European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2002; 6: 27-32

Editorial

Pathophysiology of obesity-induced insulin resistance and type 2 diabetes mellitus

P.A. TATARANNI

Obesity, Diabetes & Energy Metabolism Unit, Clinical Diabetes & Nutrition Section, NIDDK-NH-DHHS, Phoenix, Az, USA

Introduction

Obesity is clinically defined as a body mass index (BMI) of ≥ 30 kg/m^2 (a BMI of 30 represents an overweight of approximately 30 lb (14 kg) for any given height)[1]. It is a disease that is highly prevalent at all ages[2,3] and is quickly reaching pandemic proportions[4]. Obesity is associated with significant comorbidity and increased mortality[5]. The exact etiology of this disease in the majority of humans is not known. It is, however, widely accepted that obesity results from a chronic imbalance between energy intake and energy expenditure[6,7]. Obesity is heritable[8-10]; it is likely that genes (as yet, mostly unidentified) controlling eating behavior and daily physical activity interact with the environment to increase the susceptibility to weight gain in certain groups of individuals[11].

Clinicians have observed for centuries that fatter people are more likely to have type 2 diabetes mellitus (T2DM) and overwhelming evidence has accumulated to prove this clinical impression accurate. The association of obesity with T2DM has been observed in comparisons of different populations and within populations[12,13]. Prospective studies of pre-diabetic subjects have shown conclusively that obesity and its duration are major risk factors for T2DM[14-22]. Notwithstanding the remarkable consistency of the association between the two diseases, obesity is neither sufficient nor necessary for the development of T2DM[23-25]. For example, many U.S. Caucasians are overweight or obese, but less than 10% of the population has T2DM[2,26].

How does obesity cause T2DM and why does it cause it only in some people? It is easy to understand how T2DM develops in the absence of insulin secretion. Circumstantial and experimental evidence indicate that weight gain causes hyperinsulinemia and insulin resistance[27-29], but how does insulin resistance gradually result in the disease? Does insulin secretory function simply decrease with age?

The concepts of "glucotoxicity" and "lipotoxicity" have been advanced to explain the pathogenesis of T2DM. More recently it has been proposed that adipokines, i.e., hormones secreted by the adipose tissue, can impair glucose tolerance. In this editorial I tried to highlight some recent developments in the understanding of the pathophysiological links between obesity and T2DM in humans.

Glucotoxicity

Physiologically, glycemia is maintained within a very narrow range by the pancreatic insulin secretory response to fluxes of macronutrients produced by daily meals. Despite these fluctuations, fasting glycemia is homeostatically controlled, i.e., glucose always returns to the initial level after each meal. We have recently coined the expression "glucose allostasis" to better describe the changes that take place when insulin resistance ensues. In response to insulin resistance, a small increase in fasting glycemia (even in the normal glucose range) becomes

one of the signals for the compensatory increase in insulin secretion (rather than resulting from a lack of it)[30]. As long as insulin resistance and the resulting mild hyperglycemia persist, the pancreas is forced to constantly over-secrete insulin, a condition termed 'allostatic load'. Prospective analysis shows that normal glucose tolerant individuals with a high pancreatic allostatic load have an increased risk of developing type 2 diabetes compared to individuals with a low pancreatic allostatic load[30]. Thus, obesity-induced insulin resistance may cause T2DM by increasing the allostatic load of the pancreas.

One of the possible ways that an increased allostatic load can eventually lead to failure of the endocrine pancreas is through the direct detrimental affect of hyperglycemia on the beta cell, which is commonly referred to as glucotoxicity[31]. Mechanisms include decrease in expression of relevant genes (insulin receptor, GLUT2, glucokinase, inward rectifier potassium channel), beta cell de-differentiation and increased apoptosis[32,33]. Also, it has been suggested that chronic hyperglycemia per se can worsen insulin resistance[34].

Lipotoxicity

How does obesity cause insulin resistance in the first place? Many studies indicate that over a wide range of insulin action, from the greatest insulin resistance to the greatest insulin sensitivity, glucose storage, not glucose oxidation, makes a progressively greater contribution to glucose uptake[35,36]. Thus, the effect of obesity on insulin action is likely to be mediated by a progressive decline in muscle glycogen synthase activity and glycogenesis[37,38].

There is strong evidence that acute and chronic increases in fatty acid supply to peripheral tissues may play an important role in impairing glucose uptake and storage in the muscle[39-42]. A theory has been set forth proposing that the adipose tissue plays a crucial role in buffering the flux of FFA in the postprandial period and that this buffering action becomes progressively impaired as obesity develops, which would in turn expose extra-adipose tissues to excessive lipid fluxes[43]. This theory is partially supported by the following observations. Obesity-induced insulin resistance is associated with increased lipid concentrations in insulin-responsive tissues[44-47]. Normal glucose tolerant people with enlarged subcutaneous abdominal adipocytes[48] and elevated levels of FFA[49] (possible markers of reduced adipose tissue buffering action[50]) are at increased risk of developing T2DM. People with lipodystrophy (very little or no adipose tissue available to buffer daily lipid fluxes) are also insulin resistant and prone to T2DM[51].

Nonetheless, direct experimental evidence that the adipose tissue progressively loses its normal ability to buffer excessive lipid fluxes as obesity develops is still lacking and it has been difficult to directly demonstrate an increase in FFA flux to the muscle of obese subject (and in fact the reverse has been reported[52]). Finally, we are still missing an unequivocal biochemical explanation for a role for FFA in regulating glycogen synthesis. Some possible mechanisms have been proposed, including the effect of long chain fatty acids on glycogen synthase[53,54], cellular membrane fluidity[55], translocation of GLUT4 containing vesicles[56] and activation of the hexosamine pathway[57].

The toxic effect of lipids may extend to the beta cell. FFA serve as an important source of energy for most body tissues, but they have a broader function as signals in a variety of cellular processes. One such role is to enhance the responsiveness of the pancreas to a variety of insulin secretagogues[58]. However, numerous studies indicate that chronic exposure of the pancreas to elevated FFA concentrations has deleterious effect on the beta cells[59,60]. Possible mechanisms underlying the lipotoxic effect of FFA on the beta cell include overproduction of NO[61], interleukin-1B[62], and ceramide[63], the latter likely responsible for the accelerated apoptosis observed in fat-laden beta cells.

Adipokines

The adipose tissue is increasingly recognized as an endocrine organ[64] (Figure 1). Others and we have observed that many of the hormones that are secreted by the adipose tissue (TNF-α, IL-6, complement C3, MIF, adiponectin) are associated with insulin

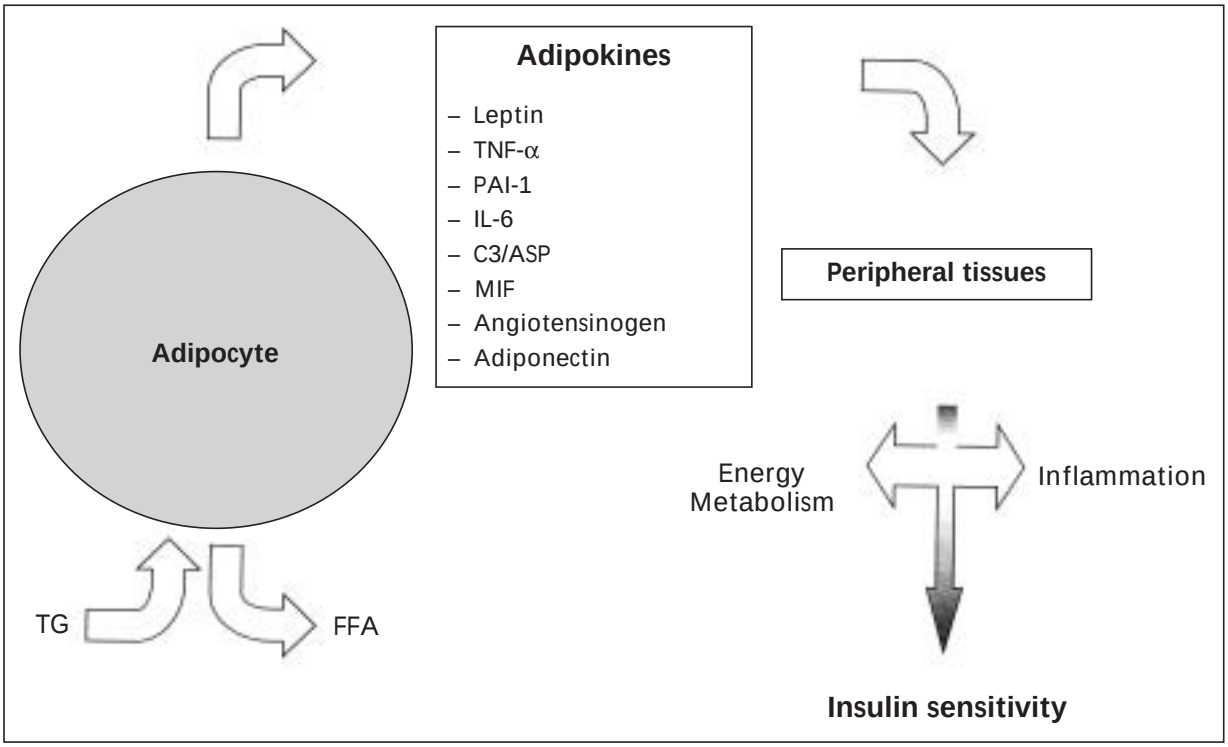

Figure 1. The adipocyte is an endocrine cell capable of secreting proteins that act as endocrine, paracrine and metabolic signals to proximal and distant tissues and organs. These signals may be the pathophysiological link between obesity and many associated comorbid conditions, including type 2 diabetes, hypertension, dyslipidemias and atherosclerosis.

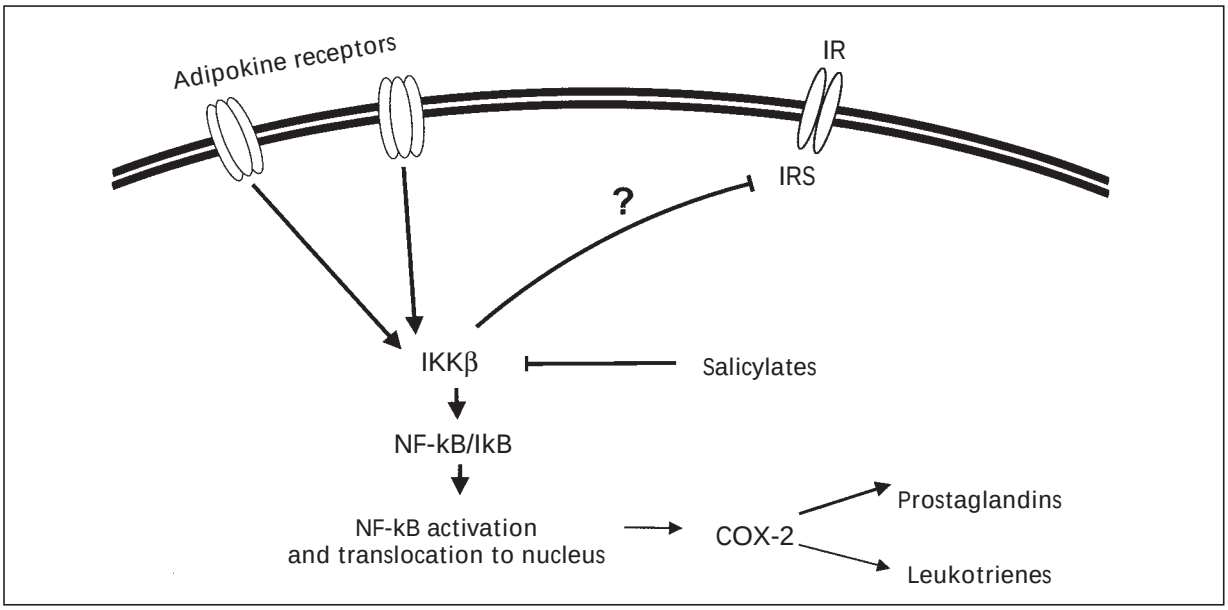

Figure 2. A schematic representation of the hypothetical link between adipokines, the NFk/IkB pro-inflammatory pathway and insulin action. The figure shows the mechanism by which salicylates, which are thought to block IKKb73, may be able to improve insulin resistance by mechanisms that remain to be elucidated. IR, insulin receptor. IRS, insulin receptor substrates.

resistance, often independently of the degree of adiposity[65-69]. More important, several prospective studies have shown a relationship between adipokines (IL-6 and adiponectin) and the risk of developing T2DM[70,71]. The exact biological mechanism underlying this association remains obscure, but in vitro studies suggest that the effect of adipokines on insulin action may be related to their ability to activate NF-κB, a transcription factor that plays a key role in inflammatory and immune responses[72]. Adipokines stimulate the pro-inflammatory effects of NF-κB by modulating the action of IkB kinase (IKK)[73]. IKK phosphorylates (inactivates) IkBs, proteins that maintain NF-κB in an inactive state in the cytoplasm[72]. Some experiments suggest that one of the catalytic subunits of IKK released in the process (IKKβ) can impair insulin action[73] (Figure 2).

While the role of the NF-κB/IKK pathway in modulating insulin action remains an area of intense investigation, there is mounting evidence that a chronic low-grade activation of the immune system may play an etiologic role in the development of T2DM. Numerous prospective studies have now shown that high levels of inflammatory markers such as sialic acid, oromucoid acid, CRP, serum immunoglobulins and WBC predict T2DM[70,74-78]. Therefore, it is possible that an adipokine-induced activation of the immune system may mediate the effect of over-nutrition on insulin resistance and later development of T2DM[79]. The effect of adipokines on insulin secretory function is unclear at this point.

Conclusion

Obesity is a major cause of type 2 diabetes (T2DM) in all affected populations. Nonetheless, obesity is neither sufficient nor necessary to develop T2DM. In some predisposed individuals and populations, obesity increases the risk of T2DM by causing insulin resistance and directly or indirectly affecting the ability of the pancreas to secrete adequate amounts of insulin.

No simple metabolic defect is likely to explain the cause of obesity-induced T2DM in large numbers of people and the precise link(s) between obesity and T2DM have yet to be unequivocally identified. A complete understanding of the causes of T2DM will require a better knowledge of the environmental and molecular genetic determinants of both insulin action and insulin secretory function, and, equally important, a better knowledge of how they interact pathophysiologically over time.

Acknowledgements

Writing this short editorial would have been impossible without the support, help and teachings of and wonderful scientific discussions with my colleagues Bo Bogardus, Jonathan Krakoff, Robert Lindsay, Eric Ravussin, Norbert Stefan, Michael Stumvoll, Barbora Vozarova, and many others, all of whom I wish to thank. A special thanks to my assistant, Susan Luther, for the editing and final preparation of the manuscript.

References

1) *NIH-NHLBI Obesity Initiative Task Force.* Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults-The Evidence Report. Obes Res 1998; 6: 1-209.

2) *Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP*. The spread of the obesity epidemic in the United States, 1991-1998. JAMA 1999; 282: 1519-1522.

3) *Ogden CL, Troiano RP, Briefel RR, Kuczmarski RJ, Flegal KM, Johnson CL*. Prevalence of overweight among preschool children in the United States, 1971 through 1994. Pediatrics 1997; 99: E1.

4) *Obesity: preventing and managing the global pandemic.* WHO/NUT/NCD/98.1, 1997.

5) *Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH.* The disease burden associated with overweight and obesity. JAMA 1999; 282: 1523-1529.

6) *Tataranni PA, Ravussin E*. Energy metabolism and obesity. In: Wadden TA, Stunkard AJ, eds. Handbook of Obesity Treatment. New York: The Guilford Press, 2002: 42-72.

7) *Tataranni PA.* Mechanisms of weight gain in humans. Eur Rev Med Pharmacol Sci 2000; 4: 1-7.

8) *Bouchard C, Perusse L.* Heredity and body fat. Ann Rev Nutr 1988; 8: 259-277.

9) *Allison DB, Kaprio J, Korkeila M, Koskenvuo M, Neale MC, Hayakawa K.* The heritability of body mass index among an international sample of monozygotic twins reared apart. Int J Obes Relat Metab Disord 1996; 20: 501-506.

10) *Sakul H, Pratley R, Cardon L, Ravussin E, Mott D, Bogardus C.* Familiality of physical and metabolic characteristics that predict the development of non-insulin-dependent diabetes mellitus in Pima Indians. Am J Hum Genet 1997; 60: 651-656.

11) *Ravussin E, Bogardus C.* Energy balance and weight regulation: genetics versus environment. Br J Nutr 2000; 83 (Suppl 1): S17-S20.

12) *West KM, Kalbfleisch JM.* Influence of nutritional factors on prevalence of diabetes. Diabetes 1971; 20: 99-108.

13) *Joslin EP.* The prevention of diabetes mellitus. JAMA 1921; 76-79.

14) *O'Sullivan JB, Mahan CM.* Blood sugar levels, glycosuria, and body weight related to development of diabetes mellitus. The Oxford epidemiologic study 17 years later. JAMA 1965; 194: 587-592.

15) *Westlund K, Nicolaysen R.* Ten-year mortality and morbidity related to serum cholesterol. A follow-up of 3,751 men aged 40-49. Scand J Clin Lab Invest Suppl 1972; 127: 1-24.

16) *Ohlson LO, Larsson B, Eriksson H, Svardsudd K, Welin L, Tibblin G.* Diabetes mellitus in Swedish middle-aged men. The study of men born in 1913 and 1923. Diabetologia 1987; 30: 386-393.

17) *Modan M, Karasik A, Halkin H, et al.* Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non-insulin-dependent) diabetes and on insulin response. The Israel study of glucose intolerance, obesity and hypertension. Diabetologia 1986; 29: 82-89.

18) *Dunn JP, Ipsen J, Elsom KO, Ohtani M*. Risk factors in coronary artery disease, hypertension and diabetes. Am J Med Sci 1970; 259: 309-322.

19) *Wilson PW, McGee DL, Kannel WB.* Obesity, very low density lipoproteins, and glucose intolerance over fourteen years: The Framingham Study. Am J Epidemiol 1981; 114: 697-704.

20) *Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK.* Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. Diabetes 1990; 39: 283-288.

21) *Lillioja S, Mott DM, Spraul M, et al*. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. N Engl J Med 1993; 329: 1988-1992.

22) *Everhart JE, Pettitt DJ, Bennett PH, Knowler WC*. Duration of obesity increases the incidence of NIDDM. Diabetes 1992; 41: 235-240.

23) *Arner P, Pollare T, Lithell H.* Different aetiologies of type 2 (non-insulin-dependent) diabetes mellitus in obese and non-obese subjects. Diabetologia 1991; 34: 483-487.

24) *Barnett AH, Eff C, Leslie RD, Pyke DA*. Diabetes in identical twins. A study of 200 pairs. Diabetologia 1981; 20: 87-93.

25) *Knowler WC, Pettitt DJ, Saad MF, Bennett PH*. Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. Diabetes Metab Rev 1990; 6: 1-27.

26) *Harris MI, Flegal KM, Cowie CC, et al.* Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994 [see comments]. Diabetes Care 1998; 21: 518-524.

27) *Weyer C, Bogardus C, Mott DM, Pratley RE.* The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999; 104: 787-794.

28) *Sims EA, Danforth EJ, Horton ES, Bray GA, Glennon JA, Salans LB.* Endocrine and metabolic effects of experimental obesity in man. Recent Prog Horm Res 1973; 29: 457-496.

29) *Mott DM, Lillioja S, Bogardus C.* Overnutrition induced decrease in insulin action for glucose storage: in vivo and in vitro in man. Metabolism 1986; 35: 160-165.

30) *Stumvoll M, Tataranni PA, Stefan N, Vozarova B, Bogardus C.* Increased glycemia physiologically accompanies insulin resistance due to incomplete beta cell compensation. Diabetologia 2002; 45: A185 (abstr).

31) *Yki-Jarvinen H*. Glucose toxicity. Endocr Rev 1992; 13: 415-431.

32) *Robertson RP, Olson LK, Zhang HJ.* Differentiating glucose toxicity from glucose desensitization: a new message for the insulin gene. Diabetes 1994; 43: 1085-1089.

33) *Weir GC, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A.* Beta-cell adaptation and decompensation during the progression of diabetes. Diabetes 2001; 50: S154-S159.

34) *DeFronzo RA.* Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988; 37: 667-687.

35) *Felber JP, Meyer HU, Curchod B, et al.* Glucose storage and oxidation in different degrees of human obesity measured by continuous indirect calorimetry. Diabetologia 1981; 20: 39-44.

36) *Lillioja S, Mott DM, Zawadzki JK, Young AA, Abbott WG, Bogardus C.* Glucose storage is a major determinant of in vivo "insulin resistance" in subjects with normal glucose tolerance. J Clin Endocrinol Metab 1986; 62: 922-927.

37) *DeFronzo RA, Gunnarsson R, Bjorkman O, Olsson M, Wahren J.* Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. J Clin Invest 1985; 76: 149-155.

38) *Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG.* Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy [see comments]. N Engl J Med 1990; 322: 223-228.

39) *Boden G.* Role of fatty acids in the pathogenesis of insulin resistance and NIDDM [published erratum appears in Diabetes 1997 Mar; 46(3): 536]. Diabetes 1997; 46: 3-10.

40) *Balasse EO, Neef MA*. Influence of nicotinic acid on the rates of turnover and oxidation of plasma glucose in man. Metabolism 1973; 22: 1193-204.

41) *Gomez F, Jequier E, Chabot V, Buber V, Felber JP.* Carbohydrate and lipid oxidation in normal human subjects: its influence on glucose tolerance and insulin response to glucose. Metabolism 1972; 21: 381-391.

42) *Kumar S, Boulton AJ, Beck-Nielsen H, et al.* Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients. Troglitazone Study Group [published erratum appears in Diabetologia 1996 Oct; 39 (10): 1245]. Diabetologia 1996; 39: 701-709.

43) *Frayn KN.* Adipose tissue as a buffer of daily lipid flux. Diabetologia 2002; 45: 1201-1210.

44) *Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE.* Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes 1997; 46: 1579-1585.

45) *Bjorntorp P*. Liver triglycerides and metabolism [editorial; comment]. Int J Obes Relat Metab Disord 1995; 19: 839-840.

46) *Greco AV, Mingrone G, Giancaterini A, et al.* Insulin resistance in morbid obesity: reversal with intramyocellular fat depletion. Diabetes 2002; 51: 144-151.

47) *Krssak M, Falk PK, Dresner A, et al.* Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study [published errata appear in Diabetologia 1999 Mar; 42 (3): 386 and 1999 Oct; 42 (10): 1269]. Diabetologia 1999; 42: 113-116.

48) *Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE.* Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. Diabetologia 2000; 43: 1498-1506.

49) *Paolisso G, Tataranni PA, Foley JE, Bogardus C, Howard BV, Ravussin E.* A high concentration of fasting plasma non-esterified fatty acids is a risk factor for the development of NIDDM. Diabetologia 1995; 38: 1213-1217.

50) *Danforth E Jr*. Failure of adipocyte differentiation causes type II diabetes mellitus? Nat Genet 2000; 26: 13.

51) *Garg A.* Lipodystrophies. Am J Med 2000; 108: 152.

52) *Colberg SR, Simoneau JA, Thaete FL, Kelley DE*. Skeletal muscle utilization of free fatty acids in women with visceral obesity [see comments]. J Clin Invest 1995; 95: 1846-1853.

53) *Wititsuwannakul D, Kim KH*. Mechanism of palmityl coenzyme A inhibition of liver glycogen synthase. J Biol Chem 1977; 252: 7812-7817.

54) *Brindley DN.* Intracellular translocation of phosphatidate phosphohydrolase and its possible role in the control of glycerolipid synthesis. Prog Lipid Res 1984; 23: 115-133.

55) *Pan DA, Hulbert AJ, Storlien LH.* Dietary fats, membrane phospholipids and obesity. J Nutr 1994; 124: 1555-1565.

56) *Glick BS, Rothman JE*. Possible role for fatty acyl-coenzyme A in intracellular protein transport. Nature 1987; 326: 309-312.

57) *Rossetti L, Hawkins M, Chen W, Gindi J, Barzilai N.* In vivo glucosamine infusion induces insulin resistance in normoglycemic but not in hyperglycemic conscious rats. J Clin Invest 1995; 96: 132-140.

58) *McGarry JD, Dobbins RL.* Fatty acids, lipotoxicity and insulin secretion. Diabetologia 1999; 42: 128-138.

59) *Bollheimer LC, Skelly RH, Chester MW, McGarry JD, Rhodes CJ.* Chronic exposure to free fatty acid reduces pancreatic beta cell insulin content by increasing basal insulin secretion that is not compensated for by a corresponding increase in proinsulin biosynthesis translation. J Clin Invest 1998; 101: 1094-1101.

60) *Paolisso G, Gambardella A, Amato L, et al*. Opposite effects of short- and long-term fatty acid infusion on insulin secretion in healthy subjects. Diabetologia 1995; 38: 1295-1299.

61) *Shimabukuro M, Ohneda M, Lee Y, Unger RH.* Role of nitric oxide in obesity-induced beta cell disease. J Clin Invest 1997; 100: 290-295.

62) *Shimabukuro M, Koyama K, Lee Y, Unger RH*. Leptin- or troglitazone-induced lipopenia protects islets from interleukin 1beta cytotoxicity. J Clin Invest 1997; 100: 1750-1754.

63) *Shimabukuro M, Zhou YT, Levi M, Unger RH*. Fatty acid-induced beta cell apoptosis: a link between obesity and diabetes. Proc Natl Acad Sci USA 1998; 95: 2498-2502.

64) *Kahn BB, Flier JS.* Obesity and insulin resistance. J Clin Invest 2000; 106: 473-481.

65) *Straczkowski M, Kowalska I, Stepien A, Dzienis-Straczkowska S, Szelachowska M, Kinalska I*. Increased plasma-soluble tumor necrosis factor-alpha receptor 2 level in leannondiabetic offspring of type 2 diabetic subjects. Diabetes Care 2002; 25: 1824-1828.

66) *Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE.* Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. Obes Res 2001; 9: 414-417.

67) *Weyer C, Tataranni PA, Pratley RE*. Insulin action and insulinemia are closely related to the fasting complement C3, but not acylation stimulating protein concentration. Diabetes Care 2000; 23: 779-785.

68) *Weyer C, Funahashi T, Tanaka S, et al*. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86: 1930-1935.

69) *Vozarova B, Metz C, Stefan N, et al.* Plasma concentrations of macrophage migration inhibitory factor are elevated in Pima Indians Compared to Caucasians and are associated with insulin resistance. Diabetologia 2002 (in press).

70) *Pradham AD, Manson JE, Rifai N, Buring JE, Ridker PM*. C-reactive protein, interleukin 6 and risk of developing type 2 diabetes mellitus. JAMA 2001; 286: 327-334.

71) *Lindsay RS, Funahashi T, Hanson RL, et al.* Adiponectin and the development of type 2 diabetes in the Pima Indian population. Lancet 2002; 360: 57-58.

72) *Li Q, Verma IM*. NF-kB regulation in the immune system. Nature Rev 2002; 2: 725-734.

73) *Yuan M, Konstantopoulos N, Lee J, et al.* Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. Science 2001; 293: 1673-1677.

74) *Schmidt SI, Duncan BB, Sharrett AR, et al.* Markers of inflammation and prediction of diabetes mellitus in adults (ARIC study): a cohort study. Lancet 1999; 353: 1649-1652.

75) *Barzilay JI, Abraham L, Heckbert SR, et al*. The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. Diabetes 2001; 50: 2384-2389.

76) *Freeman DJ, Norrie J, Caslake MJ, et al*. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes 2002; 51: 1596-1600.

77) *Lindsay RS, Krakoff J, Hanson RL, Bennett PH, Knowler WC.* Gamma globulin levels predict type 2 diabetes in the Pima Indian population. Diabetes 2001; 50: 1598-1603.

78) *Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA.* High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 2002; 51: 455-461.