Chapter 2

ACTIVATION OF INFLAMMATORY SIGNALING PATHWAYS IN METABOLIC SYNDROME: CHANGES IN ADIPOKINES AND CYTOKINES

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INTRODUCTION

Metabolic syndrome (MetS) is constellation of metabolic abnormalities such as glucose intolerance, dyslipidemia, central obesity, hypertension, insulin resistance, hyperinsulinemia and microalbuminuria [(1)]. All these risk factors increase the risk of cardiovascular disease development [(2)]. Subjects with MetS have five fold greater risk of developing Type 2 Diabetes Mellitus (T2DM) and twice fold greater risk of developing cardiovascular diseases [(3)]. In addition; individuals diagnosed with MetS, have higher risk of polycistic ovary syndrome, non alcoholic fatty liver disease, gallstone, sleep disorders, asthma and some type of cancers such as breast, colorectal, pancreas cancers [(4,5)] and mortality from all causes [(6)]. Although the mechanism underlying MetS development is not fully understood, overweight/obesity, dietary patterns, genetic disposition physical inactivity [(7)], race/ethnicity, hormone imbalances, inflammation and chronic low-grade

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inflammatory cytokine and ferritin levels at reference intervals is seen as an important step in protecting individuals against MetS development. Activation of inflammatory signaling pathways in metabolic syndrome causes changes in pro-inflammatory and anti-inflammatory cytokine levels, causing systemic inflammation and tissue damage. It is thought that studies on the relationship between inflammation and MetS and its components may help to develop new strategies to prevent and treat the MetS and related disorders.

REFERENCES

1. Kaur J. A comprehensive review on metabolic syndrome. *Cardiol Res Pract*. 2014;2014:1-21. doi:10.1155/2014/943162
2. Wilson PWF, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of Metabolic Factors and Coronary Heart Disease. *Arch Intern Med*. 1999;159:1104-1109.
3. Alberti K., Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International. *Circulation*. 2009;120(16):1640-1645. doi:10.1161/CIRCULATIONAHA.109.192644
4. Bhandari R, Kelley GA, Hartley TA, Rockett, Ian R. Metabolic Syndrome Is Associated with Increased Breast Cancer Risk: A Systematic Review with Meta-Analysis. *Int J Breast Cancer*. 2014;2014:1-13.
5. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Arterioscler Thromb Vasc Biol*. 2004;24(2):13-18. doi:10.1161/01.ATV.0000111245.75752.C6
6. Vidigal FDC, Ribeiro AQ, Babio N, Salvado JS, Bressan J. Prevalence of metabolic syndrome and pre-metabolic syndrome in health professionals : LATINMETS Brazil study. *Diabetol Syndr*. 2015;7(6):1-9. doi:10.1186/s13098-015-0003-x
7. Gill RM, Khan SA, Jackson RT, Duane M. Prevalence of the Metabolic Syndrome in Central and South American Immigrant Residents of the Washington, DC, Area. *J Nutr Metab*. 2017;2017(2005):1-6. doi:10.1155/2017/9531964

8. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflamm*. 2010;2010. doi:10.1155/2010/289645
9. Cornier M-A, Dabelea D, Hernandez TL, et al. The metabolic syndrome. *Endocr Rev*. 2008;29(7):777-822.
10. Choi K, Kim Y. Molecular Mechanism of Insulin Resistance in Obesity and Type 2 Diabetes. *Korean J Intern Med*. 2010;25(2):119-129. doi:10.3904/kjim.2010.25.2.119
11. Alborhan I. Pathophysiology of insulin resistance Individual Report for Module 1 The Post Graduate Diploma in Diabetes University of Cardiff, Wales. 2015. doi:10.13140/RG.2.1.4186.6408
12. Tanti J. Implication of inflammatory signaling pathways in obesity-induced insulin resistance. *Front Endocrinol*. 2013;3(181):1-15.
13. Sharma P. Inflammation and the Metabolic Syndrome. *Indian J Clin Biochem*. 2011;26(4):317-318. doi:10.1155/2010/289645.123
14. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011;11(2):85-97. doi:10.1038/nri2921.
15. Berberoğlu HT, Hacışevki A. Serum Ferritin ve İnflamasyon Belirteçlerinin Metabolik Sendrom ve İnsülin Direnci ile İlişkisi. 2018.
16. Aça HT, Baba B, O KC, Öztürk B, Hacışevki A. Hyperferritinemia and Inflammation in Metabolic Syndrome. In: *12th International Symposium on Pharmaceutical Sciences (ISOPS)*. ; 2018.
17. Oğuz A, Çaklılı ÖT, Çalık BT. The Prospective Urban Rural Epidemiology (PURE) study: PURE Turkey. *Turk Kardiyol Dern Ars*. 2018;46(7):613-623. doi:10.5543/tkda.2018.32967
18. Renner S, Blutke A, Dobenecker B, et al. Metabolic syndrome and extensive adipose tissue inflammation in morbidly obese Göttingen minipigs. *Mol Metab*. 2018;16:180-190.
19. Weisberg S, McCann D, Desai M, Rosenbaum M, Leibel R, Ferrante A. Obesity is assciated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003;112(12):1796-1808. doi:10.1172/JCI200319246.Introduction
20. Moschen AR, Molnar C, Enrich B, Geiger S, Ebenbichler C, Tilg H. Adipose and liver expression of interleukin (IL)-1 family members in morbid obesity and effects of weight loss. *Mol Med*. 2011;17(7-8):840-845. doi:10.2119/molmed.2010.00108
21. Mirhafez SR, Pasdar A, Avan A, et al. Cytokine and growth factor profiling in patients with the metabolic syndrome. *Br J Nutr*. 2015;113(12):1911-1919. doi:10.1017/S0007114515001038
22. Khan QA, Sola S, Khan B V. The Metabolic Syndrome: Inflammation and Endothelial Dysfunction. *Hosp Physician*. 2006:26-37.
23. Mccracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. *Clin Dermatol*. 2018;36(1):14-20. doi:10.1016/j.clindermatol.2017.09.004

24. Cooke A, Connaughton R, Lyons C, McMorrow A, Roche H. Fatty acids and chronic low grade inflammation associated with obesity and the metabolic syndrome. *Eur J Pharmacol*. 2016;15(785):207-214. doi:10.1016/j.ejphar.2016.04.021
25. Mottillo S, Filion KB, Genest J, et al. The Metabolic Syndrome and Cardiovascular Risk A Systematic Review and Meta-Analysis. *J Am Coll Cardiol*. 2010;56(14):1113-1132. doi:10.1016/j.jacc.2010.05.034
26. Goktas Z, Moustaid-moussa N, Shen C, Boylan M, Mo H, Wang S. Effects of bariatric surgery on adipokine-induced inflammation and insulin resistance. *Front Endocrinol*. 2013;4(69). doi:10.3389/fendo.2013.00069
27. Baba B, Çalışkan M, Böyük G, Hacışevki A. Leptin signaling and the reduction of er stress in islets. In: *EMBO Conference: From Functional Genomics to Systems Biology*. ; 2016:127.
28. Baba B, Çalışkan M, Böyük G, Hacışevki A. Restoring endoplasmic reticulum function by chemical chaperon pba in obesity. In: *EMBO Conference: Structure and Function of the Endoplasmic Reticulum*. ; 2016:67.
29. Shi J, Fan J, Su Q, Yang Z. Cytokines and Abnormal Glucose and Lipid Metabolism. *Front Endocrinol*. 2019;10(703). doi:10.3389/fendo.2019.00703
30. Kamari Y, Werman-Venkert R, Shaish A, et al. Differential role and tissue specificity of interleukin-1α gene expression in atherogenesis and lipid metabolism. *Atherosclerosis*. 2007;195(1):31-38. doi:10.1016/j.atherosclerosis.2006.11.026
31. Nadlonek N, Lee JH, Reece TB, et al. Interleukin-1 Beta Induces an Inflammatory Phenotype in Human Aortic Valve Interstitial Cells Through Nuclear Factor Kappa Beta. *Ann Thorac Surg*. 2013;96(1):155-162.
32. Yarim GF, Kazak F. Metabolik Sendrom ve Bileşenlerinde Sitokin Yanıtı. *Harran Üniv Vet Fak Derg*. 2016;5(1):90-99.
33. Bosek I, Kuczerowski R, Miłek T, et al. Evaluation of Interferon-Gamma in Patients with Type 2 Diabetes and Colorectal Cancer. *J Diabetes Metab*. 2016;7(1):7-10. doi:10.4172/2155-6156.100063
34. Kogan S. Role of Inflammation in Diet-Induced Obesity : A Dissertation Let us know how access to this document benefits you . 2013.
35. Rocha VZ, Folco EJ, Sukhova G, et al. Interferon-gamma, a Th1 Cytokine, Regulates Fat Inflammation Role for Adaptive Immunity in Obesity. *Circ Res*. 2008;103(5):467-476.
36. O'Rourke RW, White AE, Metcalf MD, et al. Systemic Inflammation and Insulin Sensitivity in Obese IFN-γ Knockout Mice. *Metabolism*. 2013;61(8):1152-1161. doi:10.1016/j.metabol.2012.01.018.Systemic
37. Srikanthan K, Feyh A, Visweshwar H, Shapiro J, Sodhi K. Systematic review of metabolic syndrome biomarkers: A panel for early detection, management, and risk stratification in the West Virginian population. *Int J Med Sci*. 2016;13(1):25-38. doi:10.7150/ijms.13800

38. Shoelson SE. Point : Counterpoint Comments. *J Appl Physiol 102*. 2007;102:820-823. doi:10.1152/japplphysiol.01353.2006.Why
39. El-byoumy I. Interleukin 6 as inflammatory marker and insulin resistance in obese Kuwaiti adolescents. *Integr Obes Diabetes*. 2017;3(3):1-3. doi:10.15761/IOD.1000181
40. Chedraui P, Escobar GS, Pérez-lópez FR, et al. Maturitas Angiogenesis , inflammation and endothelial function in postmenopausal women screened for the metabolic syndrome. *Maturitas*. 2014;77(4):370-374.
41. Weiss TW, Arnesen H, Seljeflot I. Components of the Interleukin-6 transsignalling system are associated with the metabolic syndrome, endothelial dysfunction and arterial stiffness. *Metabolism*. 2013;62(7):1008-1013.
42. Bao P, Liu G, Wei Y. Association between IL-6 and related risk factors of metabolic syndrome and cardiovascular disease in young rats. *Int J Clin Exp Med*. 2015;8(8):13491-13499.
43. Udenze IC, Amadi CE, Awolola NA, Makwe CC, Aije OI. The role of inflammation in the metabolic syndrome. *J Clin Sci*. 2016;13(1):17-22. doi:10.4103/1595-9587.175484
44. Emanuela F, Grazia M, Marco DR, Maria Paola L, Giorgio F, Marco B. Inflammation as a link between obesity and metabolic syndrome. *J Nutr Metab*. 2012;2012. doi:10.1155/2012/476380
45. Musialik K. The influence of chosen adipocytokines on blood pressure values in patients with metabolic syndrome. *Kardiol Pol*. 2012;70(12):1237-1242.
46. Exel E Van, Gussekloo J, Craen AJM De, Fröclich M, Wiel AB-V Der, Westendorp RG. Low Production Capacity of Interleukin-10 Associates With the Metabolic Syndrome and Type 2 Diabetes. *Diabetes*. 2002;51:1088-1092. doi:10.2337/diabetes.51.4.1088
47. Straczkowski M, Kowalska I, Nikolajuk A, Krukowska A, Gorska M. Plasma interleukin-10 concentration is positively related to insulin sensitivity in young healthy individuals. *Diabetes Care*. 2005;28(8):2036-2037. doi:10.2337/diacare.28.8.2036
48. Leon-Cabrera S, Arana-Lechuga Y, Esqueda-León E, et al. Reduced Systemic levels of IL-10 are associated with the severity of obstructive sleep apnea and insulin resistance in morbidly obese humans. *Mediators Inflamm*. 2015;2015(October). doi:10.1155/2015/493409
49. Matia-García I, Muñoz-Valle JF, Reyes-Castillo Z, et al. Correlation Between Cytokine Profile and Metabolic Abnormalities in Young Subjects. *Int J Clin Exp Med*. 2016;9(8):16596-16604.
50. Manigrasso MR, Ferroni P, Santilli F, et al. Association between Circulating Adiponectin and Interleukin-10 Levels in Android Obesity : Effects of Weight Loss. *J Clin Endocrinol Metab*. 2005;90:5876-5879. doi:10.1210/jc.2005-0281
51. Jung SH, Park HS, Kim K-S, et al. Effect of weight loss on some serum cy-

tokines in human obesity : increase in IL-10 after weight loss. *J f Nutr Biochem*. 2008;19(6):371-375. doi:10.1016/j.jnutbio.2007.05.007

52. Arhire LI, Mihalache L, Covasa M. Irisin : A Hope in Understanding and Managing Obesity and Metabolic Syndrome. 2019;10:1-12. doi:10.3389/fendo.2019.00524
53. Esfahani M, Baranchi M, Goodarzi MT. Irisin and Metabolic Disorders. *Avicenna J Med Biochem*. 2016;4(1):2-5. doi:10.17795/ajmb-33230
54. Choi Y, Kim M, Bae K, et al. Serum irisin levels in new-onset type 2 diabetes. *Diabetes Res Clin Pract*. 2013;100(1):96-101.
55. Yan B, Shi X, Zhang H, et al. Association of Serum Irisin with Metabolic Syndrome in Obese Chinese Adults. *PLoS One*. 2014;9(4):1-10.
56. Lin C, Hung Y, Tsai M, Huang TL. Increased serum brain-derived neurotrophic factor in male schizophrenic patients with metabolic syndrome. *Medicine (Baltimore)*. 2017;96(22):1-3.
57. Karczewska-kupczewska M, Straczkowski M, Adamska A, et al. Decreased serum brain-derived neurotrophic factor concentration in young nonobese subjects with low insulin sensitivity. *Clin Biochem*. 2011;44(10-11):817-820. doi:10.1016/j.clinbiochem.2011.05.008
58. Krabbe KS, Nielsen AR. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia*. 2007;50(2):431-438. doi:10.1007/s00125-006-0537-4
59. Bhusal A, Rahman H, Lee W, YC B, Suk K. Paradoxical role of lipocalin-2 in metabolic disorders and neurological complications. *Biochem Pharmacol*. 2019;169:1-12.
60. Jang Y, Lee JH, Wang Y, Sweeney G. Emerging clinical and experimental evidence for the role of lipocalin-2 in metabolic syndrome. *Clin Exp Pharmacol Physiol*. 2012;39(2):194-199.
61. Wang Y, Lam KSL, Kraegen EW, et al. Lipocalin-2 Is an Inflammatory Marker Closely Associated with Obesity , Insulin Resistance , and Hyperglycemia in Humans. *Clin Chem*. 2007;53(1):34-41. doi:10.1373/clinchem.2006.075614
62. J.M.M N, Manco M, Ibáñez J, et al. Metabolic endotoxemia and saturated fat contribute to circulating NGAL concentrations in subjects with insulin resistance. *Int J Obes*. 2010;34(2):240-249.
63. Id S, Elshaer S, Emara I, Maged M, Ak A-A. Serum sclerostin and irisin as predictive markers for atherosclerosis in Egyptian type II diabetic female patients : A case control study. *PLoS One*. 2018;13(11):1-13.
64. Popovic DS, Stokic E, Tomic-naglic D, et al. Circulating sclerostin levels and cardiovascular risk in obesity. *Int J Cardiol*. 2016;214:48-50.
65. Daniele G, Winnier D, Mari A, et al. Sclerostin and Insulin Resistance in Prediabetes : Evidence of a Cross Talk Between Bone and Glucose Metabolism. *Diabetes Care*. 2015;38(8):1509-1517. doi:10.2337/dc14-2989
66. Gaudio A, Privitera F, Pulvirenti I, Canzonieri E, Rapisarda R, Fiore C. The relationship between inhibitors of the Wnt signalling pathway (sclerostin

and Dickkopf-1) and carotid intima-media thickness in postmenopausal women with type 2 diabetes mellitus. *Diab Vasc Dis Res*. 2014;11(1):48-52.
67. Oo SM, Misu H, Saito Y, et al. Serum selenoprotein P , but not selenium, predicts future hyperglycemia in a general Japanese population. *Sci Rep*. 2018;8(1).
68. Gharipour M, Sadeghi M, Salehi M, et al. Association of Expression of Selenoprotein P in mRNA and Protein Levels with Metabolic Syndrome in Subjects with Cardiovascular Disease : Results of Selenegene Study Abstract : *J Gene Med*. 2017;19(3). doi:10.1002/jgm.2945
69. Wang LH, Liu YC, Wang JH, Lee C-J, Hsu B-G. Serum leptin level positively correlates with metabolic syndrome among elderly Taiwanese. *Tzu Chi Med J*. 2017;29(3):159-164. doi:10.4103/tcmj.tcmj
70. Obeidat AA, Ahmad MN, Haddad FH, Azzeh F. Leptin and uric acid as predictors of metabolic syndrome in jordanian adults. *Nutr Res Pr*. 2016;10(4):411-417. doi:10.4162/nrp.2016.10.4.411
71. Abate N, Sallam HS, Rizzo M, et al. Resistin: An Inflammatory Cytokine. Role in Cardiovascular Diseases, Diabetes and the Metabolic Syndrome. *Curr Pharm Des*. 2014;20(31):4961-4969.
72. Chen X, Zhang J, Liu F, Liu H-M, Song Y-Y, Liu Y-L. Association of serum resistin levels with metabolic syndrome and early atherosclerosis in obese Chinese children. *J Pediatr Endocrinol Metab*. 2013;26(9-10):855-860. doi:10.1515/jpem-2012-0326
73. Asgary S, Ziaedin S, Ghorbani A, Keshvari M, Sahebkar A, Sarrafzadegan N. Relationship between serum resistin concentrations with metabolic syndrome and its components in an Iranian population. *Diabetes Metab Syndr Clin Res Rev*. 2015;9(4):266-270.
74. Singh AK, Tiwari S, Gupta A, Natu SM, Mittal B, Pant AB. Association of Resistin with Metabolic Syndrome in Indian Subjects. *Metab Syndr Relat Disord*. 2012;10(4):286-291. doi:10.1089/met.2011.0128
75. Zou CC, Liang L, Fang H, Fu JF, Zhao ZY. Serum Adiponectin , Resistin Levels and Non-alcoholic Fatty Liver Disease in Obese Children. *Endocr J*. 2005;52(5):519-524.
76. Koç F, Tokaç M, Kocabaş V, et al. Ghrelin, Resistin and Leptin Levels in Patients with Metabolic Syndrome. *Eur J Gen Med*. 2011;8(2):92-97.
77. Utzschneider K., Carr D., Tong J, et al. Resistin is not associated with insulin sensitivity or the metabolic syndrome in humans. *Diabetologia*. 2005;48(11):2330-2333. doi:10.1007/s00125-005-1932-y
78. Shafiee G, Ahadi Z, Qorbani M, et al. Association of adiponectin and metabolic syndrome in adolescents : the caspian- III study. *J Diabetes Metab Disord*. 2015;14(89):1-6.
79. Goodarzi MT. Adiponectin and Metabolic Syndrome Prevention. *Avicenna J Med Biochem*. 2014;2(1):1-2. doi:10.17795/ajmb-21991
80. Maury E, Brichard SM. Adipokine dysregulation , adipose tissue inflam-

mation and metabolic syndrome. *Mol Cell Endocrinol*. 2010;314:1-16. doi:10.1016/j.mce.2009.07.031
81. Ghadge AA, Khaire AA, Kuvalekar AA. Adiponectin: A Potential Therapeutic Target for Metabolic Syndrome. *Cytokine Growth Factor Rev*. 2018;39:151-158.
82. Yatagai T, Nishida Y, Nagasaka S, et al. Relationship Between Exercise Training-Induced Increase in Insulin Sensitivity and Adiponectinemia in health Men. *Endocr J*. 2003;50(2):233-238.
83. Ryo M, Nakamura T, Kihara S, et al. Adiponectin as a Biomarker of the Metabolic Syndrome. *Circ J*. 2004;68(11):975-981.
84. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu F, Rimm E. Plasma Adiponectin Levels and Risk of Myocardial Infarction in Men. *JAMA*. 2015;291(14):1730-1737.
85. Blaslov K, Bulum T, Zibar K, Duvnjak L. Relationship between Adiponectin Level , Insulin Sensitivity , and Metabolic Syndrome in Type 1 Diabetic Patients. *Int J Endocrinol*. 2013;2013(1):1-7.
86. Baden MY, Yamada Y, Takahi Y, et al. Association of adiponectin with blood pressure in healthy people. *Clin Endocrinol (Oxf)*. 2013;78(2):226-231. doi:10.1111/j.1365-2265.2012.04370.x
87. Frankenberg AD Von, Nascimento F V, Gatelli LE, et al. Major components of metabolic syndrome and adiponectin levels : a cross-sectional study. *Diabetol Metab Syndr*. 2014;6(26):1-9. doi:10.1186/1758-5996-6-26
88. Lindberg S, Jensen JS, Bjerre M, et al. Low adiponectin levels at baseline and decreasing adiponectin levels over 10 years of follow-up predict risk of the metabolic syndrome. *Diabetes Metab*. 2016;43(2):134-139.
89. Falahi E, Hossein A, Rad K. What is the best biomarker for metabolic syndrome diagnosis ? *Diabetes Metab Syndr*. 2015;9(4):366-372.
90. King GA, Deemer SE, Thompson DL. Adiponectin is Associated with Risk of the Metabolic Syndrome and Insulin Resistance in Women. *Endocrinol Metab*. 2015;49(0 1):41-49. doi:10.1007/s00592-010-0192-6.Adiponectin
91. Hossein-nezhad A, Mirzaei K, Alatab S, Ahmadivand Z, Najmafshar A. Circulating Omentin-1 in Obesity and Metabolic Syndrome Status Compared to Control Subjects. *Endocrinol Metab Syndr*. 2012:8-12.
92. Batista CMDS, Yang R, Lee M, et al. Omentin Plasma Levels and Gene Expression Are Decreased in Obesity. *Diabetes*. 2007;56(6):1655-1661. doi:10.2337/db06-1506.AFDS
93. Shibata R, Takahashi R, Kataoka Y, et al. Association of a fat-derived plasma protein omentin with carotid artery intima-media thickness in apparently healthy men. *Hypertens Res*. 2011;34(12):1309-1312.
94. Pan H, Guo L, Li Q. Changes of serum omentin-1 levels in normal subjects and in patients with impaired glucose regulation and with newly diagnosed and untreated type 2 diabetes. *Diabetes Res Clin Pract*. 2010;88(1):29-33.

95. Zhong X, Zhang H, Tan H, et al. Association of serum omentin-1 levels with coronary artery disease. *Acta Pharmacol Sin*. 2011;32(7):873-878.
96. Esteghamati A, Morteza A, Zandieh A, et al. The Value of Visfatin in the Prediction of Metabolic Syndrome : A Multi- The Value of Visfatin in the Prediction of Metabolic Syndrome : A Multi-Factorial Analysis. *J Cardiovasc Transl Res*. 2012;5(4):541-546.
97. Esteghamati A, Alamdari A, Zandieh A, et al. Serum visfatin is associated with type 2 diabetes mellitus independent of insulin resistance and obesity. *Diabetes Res Clin Pract*. 2011;91(2):154-158.
98. Chang Y, Chang D, Lin K, Shin S-J, Lee Y-J. Visfatin in overweight / obesity , type 2 diabetes mellitus , insulin resistance , metabolic syndrome and cardiovascular diseases : a meta-analysis and systemic review. *Diabetes Metab Res Rev*. 2011;27(6):515-527.
99. Kolsgaard ML, Wangensteen T, Brunborg C, et al. Elevated visfatin levels in overweight and obese children and adolescents with metabolic syndrome. *Scand J Clin Lab Invest*. 2009;69(8):858-864.
100. Kim J, Kim S, Im J, Lee, Duk C. The relationship between visfatin and metabolic syndrome in postmenopausal women. *Maturitas*. 2010;67(1):67-71.
101. Mutlak S, Sabah V, Hussein RM. Apelin and Some Biomarkers in Females with Metabolic Syndrome Apelin and Some Biomarkers in Females with Metabolic Syndrome. *Biomed Pharmacol J*. 2018;11(1):247-253.
102. Angelova P, Kamenov Z, Tsakova A. Apelin and Testosterone Levels in Men with Metabolic Syndrome. *J Endocr Metab Dis*. 2014;4:35-43.
103. Saki F, Ashkani-esfahani S, Karamizadeh Z. Investigation of the Relationship Between Retinol Binding Protein 4 , Metabolic Syndrome. *Iran J Pediatr*. 2013;23(4):396-402.
104. Qi Q, Yu Z, Ye X, et al. Elevated Retinol-Binding Protein 4 Levels Are Associated with Metabolic Syndrome in Chinese People. *J Clin Endocrinol Metab*. 2007;92(12):4827-4834.
105. Yagmur E, Weiskirchen R, Ressner AM, Trautwein C, Tacke F. Insulin Resistance in Liver Cirrhosis Is Not Associated With Circulating Retinol- Binding Protein 4. *Diabetes Care*. 2007;30(5):1168-1172. doi:10.2337/dc06-2323.