

REVIEW ARTICLE

## Obesity and metabolic syndrome: Future therapeutics based on novel molecular pathways

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**Abstract** Obesity is a chronic disease, currently recognized as the triggering agent for the development of the metabolic syndrome. It is now accepted that obesity arises from an energy imbalance due to excessive food ingestion and insufficient physical activity. Mitochondria has an important role in energy balance and, interestingly, recent findings have found an association between obesity and mitochondrial dysfunction due to a defective network among regulator proteins such as peroxisome proliferator-activated receptors (PPARs), sirtuins (SIRT), and PPAR coactivator 1 alpha (PGC-1 $\alpha$ ). These molecules are currently under extensive research in aims of finding new agents that could be used in the treatment of obesity and metabolic syndrome. The paradox: some nutrients themselves, such as flavonoids, are able to modulate the previously mentioned energy regulators.

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### Obesidad y síndrome metabólico: terapéuticas futuras basadas en novedosas rutas moleculares

**Resumen** La obesidad es una enfermedad crónica que es considerada como el agente detonador para el desarrollo de síndrome metabólico. Se ha aceptado que la obesidad surge de un desbalance energético provocado por ingestión alimentaria excesiva y actividad física insuficiente. La mitocondria tiene un papel importante en tal balance energético e, interesantemente, se ha encontrado una asociación entre la obesidad y la disfunción mitocondrial debido a interacciones defectuosas entre ciertas proteínas reguladoras como los receptores activados por proliferadores de peroxisomas (PPAR), sirtuinas (SIRT) y el coactivador de PPAR (PGC-1 $\alpha$ ). Estas moléculas se encuentran actualmente bajo una amplia investigación con miras a encontrar nuevos agentes que pudiesen ser utilizados en el tratamiento de la obesidad y del síndrome metabólico. La paradoja: algunos nutrientes, como los flavonoides, son capaces por sí mismos de modular los reguladores antes mencionados.

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## Introduction

Nutrition is one of the most influential components of health. An individual lacking of an adequate nutritional status can be diagnosed as being either underweight, overweight or obese. The term "overweight" refers to an excessive ratio between body weight and height – i.e., body mass index (BMI) – such extra weight can come from lean body mass (mainly muscle), fat, or body water. In contrast, in obesity, the surplus body weight comes exclusively from fat.<sup>1,2</sup> The World Health Organization (WHO) defines obesity as a chronic disease characterized by an excessive and abnormally high proportion of fat mass in the body, to the extent that health can become impaired.<sup>2</sup> This disease develops as the result of a complex interaction between environmental and genetic factors. Certainly, there are individuals with rare genetic disorders (e.g., Prader-Willi syndrome, Cohen syndrome, leptin or melanocortin receptor deficiency, etc.), in which excess adiposity develops despite the environment; but such alterations can only explain about 5% of the cases of obesity.<sup>3–5</sup> However, in common obesity an *obesogenic* environment must be present so that the obesity-prone genotype can be expressed.<sup>6–9</sup> An obesogenic environment is defined as one that enhances fat accumulation as a result of prolonged energy imbalance due to insufficient energy expenditure – scarce physical activity – excessive energy intake – from a hyperenergetic/hypercaloric diet – or both.<sup>10,11</sup> The impact that such environment has on the expression of the genetic information is clearly shown, e.g., studies about the Pima Indians: an ethnic group settled in northern Mexico and at the south of the U.S.; hence they are separated only by the border between the two countries. Interestingly, the group settled in the U.S., exhibit a significantly higher rate of obesity than their counterparts in Mexico although they share a similar genetic background. It has been found that "the only" difference between them is energy balance: Mexican Pima have a traditional diet that includes less simple carbohydrates, more fiber and less fat along with moderate to heavy occupational and leisure physical activity.<sup>12–16</sup>

## Obesity and the metabolic syndrome

Obesity is considered a pandemic disease with an estimated prevalence of almost 500 million adults; moreover, it is projected that by 2015 approximately 700 million – worldwide – will be obese.<sup>17,18</sup> The importance of this disease relies on the fact that, by itself, obesity is a major risk factor for various diseases such as insulin resistance (IR) and type 2 diabetes, arterial hypertension and dyslipidemias (hypertriglyceridemia and low high-density lipoprotein levels).<sup>19</sup> Such abnormalities, together, make up the metabolic syndrome (MS).<sup>20,21</sup> IR was initially proposed as the core of the MS.<sup>22</sup> However, it is now recognized that obesity may be the triggering agent for each component of the syndrome since many of the underlying mechanisms correspond to the deleterious effects of certain adipokines secreted by the excess adipose tissue.<sup>23–25</sup> In this regard, the excessive fat mass that defines obesity tends to be accumulated at the abdominal region. Peri-visceral fat, unlike the subcutaneous adipose tissue, is a metabolically active organ<sup>26,27</sup> that

releases several adipokines – which have been postulated as the link between obesity and the pathophysiology of MS – such as tumor necrosis factor alpha (TNF $\alpha$ ), interleukin-6 (IL-6), transforming growth factor  $\beta$  (TGF $\beta$ ), resistin, plasminogen activator inhibitor-1 (PAI-1), and leptin.<sup>28–33</sup>

It has been suggested that, in obesity, fat cells "oversynthesize" a chemokine, the monocyte chemoattractant protein-1 (MCP-1), that recruits circulating monocytes, which, now accumulated in the adipose tissue, differentiate into macrophages which produce high levels of TNF- $\alpha$ <sup>34–36</sup> initiating a vicious circle from which the MS begins.

## Obesity-IR

TNF- $\alpha$  stimulates lipolysis, thus promotes the releasing of free fatty acids (FFA) into the circulation. The catabolism of FFA by skeletal muscle, increases intramyocellular levels of long chain acylCoA and diacylglycerol. These two molecules are powerful allosteric activators of protein kinase C (PKC), which, in turn, phosphorylates the insulin receptor substrate-1 (IRS-1) in threonine and serine amino acid residues, which impairs the functional phosphorylation on tyrosine residues.<sup>37,38</sup> Such misguided phosphorylation of IRS-1 prevents the activation of the insulin receptor, consequently disrupting the downstream signaling cascade and, in turn, impairs the glucose transporters (GLUT-4) from migrating and merging within the cellular membrane. As a result, hyperglycemia and IR develop.<sup>39,40</sup>

## IR-endothelial dysfunction (hypertension)

IR is defined as a condition in which insulin is unable to perform many of its roles, for example, those related to metabolism and cardiovascular function.<sup>41</sup> At the endothelial level, insulin does not have a metabolic role, i.e., it is not related with the recruitment of glucose transporters. Insulin rather binds to specific receptors associated with endothelial function by activating the phosphatidylinositol 3-kinase (PI3K) pathway; this pathway is responsible for the phosphorylation and activation of endothelial nitric oxide synthase (eNOS). Thus insulin has a vasodilatory effect.<sup>42,43</sup> However, when IR occurs, the PI3K pathway becomes affected, resulting in endothelial dysfunction due to a decrease in the bioavailability of nitric oxide (NO) and, consequently, a decrease in its capability to induce vasodilation. Endothelial dysfunction is a pathological state defined as an imbalance in the production of vasodilating and vasoconstricting substances, thus the endothelium is not able to carry out its normal physiologic mechanisms.<sup>44–46</sup>

## Obesity-oxidative stress-endothelial dysfunction

Obesity is not only associated to endothelial dysfunction through the alterations in fat accumulation, TNF- $\alpha$  and IP3K, but also through other abnormalities such as oxidative stress. Oxidative stress is an abnormality such as the production of reactive oxygen and nitrogen species (ROS/RNS) and the cell's ability to buffer them. Obesity-associated oxidative stress is enhanced by the increased releasing of adipokines which, in turn activate NADPH oxidase, resulting



two drugs that were frequently included in MS treatment, thiazolidinediones and fibrates, are synthetic pharmacological ligands for PPARs.<sup>70,71</sup> However, these drugs have also been associated with significant adverse effects including cholelithiasis, fluid retention, congestive heart failure, and venous thrombosis.<sup>72</sup> Hence, there is a need to develop safer and novel agonists of PPAR as obesity and MS are becoming a pandemia.

### PGC-1 $\alpha$

Another molecule implicated in energy balance and obesity is PPAR coactivator 1 alpha (PGC-1 $\alpha$ ). This coactivator interacts with transcriptional factors (such as PPARs, SIRT, etc.) and, thus enhances the expression of genes involved in energy metabolism, thermogenesis, glucose and lipid metabolism, mitochondrial thermogenesis and biogenesis, adipocyte differentiation and energy expenditure, such as: nuclear respiratory factor 1 (NRF1), PPAR $\alpha$  and PPAR $\gamma$ , Farnesoid X receptor (FXR), glucocorticoid receptor (GR), among others.<sup>73,74</sup>

The expression of PGC-1 $\alpha$  is regulated by different stimuli, for example, temperature. In this matter, the exposure to cold enhances PGC-1 $\alpha$  synthesis via protein-kinase A (PKA).<sup>75</sup> PGC-1 $\alpha$  then coactivates PPAR $\alpha$  and – this way – enhances the synthesis of certain proteins (e.g., UCP-1), that uncouple the respiratory chain and ATP synthesis, thus favors energy dissipation as heat in both brown adipose tissue and skeletal muscle.<sup>76,77</sup> However, since in large mammals brown adipose tissue is not present in a significant amount, skeletal muscle is considered as the primary thermogenic and energy metabolizing tissue.

Another stimulus that promotes the expression – mainly in skeletal muscle – of PGC-1 $\alpha$  is exercise. There are different types of skeletal muscle fibers: I, IIa, IIb and IIc. The first two have a higher oxidative metabolism since they contain more mitochondria. PGC-1 $\alpha$  induces remodeling of skeletal muscle: from type IIb to type I and IIa; this change is corroborated by a redder muscle color and an increase in oxidation of macronutrients.<sup>78</sup>

New findings have shown that PGC-1 $\alpha$  expression is down-regulated in metabolic syndrome and obesity.<sup>79,80</sup> Recently, it has been stated that high concentrations of FFA participate in the methylation of PGC-1 $\alpha$  promoter, which inhibits its expression and leads to mitochondrial dysfunction<sup>81</sup>; since its metabolites – such as DAG and ceramides – induce so. It also impairs mitochondrial biogenesis, decreases the oxidation of lipids and thermogenesis. Hence, energy storage and the development of obesity and all of its metabolic alterations are favored. For these reasons, there's great interest in using PGC-1 $\alpha$  as a powerful modulator of energy balance and a possible agent for treating obesity and the MS.

### Sirtuins

Recent studies have shown that another family of proteins is involved in the complex relationship between obesity and the MS: sirtuins (SIRT). Seven isoforms (SIRT 1–7) have been found in mammals and they are expressed in the cytoplasm, nuclei and mitochondria. SIRT activate

metabolism-related proteins – such as PGC-1 $\alpha$  – by deacetylating lysine residues.<sup>82,83</sup>

For example, SIRT-1 deacetylates PGC-1 $\alpha$  and, by this means, regulates mitochondrial biogenesis. In skeletal muscle, such deacetylation increases mitochondrial activity, leading to higher energy expenditure by means of fatty acid oxidation, thermogenesis and endurance; these three effects prevent obesity.<sup>84,85</sup>

Being a NAD-dependent enzyme, SIRT activity is influenced by the NAD/NADH ratio: thereby, NAD increases SIRT activity, whereas NADH decreases it. This means that sirtuin activity is related to the level of available energy: NAD is in high concentrations when the molecular pathways of energy metabolism (glycolysis, Krebs cycle, etc.) are not active – or have low activity – causing SIRTs to increase their activity. In fact, studies in yeast have shown that energy restriction decreases NADH levels and, consequently, SIRT activity increases.<sup>84</sup> Moreover, in animal models, prolonged fasting increases NAD levels and, consequently SIRT activity does as well.<sup>86</sup>

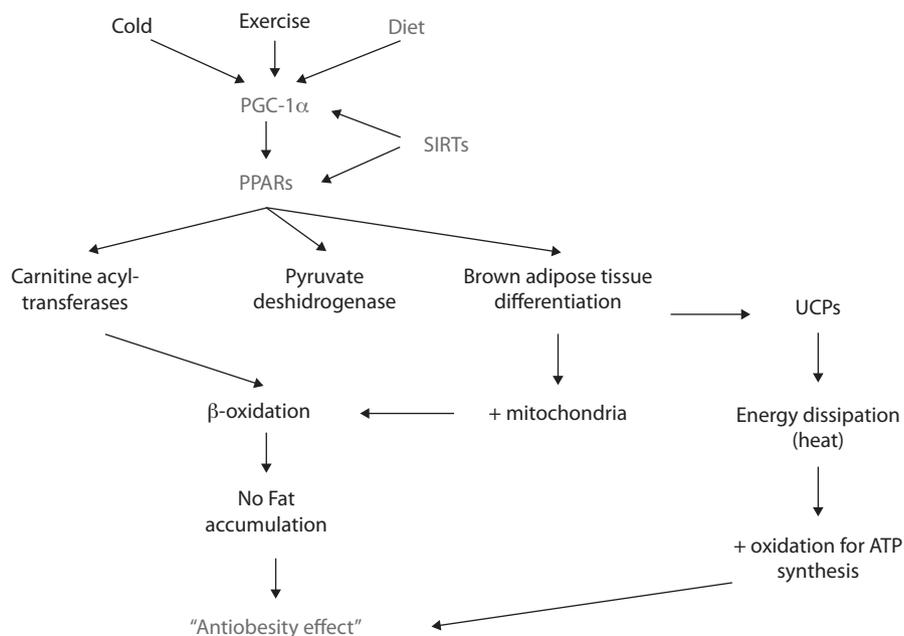
Although not all metabolic pathways in humans are completely understood, it is now accepted that SIRT-1 participates in obesity and MS in several ways; for example, by interacting with PPAR $\gamma$ .<sup>87</sup> SIRT-1 represses PPAR $\gamma$  transcriptional activity, thus leading to the inhibition of adipogenesis (defined as the mechanism by which preadipocytes differentiate into mature adipocytes) and the activation of lipolysis in white adipose tissue.<sup>88</sup> This – eventually – could lead to weight loss in terms of body fat and, thus prevents/reverses obesity (Fig. 2).

### Perspectives on a new anti-obesity therapy

From the previous lines, we can argue the importance of preventing/reversing obesity. Weight loss reduces the risk of developing type 2 diabetes and cardiovascular disease, among other pathologies. In fact, losing weight has proven to decrease arterial pressure in hypertensive patients, reduce plasmatic TG levels and total cholesterol along with increasing HDL levels; finally, it has also shown to improve glycemia in patients with type 2 diabetes and IR.<sup>89</sup>

Nowadays, a wide range of anti-obesity treatments are available although they all have the same basic principle: leading to a negative energy balance (i.e., when energy expenditure is greater than energy intake, forcing the organism to utilize its reservoirs in order to meet the nutritional requirements).<sup>89</sup>

- **Nutritional therapy.** Refers to hypoenergetic and modified in nutrient composition diets. Weight loss is usually obtained by lessening in 500 kcal the patient's current diet; sometimes, a high-protein and low-carbohydrate diet is prescribed, although this resource is not recommended for long-term goals.
- **Pharmacologic therapy.** Sibutramine and orlistat are the most studied/prescribed drugs. The first one is a serotonin reuptake inhibitor whose weight loss actions are attributed to appetite suppression (i.e., diminishes energy intake). Conversely, orlistat is the only lipase inhibitor approved for weight loss treatment; as its name implies, orlistat acts by binding to the active site of



**Figure 2** Antiobesity role of novel molecules.

pancreatic lipase, preventing – this way – fat digestion and absorption (thus, it also diminishes energy intake since less fat enters the body).

- **Surgical approaches.** These often result in weight loss by restricting the size of the stomach (thus limiting the amount of food consumed) or by bypassing a portion of the intestine (which reduces food digestion and, consequently, nutrient absorption).

Even though modifications towards a “healthy lifestyle” (i.e., correct diet and sufficient physical activity) are still the cornerstone in the treatment of obesity and MS, these interventions have shown low efficacy in the long term: a low rate of therapeutical attachment to nutritional intervention, adverse effects to drugs or surgery, etc. On the other hand, there are numerous over-the-counter dietary supplements that claim to be beneficial in losing weight and/or improving the MS features. However, these drugs lack of scientific background and – the majority of the time – were not clinically, nor preclinically, tested before, making them a potential threat to an individual’s health.<sup>90</sup>

Since obesity has an increasing prevalence, it’s not a surprise that the scientific community is interested in the development of newer agents that induce/activate all of the previously described molecules (SIRT, PPAR, PGC-1 $\alpha$ ) and, hence, can be employed in the treatment of obesity and MS. Some of this expected drugs are currently available; for example, thiazolidinediones bind to PPAR and, hence, induce brown adipose tissue differentiation, mitochondrial biogenesis and lipid oxidation. Unfortunately, they – as other pharmacologic agents do – also exhibit potentially significant adverse effects.

Fortunately, research has turned its attention to a sometimes underestimated agent: food. Several components of food have shown to perform regulatory functions related to energy balance and, thus to obesity. This means that obesity can be prevented and/or treated – in terms of

nutrition – not only by a caloric/energetic restriction but also by the participation of specific active substances present within diet that interact with the patient’s genetic material and induces the expression of certain genes and the synthesis or activation of proteins that potentially benefit the so called *obesometabolic* dysfunction. In fact, there’s a whole novel field called *nutrigenomics*, which refers to the study of the influence of an individual’s diet – and some specific food components – on the genome. This “new” field emerged after scientists recognized that nutrients – as drugs do – have the ability to interact and modulate physiological and pathophysiological molecular mechanisms.<sup>91</sup> Among such nutrients, flavonoides exhibit a particularly interesting potential.

Flavonoids are a wide group of polyphenolic compounds that are present in almost every plant and vegetable. Some of them have already shown benefits in terms of obesity and MS. For example, recent investigations demonstrated that resveratrol (a flavonoid contained in high quantities in grapes and red wine) increases SIRT-1 activity and – this way – improves mitochondrial function, probably through allosteric interaction and the activation of PGC-1 $\alpha$  in skeletal muscle.<sup>56,92</sup> Moreover, in rodent models of obesity, resveratrol has been claimed to be not only an activator of SIRT-1 but an actual inducer of its gene.<sup>93–95</sup> These mechanisms are manifested as improvements in endothelial function, decreases in lipid deposition and fat storage, muscular fiber switch, increased mitochondria size, biogenesis and density, and an increase the oxidative capacity through fatty acid oxidation.<sup>92,96</sup>

Other *nutrigenomic* agents are licorice flavonoids. These have shown to reduce (almost inhibit) weight gain in mouse diet-induced obesity models. Moreover, these flavonoid supplementation impaired abdominal fat accumulation, evidenced not only by a lower weight of the mesenteric and perirenal adipose tissues, but also by smaller size adipocytes (approximately one-third to one-half the size of those of the

control group). Licorice flavonoids also had an effect on the liver: upon histological examination, lipid droplets were abundant in the control group, but not in the supplemented group.<sup>99,100</sup>

A final example refers to polyunsaturated fatty acids (PUFAs). These have a particularly high affinity for PPARs, thus a diet high in PUFAs should translate in an increase in their actions including antiglycemic, antilipemic and anti-inflammatory effects.<sup>96</sup> Isoflavones are another kind of polyphenols that exert effects through the PPAR pathway: for example, genistein not only binds directly and activates PPAR $\alpha$  (lipogenic, as mentioned earlier) but it also is capable of downregulating PPAR $\gamma$  (adipogenic).<sup>97</sup> Other food components that have shown PPAR affinity include capsaicin, ginger and various flavonoids such as naringenin. The latter is derived from orange and grapefruit and is has been reported to increase fatty acid oxidation through PPAR $\alpha$ -mediated transcription.<sup>98</sup>

## Concluding remarks

Although studies performed so far are limited, research on the role that food exerts in the modulation of several molecular pathways has given an insight on its potential use as an alternative/complement to currently employed drugs.<sup>101</sup> As more molecules are identified to be key regulators in energy balance – hence, in the development of obesity – and the field of nutrigenomics grows, it can be expected that nutritional management of obesity and the MS will provide therapeutic interventions specifically targeted to modulate the genetic expression of such molecules, thus improving mitochondrial function and increasing the efficiency to prevent and manage such diseases.

## Conflict of interest statement

The authors declare they have no financial or personal situation that could give for conflict of interest in relation to the paper presented here.

## Contribution

All authors contributed to the idea, data collection, analysis information, drafting, critical revision and final approval thereof.

## References

- National Heart, Lung and Blood Institute/National Institute of Diabetes and Digestive and Kidney Diseases. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: the evidence report. [On line] cited 2011 June [2011 April]. Available at: <http://www.nhlbi.nih.gov/guidelines/obesity/index.htm>.
- World Health Organization (WHO). Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Ginebra; 1999.
- Loos RJ, Bouchard C. Obesity: is it a genetic disorder? *J Intern Med*. 2003;254:401–25.
- Bell GC, Walley AJ, Froguel P. The genetics of human obesity. *Nat Rev Genet*. 2005;6:221–34.
- O’Rahilly S, Farooqi IS. Genetics of obesity. *Phil Trans R Soc B*. 2006;361:1095–105.
- Snyder EE, Walts B, Perusse L, Chagnon YC, Weisnagel SJ, Rankinen T, et al. The human obesity gene map: the 2003 update. *Obes Res*. 2004;12:369–439.
- Lyon HN, Hirschhorn JN. Genetics of common forms of obesity: a brief overview. *Am J Clin Nutr*. 2005;82 Suppl:215S–7S.
- Newell A, Zlot A, Silvey K, Arail K. Addressing the obesity epidemic: a genomics perspective. *Prev Chronic Dis*. 2007;4:1–6.
- Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. *Obes Res*. 2002;10 Suppl 2:97S–104S.
- Afridi A, Khan A. Prevalence and etiology of obesity: an overview. *Pak J Nutr* 2004;3:14–25.
- Luenigo-Pérez LM, Beato-Víbora P. Obesidad y sus complicaciones. *Nutr Hosp*. 2010;3 Suppl 1:51–61.
- Ravussin E, Valencia ME, Esparza J, Bennett PH, Schulz LO. Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes*. 1994;17:1067–74.
- Baier LJ, Rennie RL. Genetic studies of the etiology of type 2 diabetes in Pima Indians: hunting for the pieces to a complicated puzzle. *Diabetes*. 2004;53:1181–6.
- Esparza J, Fox C, Harper IT, Bennett PH, Schulz LO, Valencia ME, et al. Daily energy expenditure in Mexican and USA Pima Indians: low physical activity as a possible cause of obesity. *Int J Obes Relat Metab Disord*. 2000;24:55–9.
- Schultz LO, Bennett PH, Ravussin E, Kidd JR, Kidd KK, Esparza J, et al. Effects of a traditional and western environment on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. *Diabetes Care*. 2006;29:1866–71.
- Jebb SA, Rennie KL, Cole TJ. Prevalence of overweight and obesity among young people in Great Britain. *Public Health Nutr*. 2004;7:461–5.
- World Health Organization Obesity and overweight: fact sheet 311. [On line] 2011 February [cited 2011 February]. Available at: URL: <http://www.who.int/mediacentre/factsheets/fs311/en/>.
- Organization for Economic Cooperation and Development (OECD). Obesity and the economics of prevention: fit not fat. [On line] 2010 September 23 [cited 2010 October]. Available at: URL: <http://www.oecd.org/document/31/>.
- Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of comorbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009;9:88.
- Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech*. 2009;2:231–7.
- Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. *J Clin Endocrinol Metabol*. 2007;92:399–404.
- Reaven GM. Insulin resistance, cardiovascular disease, and the metabolic syndrome: how well do the emperor’s clothes fit. *Diabetes Care*. 2004;27:1011–2.
- Shirai K. Obesity as the core of the metabolic syndrome and the management of coronary heart disease. *Curr Med Res Opin*. 2004;20:295–304.
- Despres JP, Lemieux I, Bergenton J, Pibarot P, Mathieu P, Larose E, et al. Abdominal obesity and the metabolic syndrome: a contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol*. 2008;28:1039–49.
- Phillips LK, Prins JB. The link between abdominal obesity and the metabolic syndrome. *Curr Hypertens Rep*. 2008;10:156–64.
- Despres JP. Is visceral obesity the cause of the metabolic syndrome. *Ann Med*. 2006;38:52–63.
- Despres JP. Obesity consequences of visceral adiposity. *Ann Med*. 2001;33:534–41.
- Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyörälä K, DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular

- mortality in non-diabetic European men and women. *Arch Intern Med.* 2004;164:1066–76.
29. Ruan H, Lodish HF. Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor- $\alpha$ . *Cytokine Growth Factor Rev.* 2003;14:447–55.
  30. Redinger RN. The pathophysiology of obesity and its clinical manifestations. *Gastroenterol Hepatol.* 2007;3:856–63.
  31. Ritchie SA, Connell JMC. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutr Metabol Cardiovasc Dis.* 2007;17:319–26.
  32. Kerchaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab.* 2004;89:2548–56.
  33. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. *J Clin Endocrinol Metab.* 2008;93:s64–73.
  34. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003;112:1785–8.
  35. Christiansen T, Richelsen B, Bruun JM. Monocyte chemoattractant protein-1 is produced in isolated adipocytes: associated with adiposity and reduced after weight loss in morbid obese subjects. *Int J Obes.* 2005;29:146–50.
  36. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity: inflammation, and insulin resistance. *Eur Cytokine Netw.* 2006;17:4–12.
  37. Boden G, Lebed B, Schatz M, Homko C, Lemieux S. Effects of acute changes in plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects. *Diabetes.* 2001;50:1612–7.
  38. Itani SI, Ruderman NB, Schmieder F, Boden G. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and I $\kappa$ B $\alpha$ . *Diabetes.* 2002;51:2005–11.
  39. Unger RH. Lipotoxicity in the pathogenesis of obesity-dependent NIDDM. *Diabetes.* 1995;44:863–70.
  40. Duvnjak L, Duvnjak M. The metabolic syndrome: an ongoing story. *J Physiol Pharmacol.* 2009;60 Suppl 7:19–24.
  41. Reaven JM. Insulin resistance and its consequences. In: LeRoith D, Taylor SI, Olefsky JM, editors. *Diabetes mellitus: a fundamental and clinical text.* USA: Lippincott, Williams and Wilkins; 2004.
  42. Montagnani M, Quon MJ. Insulin action in vascular endothelium: potential mechanisms linking insulin resistance with hypertension. *Diabetes Obes Metab.* 2000;2:285–92.
  43. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation.* 2006;113:1888–904.
  44. Atochin DN, Wang A, Liu VW, Critchlow JD, Dantas AP, Looft-Wilson R, et al. The phosphorylation state of eNOS modulates vascular reactivity and outcome of cerebral ischemia. *J Clin Invest.* 2007;117:1961–7.
  45. Flakoll PJ, Jensen MD, Cherrington AD. Physiological action of insulin. In: LeRoith D, Taylor SI, Olefsky JM, editors. *Diabetes mellitus: a fundamental and clinical text.* EUA: Lippincott, Williams and Wilkins; 2004.
  46. Huang PL. Unraveling the links between diabetes, obesity and cardiovascular disease. *Circ Res.* 2005;96:1129–31.
  47. Morrow J. Is oxidative stress a connection between obesity and atherosclerosis. *Arterioscler Tromb Vasc Biol.* 2003;23:368–70.
  48. Fernández-Sánchez A, Madrigal-Santillán F, Bautista M, Esquivel-Soto J, Morales-González A, Esquivel-Chirino C, et al. Inflammation, oxidative stress and obesity. *Int J Mol Sci.* 2011;12:3117–32.
  49. Semenkovich CF. Insulin resistance and atherosclerosis. *J Clin Invest.* 2006;116:1813–22.
  50. Miccoli R, Bianchi C, Penno G, Del Prato S. Insulin resistance and lipid disorders: dysregulation of lipid metabolism. *Future Lipidol.* 2008;3:651–64.
  51. Howard BV. Insulin resistance and lipid metabolism. *Am J Cardiol.* 1999;84:28J–32J.
  52. Raz I, Eldor R, Cernea S, Shafir E. Diabetes: insulin resistance and lipid metabolism. *Diabetes Metab Res Rev.* 2005;21:3–14.
  53. Bhopal RS, Rafnsson SB. Could mitochondrial efficiency explain the susceptibility to adiposity, metabolic syndrome, diabetes and cardiovascular diseases in South Asian populations. *Int J Epidemiol.* 2009;38:1072–81.
  54. Bournat JC, Brown CW. Mitochondrial dysfunction in obesity. *Curr Opin Endocrinol Diabetes Obes.* 2010;17:446–52.
  55. Rolo AP, Gomez AP, Palmeira CM. Regulation of mitochondrial biogenesis in metabolic syndrome. *Curr Drug Targets.* 2011;12:872–8.
  56. Lagousse M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussan F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 $\alpha$ . *Cell.* 2006;127:1109–22.
  57. Kota BP, Huang TH, Roufogalis BD. An overview on biological mechanisms of PPARs. *Pharmacol Res.* 2005;51:85–94.
  58. Yessoufou A, Wahli W. Multifaceted roles of peroxisome proliferator-activated receptors (PPARs) at the cellular and whole organism levels. *Swiss Med Wkly.* 2010;140:E1–10.
  59. Desvergne B, Wahli W. Peroxisome proliferator activated receptors: nuclear control of metabolism. *Endocrinol Rev.* 1999;20:649–88.
  60. Tontonoz P, Hu E, Graves RA, Budavari AI, Spiegelman BM. mPPAR $\gamma$  2: tissue-specific regulator of an adipocyte enhancer. *Genes Dev.* 1994;8:1224–34.
  61. Risérus U, Sprecher D, Johnson T, Olson E, Hirschberg S, Liu A, et al. Activation of PPAR $\alpha$  promotes reversal of multiple metabolic abnormalities: reduces oxidative stress and increases fatty acid oxidation in moderately obese men. *Diabetes.* 2008;57:332–9.
  62. Barish GD, Narkar VA, Evans RM. PPAR $\delta$ : a dagger in the heart of metabolic syndrome. *J Clin Invest.* 2006;116:590–7.
  63. Farmer SR. Molecular determinants of brown adipocyte formation and function. *Genes Dev.* 2008;22:1397–409.
  64. Wilson-Fritch L, Burkart A, Bell G, Mendelson K, Leszyk J, Nicoloso S, et al. Mitochondrial biogenesis and remodeling during adipogenesis and in response to the insulin sensitizer rosiglitazone. *Mol Cell Biol.* 2003;23:1085–94.
  65. Wilson-Fritch L, Nicoloso S, Chouinard M, Lazar MA, Chui PC, Leszyk J, et al. Mitochondrial remodeling in adipose tissue associated with obesity and treatment with rosiglitazone. *J Clin Invest.* 2004;114:1281–9.
  66. Rodríguez-Calvo R, Serrano L, Coll T, Moullan N, Sánchez RM, Merlos M, et al. Activation of the peroxisome proliferator-activated receptor  $\beta/\delta$  inhibits lipopolysaccharide-induced cytokine production in adipocytes. *Diabetes.* 2008;57:2149–57.
  67. Coll T, Barroso E, Álvarez-Guardia D, Serrano L, Salvadó L, Merlos M, et al. The role of peroxisome proliferator-activated receptors  $\beta/\delta$  on the inflammatory basis of metabolic disease. *PPAR Res.* 2010, doi:10.1155/2010/368467.
  68. Gordon S. Alternative activation of macrophages. *Nat Rev Immunol.* 2003;3:23–5.
  69. Straus DS, Glass CK. Anti-inflammatory actions of PPAR ligands: new insights on cellular and molecular mechanisms. *Trends Immunol.* 2007;28:551–8.
  70. Fuentes L, Rószter T, Ricote M. Inflammatory mediators and insulin resistance in obesity: role of nuclear receptor signaling in macrophages. *Mediat Inflamm.* 2010, doi:10.1155/2010/219583.

71. Madej A, Okopien B, Kowalski J, Zielinski M, Wysocki J, Szygula B, et al. Effects of fenofibrate on plasma cytokine concentrations in patients with atherosclerosis and hyperlipoproteinemia IIb. *Int J Clin Pharmacol Ther.* 1998;36:345–9.
72. Bassaganya J, Guri AJ, Hontecillas R. Treatment of obesity related complications with novel classes of naturally occurring PPAR agonists. *J Obes*, doi:10.1155/2011/897894.
73. Liang H, Ward WF. PGC-1 $\alpha$ : a key regulator of energy metabolism. *Adv Physiol Educ.* 2006;30:145–51.
74. Finck BN, Kelly DP. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. *J Clin Invest.* 2006;116:615–22.
75. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell.* 1998;92:829–39.
76. Scarpulla RC. Nuclear activators and coactivators in mammalian mitochondrial biogenesis. *Biochim Biophys Acta.* 2002;1576:1–14.
77. Scarpulla RC. Transcriptional activators and coactivators in the nuclear control of mitochondrial function in mammal cells. *Gene.* 2002;286:81–9.
78. Russel AP, Feilchenfeldt J, Schreiber S, Praz M, Crettenand A, Gobelet C, et al. Endurance in training humans lead to fiber type-specific increases in levels of PGC-1 $\alpha$  and PPAR $\alpha$  in skeletal muscle. *Diabetes.* 2003;52:2874–81.
79. Liang H, Ward WF. PGC-1 $\alpha$ : a key regulator of energy metabolism. *Adv Physiol Edu.* 2006;30:145–51.
80. Nagamoto F, Gu N, Fujino H, Takeda I, Tsuda K, Ishihara A. Skeletal muscle characteristics of rats with obesity, diabetes, hypertension and hyperlipidemia. *J Atheroscler Thromb.* 2009;16:576–85.
81. Fernández-Marcos PJ, Auwerx J. Regulation of PGC-1 $\alpha$ : a nodal regulator of mitochondrial biogenesis. *Am J Clin Nutr.* 2011;93:884S–90S.
82. Yang T, Sauve AA. NAD metabolism and sirtuins: metabolic regulation of protein deacetylase in stress and toxicity. *AAPS J.* 2006;E632–43.
83. Chaudhary N, Pfluger PT. Metabolic benefits from Sirt1 and Sirt1 activators. *Curr Opin Clin Nutr Metabol Care.* 2009;12:431–7.
84. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic diseases by activating SIRT1 and PGC-1 $\alpha$ . *Cell.* 2006;127:1109–22.
85. Gerhart-Hines Z, Rodgers JT, Bare O, Lerin C, Kim SH, Mostoslavsky R, et al. Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1 $\alpha$ . *EMBO J.* 2007;26:1913–23.
86. Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1 $\alpha$  and SIRT1. *Nature.* 2005;434:113–8.
87. Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, et al. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR- $\gamma$ . *Nature.* 2004;429:771–6.
88. Zillikens M, van Meurs JBJ, Rivadeneira F, Amin N, Hofman A, Oostra BA, et al. SIRT1 genetic variation in related to BMI and risk of obesity. *Diabetes.* 2009;58:2828–34.
89. Campos BSI, Hernández ML. Tratamiento de la obesidad. In: González A, Lavalle FJ, Rios JJ, editors. *Síndrome metabólico y enfermedad cardiovascular.* 3<sup>a</sup> ed. México: Intersistemas Editores; 2009.
90. Saper R, Eisenberg D, Russell SP. Common dietary supplements for weight loss. *Am Fam Physician.* 2004;70:1731–8.
91. Mutch DM, Wahli W, Williamson G. Nutrigenomics and nutrigenetics: the emerging faces of nutrition. *FASEB J.* 2005;160:2–16.
92. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature.* 2006;444:337–42.
93. Alcain FJ, Villalba JM. Sirtuin activators. *Expert Opin Ther Pat.* 2009;19:403–14.
94. Kaerberlein M, McDonagh T, Heltweg B, Hixon J, Westman EA, Caldwell SD, et al. Substrate-specific activation of sirtuins by resveratrol. *J Biol Chem.* 2005;280:17038–45.
95. Behr D, Wu J, Cumine S, Kim KW, Lu SC, Atangan L, et al. Resveratrol is not a direct activator of SIRT1 enzyme activity. *Chem Biol Drug Des.* 2009;74:619–24.
96. Feige JN, Lagouge M, Cantone C, Strehle A, Houten SM, Milne JC, et al. Specific SIRT1 activation of sirtuins, low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. *Cell Metab.* 2008;8:347–58.
97. Orggard A, Jensen L. The effects of soy isoflavones on obesity. *Exp Biol Med.* 2008;233:1066–80.
98. Mulvihill EE, Allister EM, Sutherland BG, Telford DE, Sawyez CG, Edwards JY, et al. Naringenin prevents dyslipidemia, apolipoprotein B overproduction, and hyperinsulinemia in LDL receptor null mice with diet-induced insulin resistance. *Diabetes.* 2009;58:2198–210.
99. Honda S, Tominaga Y, Yokota S. Licorice flavonoids. In: Mine Y, Miyashita K, Shahidi F, editors. *Nutrigenomics and proteomics in health and disease.* EUA: Wiley-Blackwell; 2009. p. 299–309.
100. Kamiyosama H, Honda K, Tominaga Y, Yokota S, Hasegawa S. Investigation of the anti-obesity action of licorice flavonoid oil in diet-induced obese rats. *Biosci Biotechnol Biochem.* 2008;72:3225–31.
101. Xia X, Weng J. Targeting metabolic syndrome: candidate natural agents. *J Diabetes.* 2010;2:243–9.