International Journal of Advance Research in Science and Engineering
Volume No.07, Special Issue No.04, March 2018
www.ijarse.com
IJARSE
ISSN: 2319-8354

ROLE OF ADIPOKINES AND FREE FATTY ACIDS IN INSULIN RESISTANCE- A REVIEW

Rumaisa Rashid[1], Mudasir Maqbool[1], Andleeb Jan[1], M Ishaq Geer[1*]

[1]Department of Pharmaceutical Sciences, University of Kashmir,
Hazratbal Srinagar-190006, Jammu and Kashmir, India

ABSTRACT

Insulin Resistance (IR) is a metabolic condition in which there is a defect in the insulin mediated glucose uptake particularly in muscles, adipose tissue and liver. It is a multi-faceted disruption of the communication between insulin and the interior of a target cell. Evidences have suggested that adipocytes release a variety of bioactive molecules termed adipokines including- IL-6, TNF alpha, leptin, adiponectin, resistin etc. The release of these adipokines from adipose tissue-infiltrated macrophages or by adipocytes itself leads to the chronic inflammatory state that could play a central role in IR. Excessive fat accumulation is associated with elevated plasma free fatty acid levels that cause peripheral and hepatic insulin resistance and stimulate insulin secretion. Through free fatty acid flux and adipokines, the dysfunctional adipose tissue communicates with peripheral tissues, such as liver, skeletal muscle or pancreatic beta- cells and causes metabolic adverse effects. Either directly by interaction with transcription factors or indirectly via unknown mechanisms possibly linked to fatty acid oxidation, synthesis or storage, these fatty acids may influence the expression of adipokines. Since fatty acids are the main components of adipose tissue, it is essential to clarify the biological effects of different types of fatty acids on the expression of relevant adipokines. Insulin resistance is very easy to define, but it is complex to understand at the molecular level. In this review, we focus on role of adipokines and free fatty acids in insulin resistance.

Keywords: Adipokines, Adipose Tissue, Free Fatty Acids, Glucose, Insulin Resistance.

I INTRODUCTION

Insulin Resistance (IR) is a metabolic condition in which there is a defect in the insulin mediated glucose uptake particularly in muscles, adipose tissue and liver. It is describes an impaired biological response to insulin [1-4]. It can be seen as a molecular and genetic mystery involving defective insulin signalling and glucose transport into cells. Insulin resistance is strongly associated with obesity and many studies have shown that inflammatory responses by macrophages can induce insulin resistance in obese subjects [5-7]. Insulin resistance in obesity is due to various adipocyte-derived hormones, metabolites, and cytokines released from the expanded adipose tissue. Adipose tissues secrete very important metabolic proteins called “adipokines”, some of which play an important and major role in insulin resistance [8]. These substances regulate insulin action not only locally in adipose tissue but also in skeletal muscle and liver.

Resistance to insulin stimulated glucose uptake is significantly correlated with resistance to insulin suppression of plasma FFA (free fatty acid) concentration [9]. FFAs are elevated in most obese individuals [10, 11] primarily because of an increase in the rate of lipolysis from the expanded fat cell mass [12, 13]. Rise in plasma FFA concentrations leads to hepatic and peripheral insulin resistance, while in normal subjects it is compensated by FFA induced potentiation of glucose stimulated insulin secretion.

II ADIPOKINES AND INSULIN RESISTANCE

The adipokines are cytokines i.e cell signaling proteins secreted by adipose tissue. The class includes: Leptin , Adiponectin, Apelin ,chemerin, Interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), retinol binding protein 4 (RBP4),tumor necrosis factor-alpha (TNFα), Visfatin, Omentin, vaspin, Progranulin, CTRP-4 [14] .

'Adipokine' has also been employed to describe a protein that is secreted by adipose tissue, rather than by adipocytes. However, it is preferable to restrict the term to those proteins that are released by adipocytes themselves. The principal reason for this is that cells such as macrophages which also secrete protein signals are found in a number of organs, as well as being present in adipose tissue [15, 16].

The total number of adipokines, both assumed and documented, is now well over fifty. The earliest to be identified was in practice the enzyme lipoprotein lipase, responsible for the hydrolysis of circulating triacylglycerols to non-esterified fatty acid (NEFA); this was followed in the mid-1980s by adipsin, a serine protease and part of the alternative complement pathway [17, 18].

2.1 Leptin

Leptin was the first adipokine to be discovered in 1944 [19]. It is a hormone made by adipose cells that helps to regulate energy balance by inhibiting hunger. Leptin, a product of the ob gene, is exclusively expressed by white adipose tissue (WAT) [20] and is strongly correlated with insulin sensitivity. Leptin binds to OB-R receptors, which belong to the class 1 cytokine receptor family. Binding of leptin to its receptor activates the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signal transduction pathway, leading to its numerous functions.

There is considerable amount of crosstalk between the leptin signalling and other signalling pathways, including insulin-stimulated phosphatidylinositol 3 kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) signalling [21]. Leptin improves insulin sensitivity through activation of AMP protein kinase (AMPK) [22].

2.2 Tumor Necrosis Factor α

Tumor necrosis factor (TNF) α is a pro-inflammatory cytokine involved in a wide array of physiological processes including inflammation. It is produced by variety of cells mainly but,mainly by macrophages and lymphocytes. TNFα exerts its functions through its two main receptors, p50 and p75, with subsequent activation of serine kinases, such as IκBα kinase β (IKKβ), c-Jun NH2-terminal kinase (JNK), and p38 MAPK, and increased transcription and expression of various pro-inflammatory mediators [23]. Adipose tissue also produces

TNF-α in rodents although this production is weak in humans. In rodents the pathophysiology of insulin resistance is mainly through the phosphorylation of the insulin receptor substrate-1 (IRS-1) protein on serine residues [24].

As already mentioned TNF-α is poorly expressed in humans, moreover its expression is slightly modified in human obesity [25]. In obese individuals and in animal models of obesity, TNFα expression is increased in abdominal fat and skeletal muscle [24, 26]. Study by Hotamisligil et al [24] first identified the increased plasma levels of TNFα as a causal mediator of insulin resistance in obese mice. Since then, TNFα has been shown to impair insulin signaling by decreasing tyrosine phosphorylation of insulin receptor and insulin receptor substrates (IRS) [27, 28], which is likely due to their serine phosphorylation by the serine kinase JNK1.

2.3 Interleukin-6

Interleukin-6 is a pro-inflammatory cytokine that is produced by many cell types such as fibroblasts,endothelial cells, monocytes and also released by adipose tissue (8). IL-6 production by adipocytes is increased in obesity [29, 30].

Recent studies have suggested that IL-6 could be involved in insulin resistance and its complications [30, 31]. IL-6 binds to its receptor composed of two subunits, binding to the receptor activates either Ras-mediated signalling or JAK/STAT pathway [32]. IL-6 receptor finds its place in the family of class I cytokine receptor and involves JAK/STATs (Janus kinases/signal transducers and activators of transcription) signal transduction pathway [33].

Janus kinase activation induces STAT phosphorylation, dimerisation and translocation to the nucleus to regulate target gene transcription [33]. It is well established that very tough interaction occurs between cytokine and insulin signalling pathways and this generally ends up to an impaired biological effect of insulin. Since the exact mechanisms have not yet been clearly defined, it could involve tyrosine phosphatase activation [34] or an interaction between suppressor of cytokine signalling (SOCS) proteins and the insulin receptor [35-37]. Regardless of the mechanisms involved, it has now been clearly elucidated that cytokines such as TNF-a and IL-6 are able to decrease insulin action [34-37].

2.4 Adiponectin

Adiponectin is a 30kDa hormone that is mainly secreted and expressed by adipocytes. Expression and circulating levels of adiponectin are decreased in obese humans and mice, and correlate strongly with insulin sensitivity [38]. Mice deficient in adiponectin are insulin resistant[39] and, conversely, an adiponectin administration to obese, insulin resistant mice improves insulin sensitivity [40-42].Thus in contrast to other adipokines, adiponectin levels are decreased in obese and/or type 2 diabetic patients and in patients with coronary heart diseases.

There is a strong positive correlation between adiponectinemia and insulin sensitivity. The role of adiponectin in insulin-sensitive action of adiponectin may involve the activation of AMP activated protein kinase (AMPK), which is known to regulate cellular malonyl CoA concentrations by inhibiting acetyl CoA carboxylase [22]

2.5 Retinol Binding Protein (RBP)-4

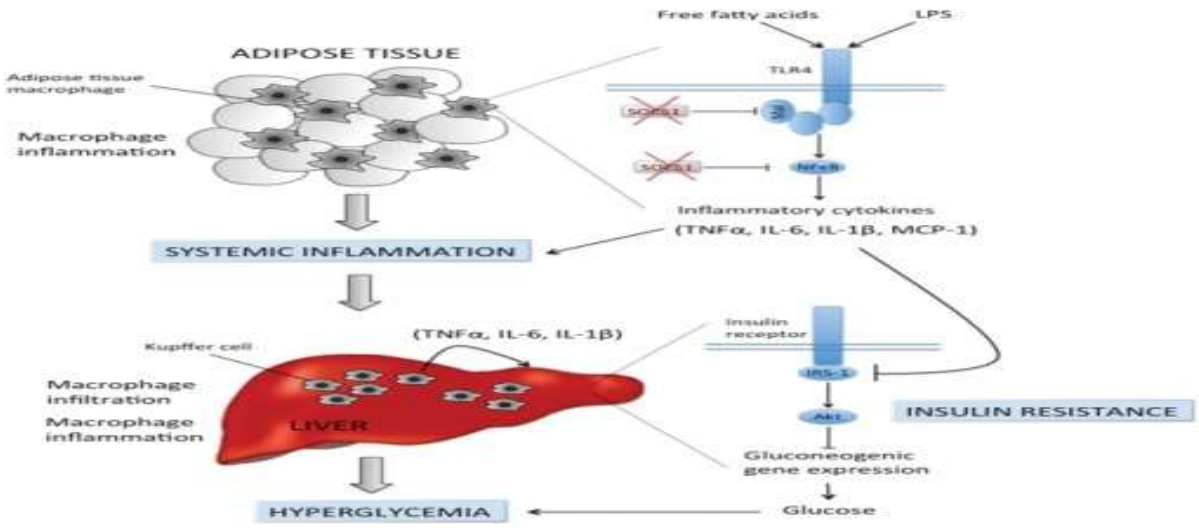
Retinol binding protein 4, plasma, also known as RBP4, is a protein [43] that in humans is encoded by the RBP4 gene [44]. Retinol-binding protein 4 has recently been described as an adipokine that contributes to insulin resistance in the AG4KO mouse model [45]. Elevated RBP-4 plasma levels, synthesised by adipocytes, were observed which suggest association of IR in this mouse model [45]. Elevated serum levels of RBP-4 are also seen in obese or type 2 diabetic humans and in IR rodents. There is a positive interrelationship between RBP-4 plasma levels and insulin resistance severity in, type 2 diabetes, obese and non-obese subjects with strong family background [46]. Injection of purified RBP-4 into mice impairs caused insulin resistance in muscle and induces the expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver [39]. Raised RBP4 levels have been reported in people with type 2 diabetes [47] . The mechanism by which a downregulation in adipocyte GLUT4 results in an increase in RBP4 expression is unknown, but it might involve sensing of glucose by adipocytes [48].

Among the RBP4-lowering agents, treatment with fenretinide [N-(4-hydroxyphenyl) retinamide] (FEN), a synthetic retinoid and anticancer agent, improves insulin sensitivity by reducing serum RBP4 levels by increasing urinary excretion [49-51] by interfering RBP4 binding to transthyretin (TTR).

III FREE FATTY ACIDS AND INSULIN RESISTANCE

Accumulation of intracellular lipid metabolites in insulin sensitive tissues plays an important role in insulin resistance of obesity and type 2 diabetes [52]. Insulin resistance at the level of the fat cell leads to increased intracellular hydrolysis of triglycerides (TGs) and release of fatty acids into the circulation. Whatever may be the molecular or environmental basis for insulin resistance in the adipose tissue, the end result is that FFA uptake by fat cells is either decreased or FFA release from fat cells is increased, confronting the liver with increased availability of energy (Fig 1).

Figure 1. Increase in FFA concentration in circulation increase basal hepatic glucose production and induce hepatic insulin resistance at different sites [53].



Muscle TG levels are increased in type 2 diabetic patients [54]. Similarly, accumulation of lipid in the liver is associated with hepatic insulin resistance [55, 56]. The hypertriglyceride- mia of insulin resistance can be considered as a Ping-Pong match between the hepatocytes and adipocytes, where VLDLs and FFAs are the Ping-Pong balls carrying energy back and forth between the liver and the adipose tissue.

Due to elevated FFA and glucose levels, there is inhibition of Krebs cycle enzymes and citrate exit from the mitochondria. Citrate then activates ACC resulting in increased malonyl-CoA and inhibition of CPT1 [57], thus prevents FFA oxidation. The above process results in accumulation of cytosolic LCFA-CoA and is bio transformed to esterification [58]. This leads to accumulation of fat esterification products, which have been involved in insulin resistance [59].

IV CONCLUSION

Insulin resistance as such is not a problem of deficiency of glucose uptake in response to insulin, however a multifaceted syndrome. Dysregulation and imbalance of fatty acid metabolism as such plays an important role in the development of IR. The increase in FFA release from or decrease in uptake of FFAs into adipocytes provides the clear link between dyslipidemia and insulin resistance. Adipokines which are directly secreted by adipocytes, induce low grade chronic inflammatory state that could play an important role obesity related insulin resistance. This provides a new potential target for drugs.

V ACKNOWLEDGEMENT

We thank our colleagues Sheeba, saima, and Asmat for their useful suggestions.

REFERENCES

[1] S.J. Hunter, W.T. Garvey, Insulin action and insulin resistance: diseases involving defects in insulin receptors, signal transduction, and the glucose transport effector system 1, The American journal of medicine 105(4), 1998, 331-345.

[2] J.R. Sowers, Role of insulin resistance and hyperinsulinemia in development of hypertension and atherosclerosis, The Journal of laboratory and clinical medicine, 123, 1994, 647-652.

[3] G.M. Reaven, H. Lithell, L. Landsberg, Hypertension and associated metabolic abnormalities—the role of insulin resistance and the sympathoadrenal system, New England Journal of Medicine, 334(6), 1996, 374-382.

[4] J.J. Nolan, B. Ludvik, J. Baloga, D. Reichart, J.M. Olefsky, Mechanisms of the kinetic defect in insulin action in obesity and NIDDM, Diabetes, 46(6), 1997, 994-1000.

[5] S.E. Shoelson, L. Herrero, A. Naaz, Obesity, inflammation, and insulin resistance, Gastroenterology, 132(6), 2007,2169-2180.

[6] M. Qatanani, M.A. Lazar, Mechanisms of obesity-associated insulin resistance: many choices on the menu, Genes & development, 21(12), 2007,1443-1455.

[7] M.A. McArdle, O.M. Finucane, R.M. Connaughton, A.M. McMorrow, H.M. Roche, Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies, Frontiers in endocrinology 4, 2013, 52.

[8] P. Trayhurn, I.S. Wood, Adipokines: inflammation and the pleiotropic role of white adipose tissue, British Journal of Nutrition, 92(3), 2004, 347-355.

[9] Y.-D. Chen, A. Golay, A. Swislocki, G. Reaven, Resistance to insulin suppression of plasma free fatty acid concentrations and insulin stimulation of glucose uptake in noninsulin-dependent diabetes mellitus, The Journal of Clinical Endocrinology & Metabolism, 64(1),1987, 17-21.

[10] E.S. Gordon, Non-esterified fatty acids in blood of obese and lean subjects, The American Journal of Clinical Nutrition, 8(5), 1960, 740-747.

[11] G.M. Reaven, C. Hollenbeck, C.-Y. Jeng, M.S. Wu, Y.-D.I. Chen, Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM, Diabetes, 37(8), 1988,1020-1024.

[12] P. Björntorp, H. Bergman, E. Varnauskas, Plasma free fatty acid turnover rate in obesity, Journal of Internal Medicine 185,(1-6,) 1969, 351-356.

[13] M.D. Jensen, M.W. Haymond, R.A. Rizza, P.E. Cryer, J. Miles, Influence of body fat distribution on free fatty acid metabolism in obesity, The Journal of clinical investigation, 83(4), 1989, 1168-1173.

[14] B. Antuna-Puente, B. Feve, S. Fellahi, J.-P. Bastard, Adipokines: the missing link between insulin resistance and obesity, Diabetes & metabolism, 34(1), 2008, 2-11.

[15] S.P. Weisberg, D. McCann, M. Desai, M. Rosenbaum, R.L. Leibel, A.W. Ferrante, Obesity is associated with macrophage accumulation in adipose tissue, The Journal of clinical investigation, 112(12), 2003,1796-1808.

[16] H. Xu, G.T. Barnes, Q. Yang, G. Tan, D. Yang, C.J. Chou, J. Sole, A. Nichols, J.S. Ross, L.A. Tartaglia, Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance, The Journal of clinical investigation, 112(12), 2003, 1821-1830.

[17] K.S. Cook, D.L. Groves, H.Y. Min, B.M. Spiegelman, A developmentally regulated mRNA from 3T3 adipocytes encodes a novel serine protease homologue, Proceedings of the National Academy of Sciences, 82(19), 1985, 6480-6484.

[18] K.S. Cook, H.Y. Min, D. Johnson, R.J. Chaplinsky, J.S. Flier, C.R. Hunt, B.M. Spiegelman, Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve, Science, 237(4813) ,1987, 402-405.

[19] J. Conde, M. Scotece, R. Gómez, V. López, J.J. Gómez-Reino, F. Lago, O. Gualillo, Adipokines: biofactors from white adipose tissue. A complex hub among inflammation, metabolism, and immunity, Biofactors, 37(6), 2011, 413-420.

[20] R.S. Ahima, J.S. Flier, Leptin, Annual review of physiology, 62(1), 2000, 413-437.

[21] G. Frühbeck, Intracellular signalling pathways activated by leptin, Biochemical Journal, 393(1), 2006, 7-20.

[22] T. Yamauchi, J. Kamon, Y.a. Minokoshi, Y. Ito, H. Waki, S. Uchida, S. Yamashita, M. Noda, S. Kita, K. Ueki, Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase, Nature medicine ,8(11) ,2002,1288.

[23] K.E. Wellen, G.S. Hotamisligil, Inflammation, stress, and diabetes, The Journal of clinical investigation, 115(5,) 2005, 1111-1119.

[24] G.S. Hotamisligil, N.S. Shargill, B.M. Spiegelman, Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance, Science, 259(5091),1993, 87-91.

[25] M.J. Yoon, G.Y. Lee, J.-J. Chung, Y.H. Ahn, S.H. Hong, J.B. Kim, Adiponectin increases fatty acid oxidation in skeletal muscle cells by sequential activation of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and peroxisome proliferator–activated receptor α, Diabetes 55(9),2006,2562-2570.

[26] P.A. Kern, M. Saghizadeh, J.M. Ong, R.J. Bosch, R. Deem, R.B. Simsolo, The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase, The Journal of clinical investigation 95(5), 1995,2111-2119.

[27] G.S. Hotamisligil, D.L. Murray, L.N. Choy, B.M. Spiegelman, Tumor necrosis factor alpha inhibits signaling from the insulin receptor, Proceedings of the National Academy of Sciences, 91(11), 1994, 4854-4858.

[28] G.S. Hotamisligil, P. Peraldi, A. Budavari, R. Ellis, M.F. White, B.M. Spiegelman, IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-α-and obesity-induced insulin resistance, Science 271(5249), 1996,665-670.

[29] S.K. Fried, D.A. Bunkin, A.S. Greenberg, Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid, The Journal of Clinical Endocrinology & Metabolism 83(3),1998, 847-850.

[30] J.-P. Bastard, M. Maachi, J.T. Van Nhieu, C. Jardel, E. Bruckert, A. Grimaldi, J.-J. Robert, J. Capeau, B. Hainque, Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro, The Journal of Clinical Endocrinology & Metabolism 87(5),2002, 2084-2089.

[31] J.-P. Bastard, C. Jardel, E. Bruckert, P. Blondy, J. Capeau, M. Laville, H. Vidal, B. Hainque, Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss, The Journal of Clinical Endocrinology & Metabolism 85(9),2000, 3338-3342.

[32] P.J. Murray, The JAK-STAT signaling pathway: input and output integration, The Journal of Immunology 178(5),2007, 2623-2629.

[33] J.N. Ihle, B.A. Witthuhn, F.W. Quelle, K. Yamamoto, O. Silvennoinen, Signaling through the hematopoietic cytokine receptors, Annual review of immunology 13(1),1995, 369-398.

[34] G. Kroder, B. Bossenmaier, M. Kellerer, E. Capp, B. Stoyanov, A. Mühlhöfer, L. Berti, H. Horikoshi, A. Ullrich, H. Häring, Tumor necrosis factor-alpha-and hyperglycemia-induced insulin resistance. Evidence for different mechanisms and different effects on insulin signaling, The Journal of clinical investigation 97(6), 1996, 1471-1477.

[35] R.A. Mooney, J. Senn, S. Cameron, N. Inamdar, L.M. Boivin, Y. Shang, R.W. Furlanetto, Suppressors of cytokine signaling-1 and-6 associate with and inhibit the insulin receptor A potential mechanism for cytokine-mediated insulin resistance, Journal of Biological Chemistry, 276(28), 2001, 25889-25893.

[36] C. Lagathu, J.-P. Bastard, M. Auclair, M. Maachi, J. Capeau, M. Caron, Chronic interleukin-6 (IL-6) treatment increased IL-6 secretion and induced insulin resistance in adipocyte: prevention by rosiglitazone, Biochemical and biophysical research communications, 311(2), 2003, 372-379.

[37] J. Rieusset, K. Bouzakri, E. Chevillotte, N. Ricard, D. Jacquet, J.-P. Bastard, M. Laville, H. Vidal, Suppressor of cytokine signaling 3 expression and insulin resistance in skeletal muscle of obese and type 2 diabetic patients, Diabetes 53(9), 2004,2232-2241.

[38] M. Stumvoll, H. Häring, Resistin and adiponectin—of mice and men, Obesity 10(11),2002, 1197-1199.

[39] N. Kubota, Y. Terauchi, T. Yamauchi, T. Kubota, M. Moroi, J. Matsui, K. Eto, T. Yamashita, J. Kamon, H. Satoh, Disruption of adiponectin causes insulin resistance and neointimal formation, Journal of Biological Chemistry, 277(29),2002, 25863-25866.

[40] A.H. Berg, T.P. Combs, X. Du, M. Brownlee, P.E. Scherer, The adipocyte-secreted protein Acrp30 enhances hepatic insulin action, Nature medicine, 7(8),2001, 947.

[41] N. Maeda, I. Shimomura, K. Kishida, H. Nishizawa, M. Matsuda, H. Nagaretani, N. Furuyama, H. Kondo, M. Takahashi, Y. Arita, Diet-induced insulin resistance in mice lacking adiponectin/ACRP30, Nature medicine 8(7),2002, 731.

[42] T. Yamauchi, J. Kamon, H. Waki, Y. Terauchi, N. Kubota, K. Hara, Y. Mori, T. Ide, K. Murakami, N. Tsuboyama-Kasaoka, The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity, Nature medicine, 7(8),2001, 941.

[43] L. Rask, H. Anundi, J. Fohlman, P.A. Peterson, The complete amino acid sequence of human serum retinol-binding protein, Upsala journal of medical sciences 92(2),1987, 115-146.

[44] M. Rocchi, A. Covone, G. Romeo, R. Faraonio, V. Colantuoni, Regional mapping of RBP4 to 10q23→ q24 and RBP1 to 3q21→ q22 in man, Somatic cell and molecular genetics, 15(2),1989,185-190.

[45] Q. Yang, T.E. Graham, N. Mody, F. Preitner, O.D. Peroni, J.M. Zabolotny, K. Kotani, L. Quadro, B.B. Kahn, Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes, Nature, 436(7049),2005,356.

[46] T.E. Graham, Q. Yang, M. Blüher, A. Hammarstedt, T.P. Ciaraldi, R.R. Henry, C.J. Wason, A. Oberbach, P.-A. Jansson, U. Smith, Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects, New England Journal of Medicine, 354(24), 2006,2552-2563.

[47] C. Basualdo, E. Wein, T. Basu, Vitamin A (retinol) status of first nation adults with non-insulin-dependent diabetes mellitus, Journal of the American College of Nutrition, 16(1), 1997,39-45.

[48] Y. Tamori, H. Sakaue, M. Kasuga, RBP4, an unexpected adipokine, Nature medicine, 12(1), 2006,30.

[49] F. Preitner, N. Mody, T.E. Graham, O.D. Peroni, B.B. Kahn, Long-term Fenretinide treatment prevents high-fat diet-induced obesity, insulin resistance, and hepatic steatosis, American Journal of Physiology-Endocrinology and Metabolism, 297(6), 2009, E1420-E1429.

[50] H. Johansson, S. Gandini, A. Guerrieri-Gonzaga, S. Iodice, M. Ruscica, B. Bonanni, M. Gulisano, P. Magni, F. Formelli, A. Decensi, Effect of fenretinide and low-dose tamoxifen on insulin sensitivity in premenopausal women at high risk for breast cancer, Cancer research ,68(22), 2008, 9512-9518.

[51] R.C. Moon, H.J. Thompson, P.J. Becci, C.J. Grubbs, R.J. Gander, D.L. Newton, J.M. Smith, S.L. Phillips, W.R. Henderson, L.T. Mullen, N-(4-Hydroxyphenyl) retinamide, a new retinoid for prevention of breast cancer in the rat, Cancer research, 39(4), 1979, 1339-1346.

[52] K.F. Petersen, G.I. Shulman, Cellular mechanism of insulin resistance in skeletal muscle, Journal of the Royal Society of Medicine, 95(Suppl 42), 2002, 8.

[53] L. Azadbakht, M.H. Rouhani, P. Surkan, Omega-3 fatty acids, insulin resistance and type 2 diabetes, Journal of Research in Medical Sciences, 16(10,) 2011.

[54] K. Falholt, I. Jensen, S.L. Jensen, H. Mortensen, A. Vølund, L. Heding, P.N. Petersen, W. Falholt, Carbohydrate and lipid metabolism of skeletal muscle in type 2 diabetic patients, Diabetic Medicine, 5(1), 1988, 27-31.

[55] Z.-W. Man, T. Hirashima, S. Mori, K. Kawano, Decrease in triglyceride accumulation in tissues by restricted diet and improvement of diabetes in otsuka long-evans tokushima fatty rats, a non—insulin-dependent diabetes model, Metabolism-Clinical and Experimental, 49(1), 2000,108-114.

[56] L. Ryysy, A.-M. Häkkinen, T. Goto, S. Vehkavaara, J. Westerbacka, J. Halavaara, H. Yki-Järvinen, Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients, Diabetes, 49(5), 2000, 749-758.

[57] J.D. McGarry, Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes, Diabetes, 51(1), 2002, 7-18.

[58] R.L. Dobbins, L.S. Szczepaniak, B. Bentley, V. Esser, J. Myhill, J.D. McGarry, Prolonged inhibition of muscle carnitine palmitoyltransferase-1 promotes intramyocellular lipid accumulation and insulin resistance in rats, Diabetes, 50(1),2001, 123-130.

[59] T.K. Lam, A. Carpentier, G.F. Lewis, G. van de Werve, I.G. Fantus, A. Giacca, Mechanisms of the free fatty acid-induced increase in hepatic glucose production, American Journal of Physiology-Endocrinology and Metabolism 284(5), 2003, E863-E873