Reumatología Clínica

Review

Insulin resistance and rheumatoid arthritis

Iván Ferraz Amaro,[a],* Federico Díaz González,[a] Carlos González Juanatey,[b] Miguel Ángel González Gay[c]

[a]*Servicio de Reumatología, Hospital Universitario de Canarias, Tenerife, Spain*
[b]*Servicio de Cardiología, Complexo Hospitalario Xeral Calde, Lugo, Spain*
[c]*Servicio de Reumatología, Complexo Hospitalario Xeral Calde, Lugo, Spain*

ARTICLE INFO

ABSTRACT

Resistance to insulin action is a feature that accompanies certain diseases among which chronic inflammatory states like rheumatoid arthritis are included. What is, what its pathogenesis is, how it is measured, and what clinical and therapeutic implications have in rheumatoid arthritis patients is a topic not familiar to rheumatologists that is reviewed in this paper.

© 2010 Elsevier España, S.L. All rights reserved.

Resistencia insulínica y artritis reumatoide

RESUMEN

La resistencia a la acción de la insulina es una situación clínica que suele acompañar a las enfermedades inflamatorias crónicas como la artritis reumatoide. Su presencia puede aumentar la morbi-mortalidad de las enfermedades a las que se asocia. En qué consiste, cuál es su etiopatogenia, cómo se mide y qué implicaciones clínicas y terapéuticas tiene en pacientes con artritis reumatoide es un tema que no es familiar para reumatólogos y que abordamos en esta revisión.

© 2010 Elsevier España, S.L. Todos los derechos reservados.

Definition

Insulin is a polypeptide hormone produced and secreted by the beta cells of the Langerhans islets in the pancreas, in the form of an inactive precursor called *proinsulin*. It is in involved in the metabolic use of nutrients, especially in carbohydrate anabolism, and its metabolic action is to maintain glucose homeostasis as well as to promote its efficient use. Its maximum effect is defined by the responsiveness to the latter, while the insulin concentration required to elicit half of the maximum response is defined as *insulin sensitivity*.

Insulin resistance (IR) is a state in which a high insulin concentration is associated with an inadequate response to glucose with normal or high levels of glycaemia. It is, therefore, a pathological condition characterised by a loss of the physiological response of peripheral tissues to insulin activity (endogenous or exogenous). The existence of IR has been known since the commercial use of insulin and initially referred to patients requiring high doses of insulin to control their hyperglycaemia. This was due to the presence of antibodies resulting from the use of non-human insulin. The disappearance of these antibodies through the use of recombinant human insulin has changed the view of the pathogenesis of IR. The clinical spectrum accompanying IR is varied and is determined by how insulin acts on different target tissues. Since this hormone promotes glucose uptake in skeletal muscle through stimulation of GLUT4 (glucose transporter type 4), IR causes this signal to occur in a defective manner, producing a decrease in glucose uptake by the muscle. In the liver, insulin in its physiological form inhibits the expression of gluconeogenic enzymes and, thus, hepatic synthesis of glucose increases in a state of IR. With regard to adipose tissue, insulin decreases the activity of certain lipases causing a decrease in the production of free fatty acids: the antilipolytic effect. Therefore, in a state of IR, there will be an increase in free fatty acids. The presence of hyperglycaemia is very common with IR in the presence of high insulin doses, but it is not uncommon to find patients with normoglycaemia having alterations such as acanthosis nigricans, hyperandrogenism, amenorrhea and infertility, polycystic ovary syndrome, obesity, alopecia, hirsutism, hypertriglyceridaemia and so on.

Currently, IR is regarded as a component of several diseases with different aetiologies and various manifestations, as listed in Table

* Corresponding author.
E-mail address: iferrazamaro@hotmail.com (I. Ferraz Amaro).

Table 1
Causes and clinical manifestations of insulin resistance

Genetic causes
  Leprechaunism, Rabson-Mendenhall syndrome (insulin receptor mutations),
    type 2 diabetes mellitus, lipodystrophy
Secondary forms
  Obesity, metabolic syndrome, polycystic ovarian syndrome
  Excess of contra-regulatory hormones (glucocorticoids, placental lactogen,
    growth hormone)
  Inactivity
  Infection, inflammation
  Anti-insulin antibodies
  Miscellaneous (uraemia, cirrhosis, ketoacidosis), Clinical manifestations
  Glucose homeostasis
  Variable, from diabetes franca to altered glycaemia when fasting, euglycaemia
    and hypoglycaemia
Clinical manifestations
  Acanthosis nigricans, alopecia
  Reproductive apparatus
  Amenorrhea, hirsutism, virilisation, infertility
  Adipose tissue
  Variable, from normal to lipoatrophy, lipohypertrophy and obesity
  Hypertriglyceridaemia
  Musculoskeletal
  Cramps, muscular hypertrophy, pseudoacromegaly

1. The relationship between insulin resistance and microvascular dysfunction as an early manifestation of atherosclerosis seems clear.[1] For some authors, all these clinical manifestations are grouped into a single syndrome called syndrome X or metabolic syndrome, in which IR would be a common denominator and the link between them all; however, according to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII),[2] the presence of IR is not required for the diagnosis of metabolic syndrome.

Measurement of insulin resistance

How to measure IR is open to debate, because there are several useful methods. The following is an abbreviated summary of the different techniques and indexes available, within which there are direct methods, indirect methods and simple substitution indexes.[3]

Direct methods

• Euglycemic hyperinsulinemic clamp. This is accepted as the standard method for determining sensitivity to insulin in humans. After an overnight fast, insulin is administered intravenously at a rate per minute dependant on body surface. This infusion of insulin leads to an insulin blood level above normal (hyperinsulinaemia). As a result, glucose usage in skeletal muscle and fat increases, while in contrast, hepatic glucose production is inhibited. Under these conditions, administration of 20% dextrose is started in order to maintain (clamp) glucose at normal levels. A condition of general equilibrium of plasma insulin, blood glucose and dextrose infusion rate is reached after several hours of constant insulin infusion. Assuming that the state of hyperinsulinaemia is sufficient to completely suppress hepatic glucose production, and since there is no net change in blood glucose concentration under these conditions, the glucose infusion rate should be equal to the glucose utilisation rate. In this way, it is possible to calculate insulin sensitivity, using the equation:

SI = glucose utilisation rate/(glucose x Δinsulin)
         (Δinsulin = insulin increase)

• Insulin suppression test. After fasting for 8 h, a dose of somatostatin is administered to inhibit endogenous secretion of

insulin and glucagon. Subsequently, insulin (25 mU•m^{-2}•min^{-1}) and glucose (240 mg•m^{-2}•min^{-1}) are administered for 3 h through a single intravenous catheter while another is used to determine glucose and insulin periodically. Glucose and insulin concentrations at a steady state are obtained after approximately 2 h. These will be higher in insulin-resistant subjects and lower in insulin-sensitive subjects. This test has the advantage over the clamp test of being less technically demanding and that the equilibrium concentration between glucose and insulin is obtained at an earlier stage.

Indirect methods

• Minimal analysis model after frequently sampled intravenous glucose tolerance test (FSIVGTT). After an overnight fast, a glucose bolus of 0.3 g/kg is administered and 20 min later, another insulin bolus of 4 mU/kg/min is administered for 5 min. After this, blood glucose and insulin measurements are taken every minute for 10 min, then every 3 min until 30 min and thereafter every 10 min until 180 minutes have passed. The data obtained are processed by a computer program designed for this purpose (minimal model software, MINMOD) to determine insulin sensitivity. With respect to the two direct methods described above, this method is different in that it uses dynamic data, rather than equilibrium concentrations and that it is reproducible and technically simpler.

• Oral glucose tolerance test (OGTT). This is widely used to diagnose glucose intolerance or type 2 diabetes. After fasting overnight and then taking 75 g of glucose, glycaemia is determined at 0, 30, 60 and 120 min. This should reflect the efficiency of the organism to dispose of glucose after an overload or eating. This method mimics the dynamics of glucose and insulin in a more physiological manner than FSIVGTT or clamp, but has the obvious disadvantage that glucose tolerance and insulin sensitivity are not equivalent concepts.

Simple substitution indexes. It is assumed that during fasting, glucose and insulin are in homeostasis and expressing a constant hepatic glucose secretion, that is, insulin secreted by β cells determines a relatively constant level of insulin, which will be higher or lower in accordance with resistance/sensitivity to it; hepatic glucose production will consequently be equivalent to the overall expenditure of glucose in fasting conditions. These indexes, which use only plasma glucose and insulin, are less costly tools that can be used in epidemiological studies, clinical trials and clinical practice. The first 4 are mentioned below: 1/insulin, glucose/insulin ratio, homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI). These are simple substitution indexes for indirect methods; the remaining are derived from dynamic models.

• Fasting 1/insulinemia. In healthy subjects, insulin elevation is related to an increased resistance to it. Therefore, the index 1/insulin would decrease as a patient becomes insulin-resistant. It has the disadvantage that insulin is not distributed normally, so there is no strong linear correlation between this index and the clamp method. Similarly, this index does not take into account the low insulin secretion that occurs in the final stages of hyperglycaemia in patients with diabetes or glucose intolerance, so it would not be appropriate for use in patients with impaired pancreatic reserves.

• Glucose/insulin ratio. In patients without diabetes, this ratio would be equivalent to the 1/insulin rate. It has the disadvantage that a specific insulinaemia may correspond to different glycaemias depending on whether the subject is diabetic or not. It is considered as a conceptually incorrect insulin sensitivity index.

• Homeostasis assessment model (HOMA). Described in 1985,[4] this model uses the dynamic interaction between glucose and insulin

levels to predict insulin sensitivity or β cell production. It assumes a positive feedback loop between liver and pancreatic cells; that is, glucose concentration is defined by hepatic production, which is inhibited by insulin, while insulinaemia is a reflection of β cell response to glucose concentration. Therefore, resistance to insulin would be determined by a diminished response of hepatic glucose production to the inhibitory effect of insulin. This model in its updated form (http://www.dtu.ox.ac.uk/homa), HOMA2, makes it possible to determine insulin sensitivity (% S) and beta cell function (%B). It correlates reasonably well with the clamp method, is useful in patients with moderate diabetes mellitus and states of insulin resistance associated to other diseases, but is not applicable in patients with severely damaged or null pancreatic function.

• Quantitative insulin sensitivity check index (QUICKI). Like the HOMA model, this represents a mathematical model of the insulin-glucose relationship, but has a different origin. It is based on the fact that the sensitivity data analysis of insulin and glucose during the first 20 min of FSIVGTT contains critical information about insulin sensitivity. In these data, fasting insulinaemia does not follow a normal distribution but its logarithmic transformation improves its correlation with the clamp method. To this end, the formula: QU1CK1=1/log insulin+log glucose has an excellent correlation with the clamp method, which is maintained in patients with diabetes or impaired β function. It has the advantage over HOMA that it correlates better with the clamp method in diabetic and obese patients.

• Matsuda index. This represents a combination that reflects both hepatic and muscular insulin sensitivity via the formula:

$$\text{Matsuda} = 10,000 \sqrt{[(\text{glucose} \times \text{insulin}) \times (\text{mean glucose during OGTT} \times \text{mean insulin during OGTT})]}$$

It has a reasonable correlation with the clamp method.

• Gutt index. Like the Matsuda index, it is a test derived from dynamic techniques which is closely correlated with the clamp method but has a complex determination:

$$\text{Gutt} = 75,000 + (G_0 - G_{120}) \times 0.19 \times \frac{\text{weight}}{120}$$
$$\times G_{\text{mean } (0-120)} \times \log \text{Insulin}_{\text{mean } (0-120)}$$

Where G0 is fasting glucose and G120 is glucose at 120 minutes.

Insulin resistance and inflammation

Since the 1950s, a certain correlation has been observed between chronic inflammatory conditions and resistance to insulin action. A relationship has been proven in the past decades between obesity and inflammation, two processes that are clearly linked with insulin resistance. Obesity studies in patients with type 2 diabetes mellitus and other conditions related to IR have found elevated levels of tumour necrosis factor (TNF), interleukin IL-6 and IL-8.[5-7] Another common feature in these states is the elevation of C reactive protein, a non-specific acute phase reactant. The existence of a low-level inflammation state has been observed in relation to obesity, although the mechanisms generating it are not known in depth. One theory is that the expansion of adipose tissue (hypertrophy and hyperplasia of adipocytes) leads to local cellular hypoxia and activation of inflammatory signalling pathways. It is also known that certain cytokines secreted by adipocytes, known as adipokines (such as resistin, adiponectin and leptin), have proinflammatory activity and are related to IR states.[8] Fatty infiltration of the liver likewise produces local inflammation in this organ that could lead to activation of Kupffer cells, which also promote states of insulin resistance. Lastly, overnutrition leads to an elevation of saturated and unsaturated free fatty acids and these acids also have proinflammatory properties, given that they activate vascular endothelial cells, adipocytes and myeloid cells.

Inflammation can also cause, independently of obesity, resistance to insulin activity. The mechanisms that have been implicated in this effect are:

1. TNFα has been linked to insulin resistance in inflammatory states. Its effects on lipid metabolism, coagulation and endothelial function are determinant in this regard. It is known to influence the insulin receptor, preventing its signal transduction after being stimulated by insulin. Independent pathways for the insulin receptor through which TNF induces IR are also known. Such mechanisms are mainly the inhibition of genes such as GLUT4.[9]

2. Similarly, it has been known for years that certain anti-inflammatory compounds such as salicylates, and more specifically aspirin, have a beneficial, insulin-sensitising effect on hyperglycaemia. This is thought to occur because they interfere with the pathway for NF-kappa B, an inflammation-related transcription factor.

3. Other factors such as Jnk1 and 2 (C-Jun N-terminal kinase 1 and 2) also seem to play a key role in inflammation, obesity and diabetes. It is known that their levels are elevated in obese mice with insulin resistance and that Jnk1-/- knockout mice develop less insulin resistance after a high-fat diet.[10]

4. Nitric oxide, involved in vasodilatation and other processes, plays an important role in IR. It is known that proinflammatory states activate the expression of Nos2, the gene responsible for iNOS (inducible nitric oxide synthase) synthesis, and Nos2 is ultimately responsible for the IR observed in states of sepsis.[11]

5. IL-10 has an anti-inflammatory effect, inhibiting TNF-induced activation of NF-kappa B. It is known that in humans there is a clear relationship between low levels of IL-10 and IR, which has led to the suggestion that this interleukin has insulin sensitising effects. This has been partly corroborated by observing mice treated with IL-10 that do not develop IR when treated simultaneously with IL-6.[12]

6. Another protein that has linked inflammation and IR is MCP1 (monocyte chemoattractant protein-1). This is a chemokine synthesised by macrophages and endothelium that promotes recruitment of monocytes into damaged or inflamed areas. It is known that knockout mice for CCR2, the MCP1 receptor, express less macrophage infiltration in adipose tissue, have less liver steatosis, show increased insulin sensitivity and have a reduced weight gain after high-fat diets. This same effect has been observed in mice treated with a pharmacological CCR2 antagonist.[13]

As has been seen, IR is a complex metabolic condition with different aetiologies such as obesity, chronic inflammation and so on, in which the aetiopathogenic sequence leading to defective insulin signal processing is still to be defined. It might be expected that the high concentration of proinflammatory factors such as TNF, IL-6, MCP1, NO, etc. that occur in chronic diseases would cause an incorrect tissue response to insulin. When obesity is the starting point, it is considered that adipocyte hypertrophy and death are the main IR activation mechanisms. If there is no obesity, then the mechanisms involved in muscle and liver tissue appear to be the determining factors in IR development.

Table 2
Studies on the influence of anti-TNFα treatments on insulin resistance

Reference	n	Anti-TNFα	Disease	Follow-up	Method	Result
Seriolo	21	Infliximab	Rheumatoid arthritis	24 weeks	HOMA, QUICKI	Improvement
Martinez-Abundis	12	Etanercept	Psoriasis	2 weeks	Clamp	No improvement
Oguz	7	Infliximab	Rheumatoid arthritis	9 months	HOMA	Improvement
Rosevinge	9	Adalimumab	Rheumatoid arthritis	8 weeks	Clamp	No improvement
Lo	56	Etanercept	Metabolic syndrome	4 weeks	HOMA	No improvement
Huvers	8	Infliximab	Rheumatoid arthritis, ankylosing spondylitis and Whipple disease	6 weeks	Clamp	Improvement
Tam	19	Infliximab	Rheumatoid arthritis	14 weeks	HOMA	Improvement
González-Gay	27	Infliximab	Rheumatoid arthritis	120 minutes	HOMA, QUICKI	Improvement
Seriolo	38	Etanercept and infliximab	Rheumatoid arthritis	24 weeks	HOMA, QUICKI	Improvement
Kiortsis	27	Infliximab	Rheumatoid arthritis	24 weeks	HOMA, QUICKI	Improvement
Ferraz-Amaro (in press)	16	Etanercept, infliximab and adalimumab	Rheumatoid arthritis	1 year	HOMA	No improvement

Clamp indicates Hyperinsulinemic Euglycemic Clamp; HOMA, Homeostatic Model Assessment; QUICKI, Quantitative Insulin Sensitivity Check Index.

Insulin resistance and rheumatoid arthritis

Although patients with RA show a high prevalence of metabolic syndrome and associated factors such as obesity, dyslipidemia or impaired glucose metabolism, few studies have specifically studied IR in this disease. The broadest study[14] recruited 94 patients with RA, in whom insulin resistance and beta cell function were studied by HOMA. It concluded that IR (HOMA-IR) was associated with markers for inflammation and disease activity such as C reactive protein, erythrocyte sedimentation rate and DAS28. Similarly, IR was related to waist circumference, presence of arterial hypertension and use of diuretics and beta-blockers. On the other hand, beta cell function (HOMA-%B) showed an inverse correlation with DAS28 and swollen and painful joints and correlated positively with steroid use. In this study, multiple regression analysis showed that the most important factor with HOMA-IR was abdominal obesity (39%-56%), with disease activity representing 5%. As for HOMA-%B, the most related factor was the cumulative steroid dose (11%-55%), whereas disease activity (as measured by DAS28 and swollen and painful joints) was responsible for 19%-25% of this deterioration of beta function.

Similarly, Chung et al[15] studied (also through the HOMA test) IR in 104 patients with RA and compared the results with those of 124 cases of systemic lupus erythematosus. They proved that patients with RA have a higher HOMA index that lupus patients, that it correlates with weight adjusted for age, gender and steroid use, and that, likewise, it is directly correlated with levels of IL6, TNFa, CRP, ESR and extent of coronary calcification.

La Montagna et al[16] also found an increased presence of IR in patients with RA, with a significant relationship between IR and subclinical atherosclerosis. According to multivariate analysis, this was mainly due to steroid dose.

Other studies[17-19] have also shown a positive correlation between C reactive protein levels and HOMA index in patients with RA, and ascribe to the latter a 21% role in raising this acute phase protein. Likewise, a clear correlation has been shown between IR, also measured by HOMA, and age, average internal thickness of the carotid, Health Assessment Questionnaire score and concentrations of cholesterol and triglycerides. With respect to analytical variables, apart from the correlation with C reactive protein, an association has also been found between IR and values of IL-2[20] in patients with RA.

The only study that contradicts this hypothesis of a relationship between IR and RA is provided by Garcia Díaz,[21] who found no differences in HOMA and QUICKI values between RA patients and controls (74 cases and controls). No relationship was found between IR and disease activity, C reactive protein and the quantification of coronary calcium, either. A relationship was found only between IR and waist circumference and subclinical vascular disease using carotid ultrasonography, although these features were not directly related to RA.

With regard to the role of different therapies on IR in patients with RA, there are no conclusive studies. Dessein[22] has shown a beneficial effect of methotrexate on insulin resistance and sensitivity using HOMA and QUICKI and has considered that this effect is caused by its anti-inflammatory activity. However, the same author also concludes that the possibility that this effect is partially mediated by other actions of classical drugs that induce remission of the lipid profile or other areas cannot be excluded.

With regard to anti-TNFα treatment, there are 10 studies in the literature on its influence over IR, which are summarised in Table 2. Each used a different IR determination method and the number of patients (7 to 56) and treatment duration (120 min to 1 year) were very variable. In 3 of them,[23-25] there was no improvement in IR with treatment (two of them used the clamp method, considered as the reference standard), while in the remaining 7 studies[26-32] there was improvement as measured by indirect methods. Only one of them,[29] which used the clamp method, showed improvement in insulin sensitivity after 14 weeks. Our own unpublished data after studying 16 patients with RA who were treated with anti-TNF showed no relationship between the blocking of this cytokine and IR.

Corticosteroids are responsible for glucose intolerance[33] and, given their wide use in RA, they could be expected to be at least partially responsible for IR in these patients. However, several studies[34-36] have found only a discreet or a nonexistent relationship between corticosteroids and the presence of metabolic syndrome or IR in patients with RA. These data suggest that their beneficial effect on inflammation counteracts their effect on IR.

Conclusion

The role of chronic inflammation is becoming more and more important in the development of atherosclerosis. Likewise, the latter seems increasingly important as a determinant of mortality in patients with RA. In light of the observations, there seems to be ample evidence supporting a relationship between insulin resistance, inflammation and RA, as is also the case in other chronic diseases. In addition, such insulin resistance plays an initial role in vascular damage and appears to be (along with other mechanisms

such as endothelial dysfunction, cellular adhesion, etc.) a link between inflammation and atherosclerosis. For all these reasons, rheumatologists should know insulin resistance better, become familiar with its concepts, learn how to measure it, relate it to other disease parameters and consider it as a another systemic manifestation of patients with RA.

Financing

Conflict of interest

The authors declare no conflict of interest.

References

1. Krentz AJ, Clough G, Byrne CD. Vascular disease in the metabolic syndrome: do we need to target the microcirculation to treat large vessel disease? J Vasc Res. 2009;46:515-26.

2. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

3. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. American Journal of Physiology. 2008;294:E15-26.

4. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-9.

5. Roytblat L, Rachinsky M, Fisher A, Greemberg L, Shapira Y, Douvdevani A, et al. Raised interleukin-6 levels in obese patients. Obes Res. 2000;8:673-5.

6. Straczkowski M, Dzienis-Straczkowska S, Stepien A, Kowalska I, Szelachowska M, Kinalska I. Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-alpha system. J Clin Endocrinol Metab. 2002;87:4602-6.

7. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest. 1995;95:2409-15.

8. Andersson CX, Gustafson B, Hammarstedt A, Hedjazifar S, Smith U. Inflamed adipose tissue, insulin resistance and vascular injury. Diabetes Metab Res Rev. 2008;24:595-603.

9. De Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS lett. 2008; 582:97-105.

10. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, et al. A central role for JNK in obesity and insulin resistance. Nature. 2002;420: 333-6.

11. Sugita H, Fujimoto M, Yasukawa T, Shimizu N, Sugita M, Yasuhara S, et al. Inducible nitric-oxide synthase and NO donor induce insulin receptor substrate-1 degradation in skeletal muscle cells. J Biol Chem. 2005;280: 14203-11.

12. Kim HJ, Higashimori T, Park SY, Choi H, Dong J, Kim YJ, et al. Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. Diabetes. 2004;53:1060-7.

13. Weisberg SP, Hunter D, Huber R, Lemieux J, Slaymaker S, Vaddi K, et al. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. J Clin Invest. 2006;116:115-24.

14. Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis Rheum. 2006;54:2765-75.

15. Chung CP, Oeser A, Solus JF, Gebretsadik T, Shintani A, Avalos I, et al. Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis Rheum. 2008;58:2105-12.

16. La Montagna G, Cacciapuoti F, Buono R, Manzella D, Mennillo GA, Arciello A, et al. Insulin resistance is an independent risk factor for atherosclerosis in rheumatoid arthritis. Diab Vasc Dis Res. 2007;4:130-5.

17. Dessein PH, Norton GR, Woodiwiss AJ, Joffe BI, Solomon A. Independent role of conventional cardiovascular risk factors as predictors of C-reactive protein concentrations in rheumatoid arthritis. J Rheumatol. 2007;34:681-8.

18. Pamuk ON, Unlu E, Cakir N. Role of insulin resistance in increased frequency of atherosclerosis detected by carotid ultrasonography in rheumatoid arthritis. J Rheumatol. 2006;33:2447-52.

19. Dessein PH, Joffe BI, Stanwix A, Botha AS, Moomal Z. The acute phase response does not fully predict the presence of insulin resistance and dyslipidemia in inflammatory arthritis. J Rheumatol. 2002;29:462-6.

20. Oncul O, Top C, Ozkan S, Cavuslu S, Danaci M. Serum interleukin 2 levels in patients with rheumatoid arthritis and correlation with insulin sensitivity. J Int Med Res. 2002;30:386-90.

21. Garcia Diaz Jde D, Lopez de Guzman A, Sivera Monzo L, Cuende Quintana E. Significado de la resistencia a la insulina en la enfermedad vascular asociada a la artritis reumatoide. Med Clin (Barc). 2008;130:197-8.

22. Dessein PH, Joffe BI, Stanwix AE. Effects of disease modifying agents and dietary intervention on insulin resistance and dyslipidemia in inflammatory arthritis: a pilot study. Arthritis Res. 2002;4:R12.

23. Martinez-Abundis E, Reynoso-von Drateln C, Hernandez-Salazar E, Gonzalez-Ortiz M. Effect of etanercept on insulin secretion and insulin sensitivity in a randomized trial with psoriatic patients at risk for developing type 2 diabetes mellitus. Arch Dermatol Res. 2007;299:461-5.

24. Rosenvinge A, Krogh-Madsen R, Baslund B, Pedersen BK. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFalpha therapy. Scand J Rheumatol. 2007;36:91-6.

25. Lo J, Bernstein LE, Canavan B, Torriani M, Jackson MB, Ahima RS, et al. Effects of TNF-alpha neutralization on adipocytokines and skeletal muscle adiposity in the metabolic syndrome. Am J Physiol Endocrinol Metab. 2007;293(1):E102-9. Epub 2007 Mar 20.

26. Seriolo B, Ferrone C, Cutolo M. Longterm anti-tumor necrosis factor-alpha treatment in patients with refractory rheumatoid arthritis: relationship between insulin resistance and disease activity. J Rheumatol. 2008;35:355-7.

27. Seriolo B, Paolino S, Ferrone C, Cutolo M. Impact of long-term anti-TNF-alpha treatment on insulin resistance in patients with rheumatoid arthritis. Clinical and Experimental Rheumatology. 2008;26:159-60, author reply 60.

28. Oguz FM, Oguz A, Uzunlulu M. The effect of infliximab treatment on insulin resistance in patients with rheumatoid arthritis. Acta Clin Belg. 2007;62: 218-22.

29. Huvers FC, Popa C, Netea MG, Van den Hoogen FH, Tack CJ. Improved insulin sensitivity by anti-TNFalpha antibody treatment in patients with rheumatic diseases. Ann Rheum Dis. 2007;66:558-9.

30. Tam LS, Tomlinson B, Chu TT, Li TK, Li EK. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin Rheumatol. 2007;26:1495-8.

31. González-Gay MA, De Matias JM, González-Juanatey C, Garcia-Porrua C, Sánchez-Andrade A, Martin J, et al. Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006;24:83-6.

32. Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis. 2005;64:765-6.

33. Pagano G, Bruno A, Cavallo-Perin P, Cesco L, Imbimbo B. Glucose intolerance after short-term administration of corticosteroids in healthy subjects.

Prednisone, deflazacort, and betamethasone. Arch Intern Med. 1989;149: 1098-101.

34. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis. 2008;196:756-63.

35. Dessein PH, Tobias M, Veller MG. Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. J Rheumatol. 2006;33:2425-32.

36. Svenson KL, Lundqvist G, Wide L, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: effects of corticosteroids and antirheumatic treatment. Metabolism. 1987;36:944-8.