while C-reactive protein (CRP) is the principal downstream mediator of the acute phase response and is primarily derived via IL-6–dependent hepatic biosynthesis. [8] A recent study showed that IL-6 and CRP are two sensitive physiological markers of subclinical systemic inflammation associated with hyperglycemia, insulin resistance, and overt type 2 diabetes mellitus. [9]

obeikandl.com

Lipoprotein retention by extracellular proteoglycans (PGs) in the arterial intima is a key event in the initiation of atherosclerotic disease. Syndecan-1 provides a path for lipoprotein lipase-enriched LDL, and apoE-VLDL binding and internalization. [10] Syndecan-1 level was reported to be increased and negatively correlated with apolipoprotein-A1 (apoA1) in patients with type 2 diabetes. [11]

Among the agents receiving more attention in the field of therapy of diabetes are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins. Statins are potent inhibitors of cholesterol biosynthesis. [12] In clinical trials, statins were found to be beneficial in the primary and secondary prevention of coronary heart disease. However, the overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting “pleiotropic” effects of statins. [13]

Very recently, it has been shown that statins stimulated shedding of syndecan-1 from the surface of myeloma cells. [14] As inflammation plays an important role in the pathogenesis of type 2 diabetes and may predict it as mentioned previously, [9] syndecans could therefore serve as new targets for the prevention of pathologic inflammatory events. Accordingly, the beneficial effects of statins therapy by both inhibiting deposition of lipids and decreasing inflammation might be associated to changes in syndecan-1 level in patients with type 2 diabetes.

obeikandi.com

AIM OF THE WORK

The aim of this study is to assess the serum levels of syndecan-1, interleukin-6 and C-reactive protein in statin-treated patients with type 2 diabetes mellitus.

obeikandl.com

SUBJECTS AND METHODS

The present study will be conducted on 50 subjects recruited from the department of Internal Medicine in the Medical Research Institute categorized as follows:

Group 1: Including forty patients with type 2 diabetes mellitus subdivided into 2 subgroups:

Group A: Including twenty patients receiving a daily night dose of 40 mg simvastatin for 10 weeks.

Group B: Including twenty patients without statin treatment.

Group 2: Including ten healthy volunteers of matching age and sex to the patients, used as the control group.

Subjects with conditions other than diabetes that can affect serum levels of syndecan-1 and/or inflammatory markers as tumors or collagenic disorders are excluded from the study.

Patients and controls are asked to sign a written informed consent form indicating their acceptance to participate. The study will be conducted after institutional ethics requirements are met.

Methods

All enrolled subjects will undergo the following clinical and biochemical analyses**:**

obeikandi.com

A. Detailed personal history taking and thorough clinical examination with special stress on duration and type of treatment of diabetes, manifestations of diabetic complications and measurement of blood pressure.

B. Twelve leads standard electrocardiogram (ECG).

C. Laboratory investigations:

Blood samples are collected from all participants for the assessment of the following:

1- Fasting and postprandial serum levels of glucose. [15]

2- Fasting serum levels for the determination of total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), very low density lipoprotein (VLDL) and triglycerides (TG). [16]

3- Glycated hemoglobin (HbA1c). [17]

4- Serum aminotransferases (AST and ALT) and creatine phosphokinase (CPK). [18]

5- Serum Apolipoprotein A-1 and Apolipoprotein-E by turbidimetry. [16]

6- Determination of serum level of Syndecan-1 by ELISA technique. [19]

7- Determination of serum level of IL-6 by ELISA technique. [20]

8- Determination of serum high-sensitivity C-reactive protein (hs-CRP) levels by turbidimetry. [21]

obeikandl.com

Random urine samples are collected from all participants for the determination of urinary levels of albumin and creatinine [albumin excretion is expressed as the ratio of urinary albumin to urinary creatinine (mg/g)]. [22]

All diabetic patients will be informed about the main side effects of simvastatin and advised to:

1. Avoid any drug that may increase the risk of statin-induced myopathy. These drugs include gemfibrozil, niacin, verapamil, diltiazem, amiodarone, cyclosporine, azole and macrolides.

2. Report any muscle pain or weakness and to stop the medication immediately for severe muscle pain, brown urine or doubling of ALT and/or AST, and elevation of CPK.

ALT, AST and CPK assays are repeated every 4 weeks, while all laboratory investigations will be repeated for the patients group after the 10th week of simvastatin administration.

obeikandl.com

ANALYSIS OF RESULTS

The results of this study will be tabulated and statistically analyzed using ANOVA, paired-t and Chi-square tests.

obeikandl.com

REFERENCES

1-Szkudelski T, Szkudelska K. Anti-diabetic effects of resveratrol. Ann N Y Acad Sci 2011; 1215:34-9.

2-Zimmet P, Alberti K, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414:782-7.

3-Nesto RW. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs 2005; 5:379-87.

4-Kumar A, Singh V. Atherogenic dyslipidemia and diabetes mellitus: what's new in the management arena?. Vasc Health Risk Manag 2010; 6:665–9.

5-Ebara T, Conde K, Kako Y, Liu Y, Xu Y, Ramakrishnan R, et al. Delayed catabolism of apoB-48 lipoproteins due to decreased heparan sulfate proteoglycan production in diabetic mice. J Clin Invest 2000; 105:1807-18.

6-Alexopolou L, Multhaupt H. Syndecans in wound healing, inflammation and vascular biology. Int J Biochem Cell Biol 2009; 39:505-28.

7-Hayashida K, Parks W, Park P. Syndecan-1 shedding facilitates the resolution of neutrophilic inflammation by removing sequestered CXC chemokines. Blood 2009; 114:3033-43.

8-Aruna D, Joann E, Nader R, Julie E, Paul M. C-reactive protein, IL-6 and risk of developing type 2 diabetes mellitus. JAMA 2001; 286:327-34.

obeikandl.com

9-Marc Y, Steven E. Type 2 diabetes as an inflammatory disease. Nature Reviews Immunology 2011; 11:98-107.

10-Wilsie L, Gonzales A, Orlando R. Syndecan-1 mediates internalization of apoE-VLDL through a low density lipoprotein receptor-related protein (LRP)-independent, non-clathrin-mediated pathway. Lipids in Health and Disease 2006; 5:23.

11-Wang J-B, Zhang Y-J, Zhang Y, Guan J, Chen L-Y, Fu C-H, et al. Negative correlation between serum syndecan-1 and apolipoprotein A1 in patients with type 2 diabetes mellitus.Acta Diabetol 2010; 47:187-270.

12-Endres M. Statins and stroke. J Cereb Blood Flow Metab 2005; 25:1093–110.

13-James K. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005; 45:98-114.

14-Janosi J, Sebestyen A, Bocsi J. Mevastatin-induced apoptosis and growth suppression in U266 myeloma cells. Anticancer Res 2004; 3:817-22.

15.David B, Sacks M. Carbohydrates. In: Tietz Text Book of Clinical Chemistry and Molecular Diagnostics. Burtis CA, Ashwood ER, Bruns DE. (eds). 4 th ed. Elsevier Saunders Company, St Louis.2006, pp.868-73.

16.Nader R, Russell W. Lipids, Lipoproteins, Apolipoproteins and other Cardiovascular Risk Factors. In: Tietz Text Book of Clinical Chemistry and Molecular Diagnostics. Burtis CA, Ashwood ER, Bruns DE. (eds). 4 th ed. Elsevier Saunders Company, St Louis.2006, pp.941-54 (Lipid profile), 916-34 (Apolipoprotein-A1), 961-2 (Apolipoprotein-E).

openkandi.com

17.Jeppsson J, Kobold U, Finke A, Hoelzel W, Hoshino T, Miedema K, et al. Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med 2002; 40: 78-9.

18.Mauro P, Renze B, Wounter W, Van S. Enzymes. In: Tietz Text Book of Clinical Chemistry and Molecular Diagnostics. Burtis CA, Ashwood ER, Bruns DE. (eds). 4 th ed. Elsevier Saunders Company, St Louis.2006, pp.605-6 (ALT, AST), 1652-3 (CPK).

19-Wanping S, Fengmeng W, Fang X. A Novel Anti-Human Syndecan-1 (CD138) Monoclonal Antibody 4B3: Characterization and Application. Cellular & Molecular Immunology 2007; 4:209-14.

20-Leng S, McElhaney J, Walston J, Xie D, Fedarko N, Kuchel G. ELISA and multiplex technologies for cytokine measurement in inflammation and aging research. J Gerontol A Biol Sci Med Sci 2008; 63:879-84.

21- Kimberly M, Vesper H, Caudill S, Cooper G, Rifai N, Dati F, et al. Standardization of immunoassays for measurement of high-sensitivity C-reactive protein.Phase I: evaluation of secondary reference materials. Clin Chem 2003; 49:611-6.

22.Edmund L, David J, Christopher P. Kidney Function Tests. In: Tietz Text Book of Clinical Chemistry and Molecular Diagnostics. Burtis CA, Ashwood ER, Bruns DE. (eds). 4 th ed. Elsevier Saunders company, St Louis.2006, pp.798-801 (creatinine), 813-7 (urinary albumin to urinary creatinine ratio).

obeikandi.com

الملخص العربى

إختلال الدهون المصاحب لمرضى السكرى من النوع-٢ هو أحد عوامل الخطورة الرئيسية للإصابة بأمراض القلب و الاوعية الدموية و اللذين يعتبران من الأسباب الرئيسية للوفاة فى هؤلاء المرضى.

من البصمات المميزة لمرضى السكرى النوع-٢ هو إرتفاع مستوى السكر فى الدم و مقاومة الأنسولين و نقصه. كما يلعب الإلتهاب المصاحب لمرضى السكرى دوراً فعالاً فى استمرار المقاومة للإنسولين و التى بدورها تؤدى إلى إختلال الدهون المصاحب و المميز لمرضى السكرى من النوع-٢.

يعتبر سينديكان-١ -أحد البروتيوجلايكينات- من المستقبلات الكبدية الرئيسية لبقايا البروتينات الدهنية والليبوبروتينات الغنية بالدهون الثلاثية التى لها دوراً فعالاً فى هدم هذه الجزيئات بالكبد. علاوة على هذا، فإن للسينديكان-١ المرتبط بالغشاء الخلوى دوراً وسيطا فى عملية إبتلاع الليبوبروتينات الغنية بصميم البروتين الشحمى-باء (apo-B) و المقترنة بإنزيم ليبيز البروتين الشحمى. كما أن تحرر جزئ السينديكان-١ من سطح أغشيه الخلايا الحاملة له يساهم فى تقليل الإلتهاب المصاحب لمرضى السكرى من خلال التخلص من الكيموكينات المصاحبة للإلتهاب.

الاستاتينات هى من أوائل العقاقير المستخدمة في علاج ارتفاع الكولسترول. بصرف النظر عن دورها الأساسى فى خفض الدهون ألا أن لها خصائص أخرى كمضادات للإلتهابات و مكافحة تصلب الشرايين .

استهدف البحث دراسة تقييم التغير فى مستويات كل من السينديكان-١، والدهون، و الإنترليوكين-٦ و بروتين سي التفاعلي في مصل مرضى السكرى من النوع-٢ و كذلك دراسة التأثير المحتمل (بعيدا عن تقليل الكولستيرول) لاستخدام أحد الاستاتينات (السيمفاستاتين) على مستوى سينديكان-١ مستهدفا تقليل الإلتهاب المصاحب لداء السكرى.

وقد أجريت هذه الدراسة على عدد ٤٠ مريضا يعانون من داء السكري نوع-٢ مقسمين الى مجموعتين:

الأولى: وشملت عدد ٢٠ مريضا بداء السكرى نوع-٢ يتلقون العلاج التقليدى لمرض السكرى.

الثانيه: و شملت عدد ٢٠ مريضا بداء السكرى نوع-٢ يتلقون العلاج التقليدى لمرض السكرى بالإضافه الى جرعه من السيمفاستاتين (٤٠ ملجرام/يوم) عن طريق الفم بمعدل قرص واحد يوميا لمدة عشرة أسابيع.

كما اشتملت الدراسه أيضا على عشرة أصحاء كمجموعة ضابطة.

و قد تم فحص جميع الاشخاص فحصا اكلينيكيا و تعيين بعض المعايير البيوكيميائية فى مصل الدم فى بداية الدراسة و بعد عشرة أسابيع من العلاج لكلتا المجموعتين من المرضى شاملة: قياس مستوى الجلوكوز (صائم و بعد الإفطار بساعتين)، و السكر التراكمى، و الكولسترول الكلى، و البروتين الشحمى مرتفع الكثافه، و البروتين الشحمى منخفض الكثافه، و الدهون الثلاثية، صميم البروتين الشحمى (أ،هـ). بالإضافه الى قياس معدل الزلال البولى الى نسبه الكرياتنين فى البول. كما تم قياس مستويات إثنين من المؤشرات الحيوية للإلتهاب وهما بروتين سى التفاعلى والإنترليوكين-٦، علاوة على ذلك، تم قياس مستوى السينديكان-١ بطريقة الاليزا.

و قد أسفرت النتائج عن:

١) وجود زيادة ذات دلالة إحصائية في مستوى كل من: الجلوكوز (صائم و بعد الإفطار) و السكر التراكمى فى مصل دم مجموعتى المرضى مقارنه بالمجموعة الضابطة.

٢) نقص ذو دلالة إحصائية فى مستويات الكولسترول الكلى، والبروتين الشحمى منخفض الكثافه، و الدهون الثلاثية و صميم البروتين الشحمى-هـ (apo-E) و كذلك إرتفاع ذو دلالة إحصائية فى مستويات البروتين الشحمى مرتفع الكثافة، و صميم البروتين الشحمى-أ في مصل دم مرضى السكري المعالجون بالاستاتين مع العلاج التقليدى للسكرى مقارنة بالمستويات المناظرة قبل بدء العلاج بالاستايتن. في المقابل، لم تكن هناك تغييرات كبيرة في هذه المعايير بعد عشرة أسابيع في مرضى السكري المعالجون بالعلاج التقليدي مقارنه مع المستويات المناظره قبل عشرة اسابيع من بدء الدراسة.

٣) وجود نقص ذو دلالة احصائية فى مستويات كل من بروتين سى التفاعلى و الإنترليوكين-٦ في مصل دم مرضى السكري المعالجون بالاستاتين مع العلاج التقليدى للسكرى مقارنة بالمستويات المناظرة قبل بدء العلاج بالاستايتن. في المقابل، لم تكن هناك تغييرات ملحوظة في هذه المعايير بعد عشرة اسابيع في مرضى السكري المعالجون بالعلاج التقليدي مقارنة مع المستويات المناظرة قبل عشرة أسابيع من بدء الدراسة.

٤) وجود زيادة ذات دلالة احصائية فى مستوى السينديكان-١ فى مصل دم مرضى السكري المعالجون بالاستاتين مع العلاج التقليدى للسكرى مقارنة بالمستويات المناظرة قبل بدء العلاج بالاستاتين. في المقابل، لم يكن هناك تغيير ملحوظ في هذا المعيار بعد عشرة أسابيع في مرضى السكري المعالجون بالعلاج التقليدي مقارنه مع المستوي المناظر قبل عشرة أسابيع.

الإستنتاج:

من خلال هذه الدراسة يمكن إستنتاج أن زيادة تحرر جزئ السينديكان-١ من سطح الغشاء الخلوى بواسطة الاستاتين يمكن أن يكون هدفا جديدا للوقاية من تصلب الشرايين و الإلتهابات المصاحبه لمرضى السكرى من النوع-٢.

على الرغم أن هذه الدراسة بإمكانها القاء الضوء على أهمية السينديكان-١ فى منع حدوث تصلب الشرايين وتقليل الإلتهاب المصاحب لمرضى السكرى من النوع-٢ إلا أن طبيعة و أهمية الدور الذى يلعبه السينديكان-١ بحاجة إلى مزيد من الأبحاث المستفيضة.

التوصية:

من خلال هذه الدراسة يوصى بإجراء أبحاث أخرى إضافيه لدعم إستنتاجات هذا البحث باستخدام الاستاتينات لفترة أطول من الوقت على عدد أكبر من مرضى السكري النوع-٢.

openkandil.com

مستوى السينديكان -١ و الإنترليوكين -٦ والبروتين سى التفاعلى فى مصل الدم لمرضى السكرى نوع (٢) المعالجون بالاستاتين.

رسالة

مقدمة إلى معهد البحوث الطبية– جامعة الإسكندرية
ايفاءا جزئيا لشروط الحصول على درجة

الدكتوراه

فى

الكيمياء الحيوية

مقدمة من

محمد عبد اللطيف محمود

ماجستير في المناعه الطبية
معهد البحوث الطبية
جامعة الاسكندرية
٢٠٠٨

معهد البحوث الطبية
جامعة الإسكندرية
٢٠١٤

obeikandl.com

مستوى السينديكان -١ و الإنترليوكين -٦ والبروتين سى التفاعلى فى مصل الدم لمرضى السكرى نوع (٢) المعالجون بالاستاتين.

مقدمة من
محمد عبد اللطيف محمود

ماجستير في المناعه الطبية
معهد البحوث الطبية
جامعة الاسكندرية
٢٠٠٨

للحصول على درجة
الدكتوراه
فى
الكيمياء الحيوية

لجنة المناقشة والحكم على الرسالة **موافقون**

أ.د. ايمان عبد المنعم شرف .....
أستاذ الكيمياء الحيوية
معهد البحوث الطبيه
جامعة الإسكندرية (مشرفاً ورئيس لجنه الحكم)

أ.د. وفاء محمود السيد عبد الرحيم .....
أستاذ مساعد الكيمياء الحيوية
معهد البحوث الطبية
جامعة الإسكندرية (مشرفا وممتحنا)

أ.د. بشاى فلتاؤس مينا .....
استاذ الكيمياء الحيويه
معهد البحوث الطبية
جامعة الإسكندرية (ممتحن داخلى)

أ.د. أحمد ياسين نصار .....
استاذ الكيمياء الحيويه
كليه الطب
جامعه اسيوط (ممتحن خارجي)

obeikandi.com

السادة المشرفون	التوقيع
أ.م.د/ وفاء محمود السيد عبد الرحيم استاذ مساعد بقسم الكيمياء الحيوية معهد البحوث الطبية جامعة الاسكندرية	.....
أ.د/ ايمان عبد المنعم شرف استاذ الكيمياء الحيويه معهد البحوث الطبية جامعة الاسكندرية	.....
أ.د/ ايمان وجدى جابر استاذ بقسم الأمراض الباطنه معهد البحوث الطبية جامعة الإسكندرية	.....

obeikandl.com