ARCHIVOS LATINOAMERICANOS DE NUTRICION
Organo Oficial de la Sociedad Latinoamericana de Nutrición
Vol. 42 Nº 3-S, 1992

Insulin resistance in obesity

Benjamín Caballero, M.D., Ph.D.

Center for Human Nutrition Department of International Health School of Hygiene and Public Health
The Johns Hopkins University

INTRODUCTION

Insulin resistance has been identified as a manifestation of obesity several decades ago, based on the presence of excessive circulating insulin levels in obese individuals (1). Most persons with uncomplicated obesity exhibit an exaggerated plasma insulin response during an oral glucose tolerance test, which is necessary to maintain a normal plasma glucose response after the glucose challenge, due to a decreased sensitivity to insulin in target tissues. A similar increased insulin output in the obese may be demostrated after regular, carbohydrate-containing meals (2).

Insulin resistance is also present in a variety of other conditions, both physiological, such as puberty (3) and pregnancy (4, 5), and pathological such as acute infections (6), achromegaly (7,8), Turner syndrome (9), aplastic anemia (10), and others.

The insulin clamp technique (11) allow for a precise quantitation of the effects of insulin resistance, by isolating insulin's action from those of the other counterregulatory hormones participating in glucose homeostasis, and by permitting the comparative assessment of insulin-dependent responses over a wide range of plasma insulin concentrations. Insulin clamp studies show that that the two main expressions of the insulin reistance of obesity are a decreased insulin-stimulated peripheral glucose uptake, and an impaired suppression of hepatic glucose production (12,13).

INSULIN RESISTANCE, SENSITIVITY AND RESPONSIVENESS

Early definitions of insulin resistance are based on the "need for greater than normal amounts of insulin" to elicit a normal biological response (14). As pointed out by Kahn (15), this definitions is based on a "greater than normal" insulin output, and assumes that a "normal response" may be achieved if enough insulin is available. But with the use of the insulin clamp technique it became apparent that some individuals never achieved a "normal response", even when receiving very high insulin doses. Similarly, other individuals exhibited impaired insulin-mediated responses even at "normal" insulin concentrations. Consequently, Kahn and others (15) proposed to use the term resistance as a generic descriptions of impaired biological response at the cellular, regional or whole body level. The term decreased sensitivity should describe prereceptor or receptor impairment, and impaired responsiveness should be used to describe the inability to reach normal maximal biological response, regardless of the level of insulin, reflecting a post-receptor defect.

Both impaired sensitivity and impaired responsiveness to insulin can be identified in obese populations (figure 1). Some obese individuals with impaired insulin-dependent glucose disposal at physiological insulin levels can nevertheless achieve normal levels of maximal glucose disposal at very high insulin concentrations. This insulin resistance is related to prereceptor and receptor events. Other obese persons cannot reach maximal response, regardless of insulin dose, evidencing post-receptor insulin resistance (16). This type of insulin resistance is usually associate with severe obesity and central body fat distribution.

The main determinant of pancreatic insulin output is portal vein glucose concentration. However, insulin plays an important role in a number of other functions. The available evidence suggests that insulin resistance does not affect homogeneously all insulin-dependent funtions. For example, insulin-stimulated potassium uptake is impaired in

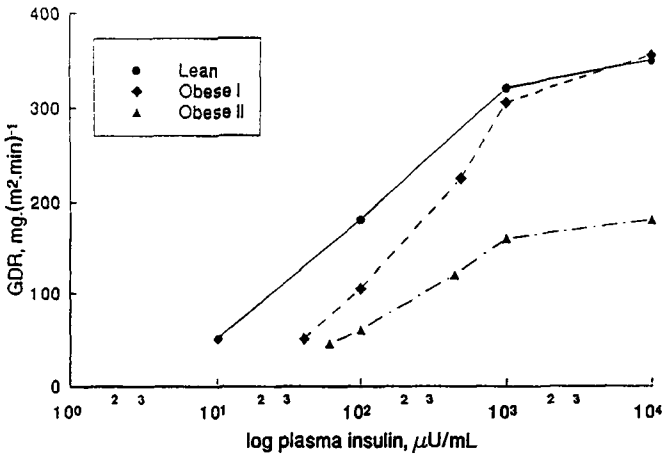

FIGURE 1

Glucose disposal rate (GDR) during euglycemic insulin clamp studies in obese and lean control persons. Obese I exemplifies insulin resistance related to receptor events (decreased affinity, number, etc), which can be overcome by large insulin doses. In contrast, group II exhibits a response typical of post-receptor insulin resistance: maximal insulin-mediated response is never achieved, even at plasma insulin levels at which presumably all receptors are occupied. Data from Kolterman et al. (Ref. 16).

insulin-resistant obese (17), but plasma leucine flux and oxidation appear to be preserved (18).

MECHANISM OF INSULIN RESISTANCE OF OBESITY

Many of the large body of data documenting the consequence of insulin resistance in obesity also point to possible mechanisms. A precise understanding of how and why insulin resistance and hyperinsulinemia develop in obesity is however still imcomplete. Most factors known to affect tissue response to insulin can be classified as acting at the receptor or at the post-receptor sities.

Receptor events

Substrate plasma concentrations: Acute increases in circulated free fatty acids during clamp studies prevent the normal decline in hepatic glucose output (19). Elevated plasma glucose levels also appear to contribute to insulin resistance, as documented by the effects of long-term glucose infusions and sucrose feeding in the rat (20,21). Changes in substrate concentrations may of course be caused by diet, but they may also be a consequence of insulin resistance itself. For example, a decreased response to insulin may decrease lipoprotein lipase activity, impair VLDL triglyceride matabolism, and lead to increased triglyceride levels. Thus, substrate-mediates changes in insulin sensitivity may result from alterations in other insulin-dependent processes.

An increased circulating insulin levels has also been implicated in a feedback circle perpetuating insulin resistance (22). High insulin levels are caused not only by hypersecretions, but also by decreased clearance. In some studies, insulin clearance rate was found to be inversely related to body mass index (23).

A decreased number of insulin receptors per cell in target tissues as a mechanism of insulin resisance has been documented in a number of in vitro studies and supported by whole-body measurement of insulin action using the insulin clamp. The typical right shift of the insulin dose-response curve suggests a decreased formation of hormone-receptor complexes (24,25). Although adipose cell hypertrophy in obesity may lead to a decreased number of receptors per cell, adipose tissue plays a secondary role in determining the overall insulin-mediated glucose metabolism, given the preeminence of the skeletal muscle tissue in this regard. Instead, it is possible that elevations in circulating insulin levels can lead to a down-regulation of its receptors, initiating the loop of hyperinsulinemia and insulin resistance.

Decreased insulin binding in adipocytes has been demostrated in obesity (26) and in a number of conditions associate with severe insulin resistance (27).

A decreased receptor number may be only one of several factors producing impaired insulin sensitivity. In many tissues, only a small proportion of receptors need to be occupied in order for insulin to exert its maximal biological action. For example glucose transport in adipocytes reaches its maximun with only 10% of occupancy (28). How a decreased number of receptors per cell affects the proportion of occupied ones required for maximal biological action, and whether this affects the random probability of insulin binding is unclear. In other tissues. The biological response increases linearly with receptor occupancy, up to the maximal response (29).

Post-receptor events

Several of the pre-receptor changes affecting insulin response, such as plasma concentrations of free fatty acids, triglycerides and glucose, actually, act at the post-receptor levels. Increased rates of fatty acid oxidation inhibit glucose utilization by utilizing NAD, increasing the intracellular levels of acethyl-CoA, which is an inhibitor of pyruvate dehydrogenase, and of citrate, which inhibits phosphofructokinase. The accumulation of phosphorylated glucose leads eventually to the feedback inhibition of glucose transport into the cell (30,31).

Alternations in the molecular or functional integrity of the insulin receptor have been described in a few genetic disorders, and include impaired proreceptor processing (32), defective tyrosine kinase-dependent coupling (33), or decreased post-binding activation of glucose transporters (34).

As mentioned above, although specific factors affecting each of the step of insulin action are well documented, there is no unifying theory on how some or all of them may act during the development of insulin resistance. Experimental data supports the notion that insulin resistance can be produced by diet. But the possibility of a post-receptor alteration as a primary event cannot be ruled out. For example, inhibition of glucose uptake by high intracellular free fatty acid levels may lead to hyperglycemia, which would trigger an increased in insulin output. Sustained hyperinsulinemia could then exert a down-regulation of its receptor, leading to a vicious circle of decreased sensitivity to insulin relative to "normal" levels (35).

INSULIN RESISTANCE AND HYPERTENSION

Hypertension is a well recognized complication of obesity, and about 30% of hypertensive patients are obese, and these tend to have central fat distribution (36). Both hyperinsulinemia and upper-body fat distribution are risk factors for hypertension and other cardiovascular disease (37,38). But hyperinsulinemia and insulin resistance are also present in non-obese, non-diabetic hypertensive individuals, who display a similar pattern of impaired insulin-mediated glucose and fat metabolism as do the obese (39). This insulin resistance is not explained by sex, age, body mass index or waist:hip ratios (40), and is also present in several genetically hypertensive animal models, such as the SHR rat (41,42).

Several biological actions of insulin are related to blood pressure and cardiovascular functions (Table 1), some of them involving a close interaction with the sympathetic nervous system. For example, insulin-mediated glucose disposal can be normalized in hypertensive patients by 1-receptor blockade (44). In turn, insulin stimulates sympathetic nervous system activity (45), an action that appears to be preserved in insulin resistance states (46). Insulin also enhaces renal Na reabsorption (47), and by this mechanism may increase renal perfusion pressures. Studies in individuals with insulin resistance have found that there is a correlations between degree of resistance and capillary type and density (48), and between insulin levels and skeletal muscle blood flow (49). However, alterations in the vascular adrenergic tone may in fact precede and be a causal of impaired insulin action. Changes in capillary structure and tone, evolving independently of insulin, cause progresive decline in the response to insulin of target tissues, creating a vicious in which the increased insulin production leads to additional, insulin-dependent alterations in fluid volume and vascular tone (50).

ETHNIC DIFFERENCES IN INSULIN RESISTANCE

Although elevated insulin levels is an universal feature of obesity, the correlations between plasma insulin levels and hypertension or other manifestation of cardiovascular disease varies in different ethnic groups. other parameters associated with hyperinsulinemia, such as body fat distribution, also have variable degree of predictive value in populations with different genetic backgroupd. McKeige et al (51) found that, for a given waist:hip ratio, the risk of developing diabetes is significantly higher in hyperinsulinemic Asians than in White Europeans. Similarly the correlation between insulin-mediated glucose diposal and blood pressure is significant only in whites, but not in blacks or in pima Indians (52). Thus, the long-term consequences of insulin resistance and hyperinsulinemia are subjected to important genetic modulation.

The insulin resistance of uncomplicated obesity is in most cases reversible. Weigh reduction and careful diet monitoring are frequently sufficient to improve insulin sensitivity and reduce basal plasma insulin levels. Dietary supplementation with ω-3 fatty acid improved the diet-induced insulin resistance in rats (53),but its role in human insulin resistance remains to be explored. Physical activity has also a well establised role in improving insulin sensitivity (48,54-57).

TABLE 1
INSULIN ACTIONS ON BLOOD PRESSURE

VASOCONSTRICTION	VASODILATION
• Vascular Hypertrophy	• (-) NE -induced vasoconstriction
• (+) Sympathetic tone	• (+) Ca ATPase
• (+) Renal Na retention	• (+) Na/K ATPase
• (+) Na/k cotransport	
• (-) Vasodilator eicosanoids	

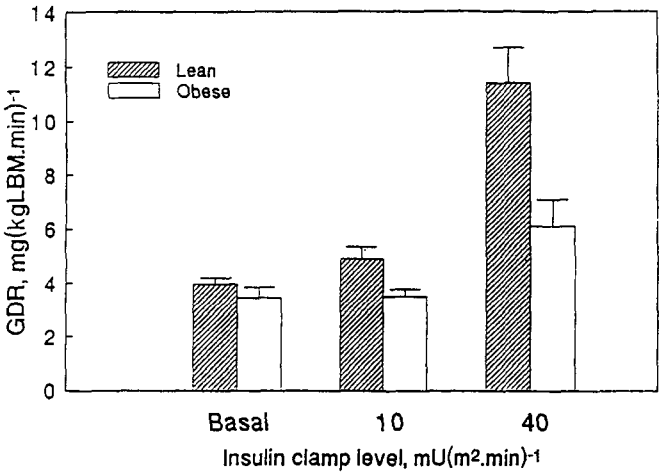

FIGURE 2

Glucose disposal rate in moderately obese and in lean controls, measured at two levels of euglycemic insulin infusion. Differences between lean controls and obese at 10 and 40 mU levels are statistically significant. Data from Caballero et al. (Ref. 18).

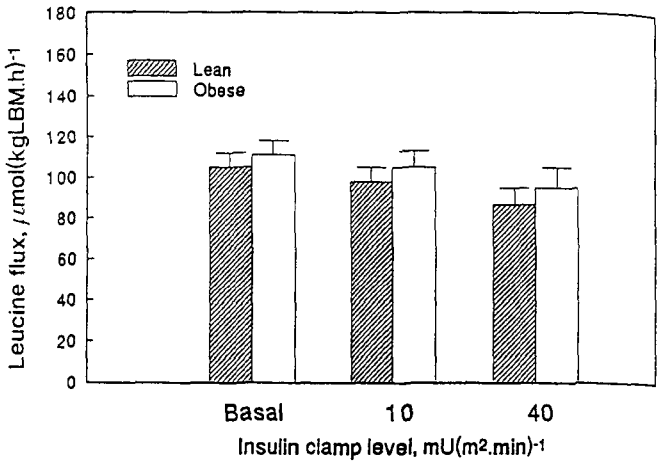

FIGURE 3

Plasma leucine flux during the same study described in Figure 2. No significant differences between obese and lean controls in basal or insulin-stimulated amino acid flux. Data from Caballero et al. (Ref. 18).

REFERENCES

1. Karam, J. H. G. M. Grodsky, and P. H. Forsham. Excessive insulin response to glucose in obese subjects measured by immunochemical assay. Diabetes 12:197-204, 1963.
2. Caballero, B., N. Finer, and R. J. Wurtman. Plasma amino acid and insulin levels in obesity: response to carbohydrate intake and tryptophan supplements. Metabolism 37:672-676, 1988.
3. Amiel, S. A., S. Caprio, R. S. Sherwin, G. Plewe, M. W. Haymond and W. V. Tamborlane. Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism.J. Clin. Endocrinol. Metab. 72:2:277-282, 1991.
4. Hauguel, S., M. Gilbert, and J. Girard. 1987. Pregnancy-induced insulin resistance in liver and skeletal muscle of the conscious rabbit. American Journal of Physiology 252:E165-E169, 1987.
5. Hornnès, P. J. On the decreased of glucose tolerance in pregnancy. A review. Diabetes Metab. 11:310-315, 1985.
6. Yki-Jarvinen, H., K. Sammalkorpi, V. A. Koivisto and E. A. Nikkila. 1989. Severity, duration and mechanisms of insulin resistance during acute infections. J. Clin. Endocrinol. Metab. 69:2:317-323, 1989.
7. Goldman. R. F. and E. R. Buskirk. A methods for underwater weighing and the determination of body density. In TEchniques for Measuring Body Composition. Brozek, J; Hershel, A. 78-79 1961.
8. Low, L., S. D. Chernausek and M. A. Sperling. Acromegaloid patients with type A insulin resistance: Parallel defects in insulin and insulin-like growth factor-I receptors and biological responses in cultured fibroblasts. J. Clin. Endocrinol. Metab. 69:2:329-337, 1989.
9. Caprio, S., S. Boulware, M. Daimond, R. S. Sherwin, T. O. Carpenter, K. Ruben, S. Amiel, M. Press and W. V. Tamborlane. Insulin resistance: An early metabolic defect of turner's syndrome. J. Clin. Endocrinol. Metab. 72:4:832-836, 1991.
10. Issaragrisil, S., S. Vannasaeng and A. Painkijagum. Glucose intolerance, hyperinsulinemia and insulin resistance in aplastic anemia. Metabolism 38:3:204-207, 1989.
11. DeFronzo, R. A., J. D. Tobin, and R. Andres. Glucose clamp technique: a method for quantifying insulin secretion and resistance. American Journal of Physiology 237:E214-E223, 1979.
12. DeFronzo, R. A. Insulin secretion, insulin resistance, and obesity. Intl. J. Obesity 6:73-82, 1982.
13. DeFronzo, R. A., A. Golay and J. P. Felber. Glucose and lipid metabolism in obesity and diabetes mellitus. In Substrate and Energy Metabolism in Man. J. S. Garrow and D. Halliday, editors. John Libbey, London. 70-81, 1985.
14. Berson, S. A and R. S. Yalow. Insulin "antagonism" and insulin resistance. In Diabetes Mellitus: Theory and Practice. M. Ellenberg and H. Rifkin, editors. McGraw-Hill, New York. 388-423, 1970.
15. Kahn, C. R. Insulin resistance, insulin sensitivity, and insulin unresponsiveness: a necesary distinction. Metabolism 27(S.A):1893-1902, 1978.
16. Kolterman, O. G., J. Insel, M. Saekow, and J. M. Olefky. Mechanisms of insulin resistance in human obesity. Evidence for receptor and postreceptor defects. Clin. Invest. 65:1272-1284, 1980.
17. DeFronzo, R. A. Obesity is associated with impaired insulin-mediated potassium uptake. Metabolism 37:105-108, 1988.

18. Caballero, B and R. J. Wurtman. Differential effects of insulin resistance on leucine and glucose kinetics in obesity. Metabolism 40:51-58, 1991.

19. Bevílacqua, S., R. Bonadonna, G. Buzzigoli, C. Boni, D. Ciociaro, F. Maccari, M. A. Giorico and E. Ferrannini. Acute elevation of free fatty acid leads to hepatic insulin resistance in obese subjects. Metabolism 36:502-506, 1987.

20. Hager, S. R., A. L. Jochen and R. K. Kalkhoff. Insulin resistance in normal rats infused with glucose for 72 h. American Journal of Physiology 260:E353-E362, 1991.

21. Wright, D. W., R. I. Hansen, C. E. Mondon and G. M. Reaven. Sucrose-induced resistance in the rat: modulation by exercise and diet. Am. J. Clin. Nutr. 38:879-883, 1983.

22. Rizza, R. A., L. J. Mandarino, J. Genest B. A. Baker and J. E. Gerich. Production of insulin resistance by hyperinsulinemia in man. Diabetologia 28:70-75, 1985.

23. Davidson, M. B., M. D. Harris and C. S. Rosenberg. Inverse relationship of metabolic clearance rate of insulin to body mass index. Metabolism 36:219-222, 1987.

24. Kolterman, O. G., G. M. Reaven and J. M. Olefsky. Relationship between in vivo insulin resistance and decreased insulin receptors in obese man. J. Clin. Endocrinol. Metab. 48:487-494, 1976.

25. Olefsky, J., V. C. Bacon and S. Baur. Insulin receptors of skeletal muscle: specific insulin binding sities and demostration of decreased number of sites in obese rats. Metabolism 25:179-191, 1976.

26. Olefsky, J. M. Decreased insulin binding to adipocytes and circulating monocytes in obesity. J. Clin. Invest. 57:1165-1172, 1976.

27. Takata, Y., M. Kobayashi, H.Maegawa, N. Watanabe, O. Ishibashi, Y Shigeta and A. Fujinami. A primary defect in insulin receptor in a young male patient with insulin resistance Metabolism 35:950-955, 1986.

28. Olefsky, J. M. Effects of fasting on insulin binding, glucose transport, and glucose oxidation in isolated rat adipocytes: relationships between insulin receptors and insulin action. J. Clin. Invest. 58:1450-1460, 1976.

29. Kahn, C. R. Membrane receptors for polypeptide hormones. In Methods in Membrane Biology, Vol. 3. E. D. Korn, editor. Plenum Press, New York. 81-146, 1975.

30. Randle, P. L., E. A. Newsholme and P. B. Garland. Regulation of glucose uptake by muscle. Effects of fatty acids, Ketone bodies and pyruvate, and of alloxan, diabetes and starvation on the uptake and metablic fate of glucose in rat heart and diaphragm muscles. Biochem. J. 93:652-665, 1964.

31. Randle, P. J., P. B. Garland, C. N. Hales, et. al. The glucose-fatty acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785-789, 1963.

32. Sasaoka, T., Y. Shigeta, Y. Takata, O. Ishibashi, M. Sugibayashi, A. Hisatomi and M. Kobayashi. Unprocessed insulin proreceptor in cultured fibroblasts from a patient with extreme insulin resistance. Metabolism 38:10:990-996, 1989.

33. Yamamoto, R., T. Shiva, K. Tobe, Y. Shibasaki, O. Koshio, T. Izumi, M. Odawara, Y. Mikami, N. Matsuura, Y. Akanuba, F. Takaku, and M. Kasuga. Defect in tyrosine kinase activity of the insulin receptor from a patient with insulin resistance and acanthosis nigricans. J. Clin. Endocrinol. Metab. 74:4:869-878, 1990.

34. Ciaraldi, T., O. Kolterman and J. Olefsky. Mechanism of the postreceptor defect in insulin action in human obesity Decrease in glucose transport system activity. J. Clin. Invest. 68:875-880, 1981.

35. Clark, M. G., S. Rattigan and D. G. Clark. Obesity with insulin resistance: experimental insights. Lancet 2:1236-1240, 1983.

36. Blair, D., J. P. Habicht, E. A. H. Sims; D. Sylwester and S. Abraham. Evidence for an increased risk for hypertension with centrally located body fat and the effect of race and sex on this risk. Am. J. Epidimiol. 119:536-540, 1984.

37. Haffner, S M., D. Fong, H. P. Hazuda, J. A. Pugh and J. K. Patterson. Hyperinsulinemia, upper body adiposity, and cardiovascular risk factors in non-diabetics. Metabolism 37:338-345, 1988.

38. Garcia-Webb, P. Insulin resistance -a risk factor for coronary heart dissease. Scand. J. Clin. Lab. Invest. 43:677-685, 1983.

39. Ferrannini,E., G. Buzzigoli, R. Bonadonna, M. A. Giorico, M. Oleggini, L. Graziadei, R. Pedrinelli and L. Brandi. Insulin resistance in essential hypertension. N. Engl. J. Med. 317:350-357, 1987.

40. Pollare, T., H. Lithell, and C. Berne. Insulin resistance is a characteristic feature of primary hypertension independent of obesity. Metabolism 39:2:167-174, 1990.

41. Mondon, C. E. and G. M. Reaven. Evidence of abnormalities of insulin metabolism in rats with spontaneous hypertension. Metabolism 37:303-305, 1988.

42. Hulman, S. B. Falkner and Y. Q. Chen. Insulin resistance in the spontaneously hypertensive rat. Metabolism 40:4:359-361, 1991.

43. Pollare, T., H. Lithell, I. Selinus and C. Berne. Application of prazosin is associated with an increase of insulin sensitivity in obese patients with hypertension. Diabetologia 31:415-420, 1988.

44. Attvall, S., B. M. Eriksson, J. Fowelin, H. Schenck, I. Langer and U. Smith. Early posthypoglycemic insulin resistance in man is mainly an effect of beta-adrenergic simulation. J. Clin. Invest. 80:437-442, 1987.

46. O'Hare, J. A., K. Minaker, J. B. Young, J. W. Rowe, J. A. Pallotta and L. Landsberg. Insulin increased plasma norepinephrine (NE) and lowers plasma potassium equally in lean and obese men. Clin. Res 33:441A abstract, 1985.

47. DeFronzo, R. A., C. R. Cooke, R. Andres, G. R. Faloona, and P. J. Davis. The effect of insulin on renal handling on sodium, potassium, calcium, and phosphate in man. J. Clin Invest. 55:845- 855, 1975.

48. Lillioja, S., A. A. Youg, C. L. Culter, J. L. Ivy, G. H. Abbott, J. K. Zawadzki, H. Yki-Jarvinen and L. e. t. a. l. Christin. Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. J. Clin. Invest. 80:415-424, 1987.

49. Laakso, M, S. V. Edelman, G. Brechtel and A. D. Baron. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. Clin. Invest. 85:1844-1852, 1990.

50. Egan B. M. Neurohumoral, hemodynamic and microvascular changes as mechanism of insulin resistance in hypertension: a provocative but partial picture. Intl. J. Obesity 15:133-139, 1991.

51. McKeigue, P. M., B. Shah and M. G. Marmot. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 337:382-386, 1991.

52. Saad, M. F.,S. Lillioja, B. L. Nyomba, C. Castillo, R. Ferraro, M. D. Gregorio, E. Ravussin, W. C. Knowler and C. Borgardus. Racial differences in the relation between blood pressure and insulin resistance. N. Engl. J. Med. 324:11:733-739, 1991.

53. Storlien, L. H., E. W. Kraegen, D. J. Chisholm, G. L. Ford, D. G. Bruce and W. S. Pascoe. Fish oil prevents insulin resistance induced by high-fat feeding in rats. Science 237:885-888, 1987.

54. Bjorntorp, P., K. deJounge, L. Sjostrom, and L. Sullivan. The effects of physical training on insulin production in obesity. Metabolism 19:631-638, 1970.

55. Holm, G., L. Sullivan, R. Jagenburg and P. Bjorntorp. Effects of physical training and lean body mass on plasma aminoacids in man. J. Appl. Physiol. 45:117-181, 1978.

56. Fahlen, M., J. Stenberg and P. Blorntorp. Insulin secretion in obesity after exercise. Diabetologia 8:141-144, 1972.

57. Mikines, K. J., B. Sonne, P. A. Farrel, B. Troiner, and H. Galbo. Effect of physical exercise on sensitivity and responsivenness to insulin in humans. American Journal of Physiology 254:E248-E25, 1988.