Obesity and Lifestyle-Related Diseases

Shuji Inoue, Toshimasa Osaka, Kazunori Sango, Yoshio Namba

Division of geriatric Health and Nutrition, National Institute of Health and Nutrition Tokyo, Japan

INTRODUCTION

Obesity is mainly caused by overeating and inactivity. In developed and developing countries, it is now recognized that the morbidity and mortality rate are increased in individuals classified as obese. It is believed that the higher morbidity and mortality rate of obese people are due to the increased incidence lifestyle-related diseases. Obesity is the most important risk factor for the incidences of lifestyle-related diseases. Among the lifestyle-related diseases associated with obesity, diabetes hypertension, hyperlipidemia, atherosclerosis and certain types of malignant cancers (uterine, breast, prostatic, colon and so on) are prominent. Factors which increase the morbidity rate of obese people include a degree of obesity and abnormal fat distribution, such as upper body obesity and visceral obesity. Recently, the definition of "pathological obesity" has been a matter of dispute.

1. Definition and Diagnosis of Obesity

Obesity is excessive fat accumulation, but not over-weightedness. The average human body usually consists of 82% lean body mass, which is essential for sustaining daily life and physical activities, and 18% body fat, which in essence is energy stored for emergency situations. Thus, obesity can be defined as "overstorage of body fat beyond 18%."

According to this definition, obesity should be diagnosed by measuring stored fat in the body. Although there are presently many methods to measure body fat, there are no methods for measuring body fat, easily, accurately and inexpensively.

Obesity is therefore determined based on three diagnostic methods: standard body weight, physique index and measurement of subcutaneous fat thickness. Standard body weight is most popular method applied throughout the world, however, standard body weight is determined differently in each country. Even in Japan, there are several scales of standard body weight, such as the slightly modified Broca scale and Matsuki scale[1], Minowa scale[2], the Japan Ministry of Public welfare scake[3], and the Meiji Life Insurance Company scale[4]. However, theses scales were not necessarily determined based on scientific evidence.

Under these circumstances, the Japan Society for the Study of Obesity (JASSO) decided to propose a standard body weight scale based on scientific evidence until the methods for measurement of genuine body fat will be established.

In Japan, it has been reported that the incidence of

Correspondence: Shuji Inoue
Department of Nutrition and Physiology, Kyoritsu Women's University

Table 1. Criteria for Obesity Based on Standard Body Weight (height 2 (m)×22) and Body Mass Index (BMI) in Japan (1992)

	relative body weight (%)	BMI
lean	<90	<20
normal	≥ 90～<110	≥20～<24
overweight	≥110～<120	≥24～<26.4
obesity	≥120	≥26.4

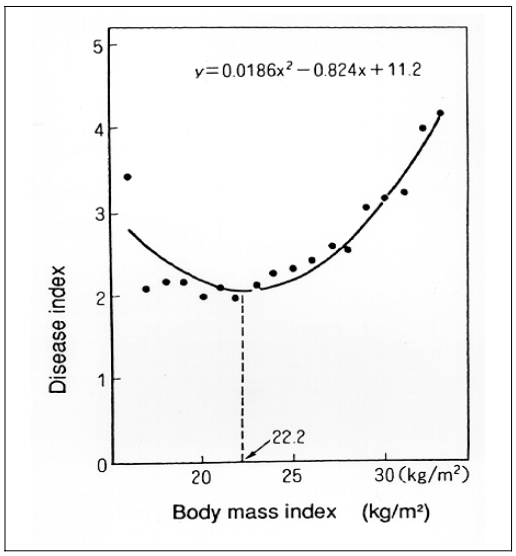


Fig. l. Relation between body mass index and morbidity in obesity.

obesity-related diseases is observed least frequently when the body mass index, one of the physique indices applied as an obesity marker, is about 22 (Fig. 1)[5]. Body mass index (BMI) is calculated by dividing body weight by the square of the height. The results of Tsukahara and Tamura[4] identify the BMI for ideal body weight, defined as "highest longevity expectance," at approximately 23.

Considering the viewpoint of quantity of life, the JASSO committee defined standard body weight as "a weight equivalent to the value of least incidence of the BMI morbidity rate (i.e., a BMI of 22), and recommended that standard body weight to be determined as multiplying the square of height by 22 (height2 (m) x 22).

The committee proposed the criteria for obesity using %overweight and BMI in 1992 Table l[6]. The value of 26.4 is equivalent to 20% above standard body weight. The criteria of obesity was determined on medical concept but not on medical evidence at that time.

2. Criteria of obesity and pathological obesity based on medical evidence in Japan

In 1997, WHO initiated the educational movement of International Obesity Task Force (IOTF) as assessed that obesity is serious health hazard in both developed and developing countries cooperated with International Association for the Study of Obesity (IASO), and proposed the criteria of overweight and obesity (Table 2).

In the same period, JASSO has studied on the relatonship between degree of obesity (BMI) and hypertension, diabetes, hyperlipidemia (triglycerides, HDL-cholesterol and total cholesterol) with the assistance of Japanese Ministry of Health and Welfare. Total one hundred fifty thousand men and women above 30 years old of age were recruited from 15 cohorts in Japan[7].

The results were as follows: when morbidity rate in BMI 22 was estimated as 1, odds ratio over 2 times over were BMI 25 in hypertension, hypertnglyceridemia and hypo-HDL-cholesterolemia,

Table 2. Comparison of Clasification of Obesity (1999)

BMI	JASSO	WHO
<18.5	Under weight	Under weight
18.5≦~<25	Normal weight	Normal weight
25≦~<30	Obesity (1○)	Preobese (Over weight)
30≦~<35	Obesity (2○)	Obesity (Ⅰ)
35≦~<40	Obesity (3○)	Obesity (Ⅱ)
40≦	Obesity (4○)	Obesity (Ⅲ)

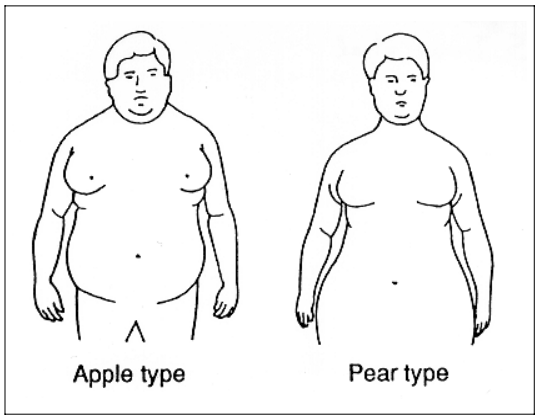


Fig. 2. Illustration of upper body (apple type) obesity and lower body (pear type) obesity.

BMI 29 in hypercholesterolemia, and BMI 27 in diabetes. If we consider BMI≧30 as obesity, we can not explain the rapidly increased incidence of these diseases in Japan since prevalence of obesity in this criteria is less than 3%.

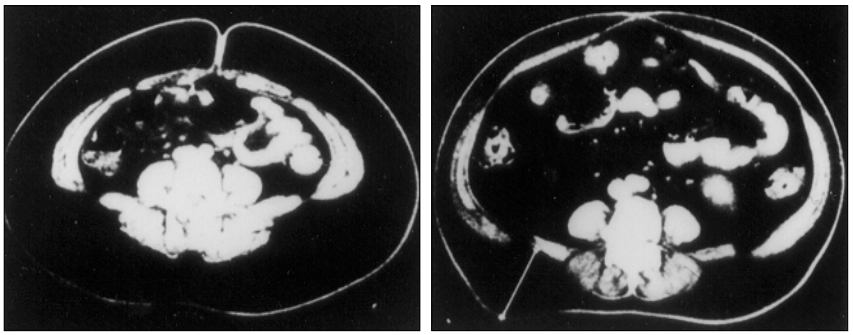
Taken togethert the JASSO committee decided to define BMI≧25 as obesity. the proposed criteria for obesity showed in comparison with WHO criteria (Table 2). This criteria has been also accepted to use the definition of obesity in the committee of Asia-Oceania region in LASO.

Next issue to be determined is how to differentiate pathological obesity from simple obesity. In addition to the degree of obesity, fat distribution is also an important factor for the incidence of obesity-related diseases. Obesity is classified into two typed by fat distribution: 1) upper body obesity, or abdominal obesity, in which fat mainly accumulates in the uppeer abdominal area (so-called "apple type obesity"); and 2) lower body obesity, in which fat mainly accumulates under the gluteal area (so-called "pear type obesity") (Fig. 2). The incidence of obesity-related diseases is more frequently associated with upper body obesity than lower body obesity[8]. Previously two types were presumed to be diffierentiated applying waist-hip ratio, but it has turned out that waist circumference is a more appropriate indicator. It has also been reported that upper body obesity can be classified into two types by abdominal computed tomographic (CT) scanning: 1) visceral fat obesity, in which fat mainly accumulates around the visceral organs in the abdominal cavity; and 2) subcutaneous fat obesity, in which fat mainly accumulated in the subcutaneous tissue of the abdominal wall as Shown in Fig. 3. Viscera fat obesity has proved to be of greater danger for the incidence of obesity-related diseases[9].

Under these circumstances, the JASSO committee proposed the criteria for pathological obesity shown in Table 2[10].

3. Prevalence and causes of obesity in Japan

We evaluated the prevalence of obesity according



a. Subcutaneous fat obesity b. Visceral fat obesity

Fig. 3. Illustration of visceral fat obesity (left) and subcutaneous fat obesity (right) by abdominal CT scanning.

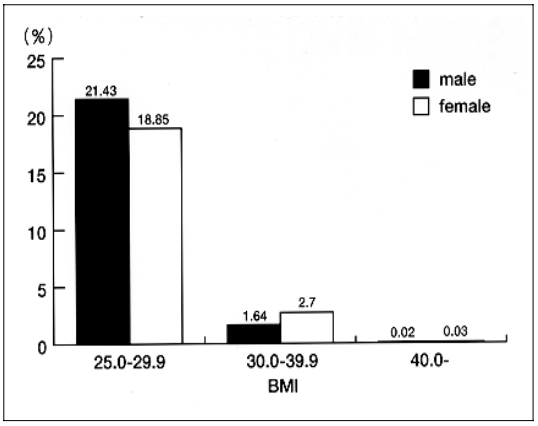


Fig. 4. Prevalence of obesity in Japan according to the criteria of JASSO and WHO.

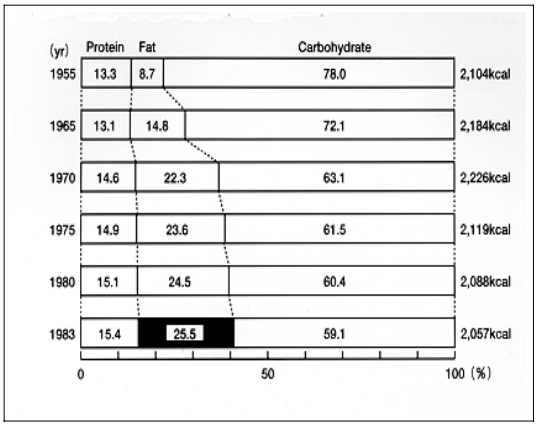


Fig. 5. Daily caloric intake and caloric content in Japan.

to the new criteria using the same population of the morbidity study as mentioned above. The prevalence of obesity in men and women were 21.43% and 18.85%, respectively, which leads to 20% of the average prevalence (Fig. 4). This implies that 1 out of 5 adult persons are obesity in Japan. These findings indicate that the degree of obesity is low, but obesity-related problems are similar to those in western societies in Japan.

What causes the increased prevalence obesity in Japan. Several causes of obesity have advanced: 1) overeating, 2) errors of eating pattern, 3) inactivity, 4) heredity, and 5) disturbance in thermogenesis. Hyperphagia and inactivity are two major risk factors for obesity. Hyperphagia may be an important factor in individuals, however, average energy intake in adult people in Japan has not been increased or rather declined (Fig. 5). During these periods, prevalence of obesity has increased 2 of 3 times higher. This indicate inactivity may be a main cause for the increased incidence of obesity in Japan. This figure also tel1s us the increased high fat

content in energy intake may also contribute to the increased incidence of obesity.

4. Obesity and Lifestyle-related Diseases

Until recently, the relation between obesity and lifestyle-related diseases has been recognized epidemiologically, however, the causal relationship has needed to be clanfied in the biochemical and physiologcal bases.

1) Obesity and Diabetes Mellitus

Obesity and type Ⅱ or non-insulin-dependent diabetes (NIDDM) frequently occur together. A number of studies have shown that obesity is a strong risk factor for the development of type Ⅱ diabetes. Two hypotheses have been promoted relating to the development of diabetes from obesity: 1) insulin resistance, and 2) insulin secretary deficiency. The insulin resistance theory implies that an obese individual maintains a sufficient capacity to secret insulin, however, the insulin activity required for glucose disposal is reduced, resulting in hyperglycemia. The insulin secretary deficiency theory implies that an obese individual cannot meet increased insulin requirements induced by obesity, which leads to a deficiency in insulin secretion and results in hyperglycemia.

We have obtained the results of a study that shows a three-step process in which obesity leads to diabetes. Rats suffering from ventromedial hypethalamic (VMH) obesity were fed with manipulation of high fat foodstuffs. The steps are as follows:

① Defect in receptor binding

We examined the plasma glucose and insulin responses to oral glucose load (l g/kg) as well as receptor binding of insulin in VMH obese rats fed a laboratory chow diet (low-fat diet) using erythrocytes and thymocytes, which in contrast to adipocytes do not increase in size. The glucose tolerance curve of the rats was impaired with hyperinsulinemia, but did not reach the level of diabetes. Insulin binding decreased compared to that of the control rats. A Scathard analysis revealed that insulin binding was decreased due to the reduction in the number of receptors, however, not by the reduction of affinity. This is a characteristic feature of insulin binding in all types of animal obesities, as well as a characteristic in human obesity[11].

② Defect in post-receptor binding

We examined the plasma glucose and insulin responses to oral glucose load (l g/kg) and the glucose transporter 4 (GLUT 4) gene expression and content in muscle and adipose tissue in VMH obese rats fed a high-fat diet. Fasting plasma glucose increased significantly in these rats, and the glucose tolerance curve was moderatedly impaired with marked hyperinsurinemia, resulting in the manifestation of diabetes. The gene expression and content of GLUT 4 were significantly lower, both in muscle and adipose tissues, The reduction was especially notable in the adipose tissue. It has been indicated that muscle tissue plays a major role, and adipose tissue plays a minor role on glucose utilization in obesity[12]. However, our results suggest that adipose tissue also plays an important role in glucose disposal in obese individuals. The results are consistent with the effects of thiazolidinedione, an insulin sensitizer agent[13].

③ Defect in insulin secretion

We examined the plasma glucose and insulin responses to oral glucose load (l g/kg) as well as GLUT 4 gene expression and content in muscle and adipose tissues in VMH obese rats fed a high-fat diet after being administered a small dose of streptozotocin (25 mg/kg) to reduce pancreatic β-cell reserve. Fasting plasma glucose was markedly elevated in these rats, and the glucose tolerance curve was markedly impaired with deficiency in insulin secretion, thus resulting in severe diabetes.

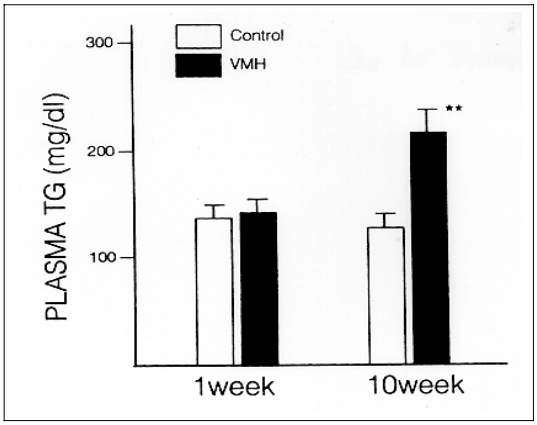


Fig. 6. Fasting plasma triglycenrides in rats 1week and 10weeks after ventromedial hypothalamic lesions *p<0,01 (permission of American Journal of Physiology)

The gene expression and content of GLUT 4 was also reduced both in muscle and adipose tissues.

We therefore explain the three-step process in diabetic manifestation related to obesity as follows: In the first step, when a defect in receptor binding is recognized, the phenomenon is overcome by stimulating the activity of spare receptors through increased insulin secretion. This maintains the glucose metabolism within normal or slightly impaired range. In the second step, when a defect in postreceptor binding together with a defect in receptor binding is recognized, the glucose metabolism is further impaired, resulting in diabetes even though insulin secretion is markedly increased. This phenomenon implied that insulin resistance in obese individuals leads to diabetes. In the third step, insulin secretion eventually decreases, resulting in sever diabetes with a deficiency in insulin secretion, if the pancreatic β-cell reserve is genetically or acquiredly disturbed. This implies that a deficiency in insulin secretion in obese individuals leads to diabetes. These results are consistent with the human-study results by Paulsen, et al[14].

2) Obesity and Hypertension

Hypertension is very often associated with obesity. Population studies show that a rise in blood pressure is associated with a increase in body weight[15]. The Framingham Study showed that an excess body weight only 20% over one's ideal body weight is associated with an eightfold increase in the incidence of hypertension later on[l6].

There are many factors presumed to cause hypertension in obese individuals. Recently, the focus has shifted to hyperinsulinemia, which is commonly observed in obese individuals. DeFronzo, et al.[17] demonstrated that insulin infusion decreased urinary sodium excretion, suggesting that insulin stimulates tubular sodium reabsorption and increases sodium retention, Insulin also reportedly stimulates sympathetic nervous activity, which results in vessel contraction[18]. However, it has been reported that hyperphagia, which is also commonly observed in obese individuals, may stimulate sympathetic nervous activity[19], leaving the results of insulin stimulation on the sympathetic nervous system a controversial matter. The role of hyperinsulinemia on hypertension in obese individuals must therefore be elucidated by further investigations. In fact, we observed normal levels of blood pressure in VMH obese rats, which shows sympathetic suppression after VMH lesions.

3) Obesity and Hyperlipidemia

Hyperlipidemia is also very often associated with obesity. According to a report by Carlson and Erickson[20], characteristic features of hyperlipidemia in obese individuals include an increase in triglycerides and an decrease in HDL-cholesterol in the serum. Seruma cholesterol may increase or remain normal.

We investigated the mechanism of hypertriglyceridemia utilizing obese rats with VMH lesions[21]. As shown in Fig. 6, the VMH lesioned

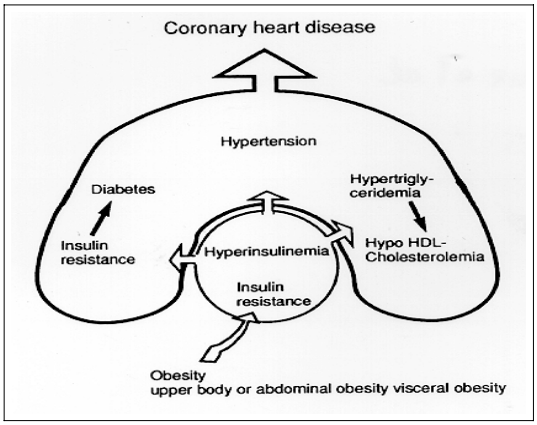


Fig. 7. Illustration of clustering syndrome for coronary heart disease.

rats showed hypertriglyceridemia only after obesity was established. We examined triglyceride production by measuring the triglyceride secretion rate, and triglyceride removal by measuring postheparin plasma-lipoprotein lipase activity. We observed that both parameters increased, probably due to hyperinsulinemia before and after the establishment of obesity in these rats. These results suggest a possible mechanism of hypertriglyceridemia in obese individuals: Prior to the establishment of obesity, adipose tissue adequately uptakes circulating triglyceride because the tissue has sufficient uptake capacity; hence, hypertriglycendemia dose not develop. After the establishment of obesity, the tissue cannot adequately uptake the circulating triglyceride because of capacity limitations. resulting in hypertriglycemia despite enhanced triglyceride secretion and increased LPL activity. The mechanism of hypertriglyceridemia in these rats is different from that of other obese animals, in which hypertriglyceridemia is the results of hypersecretion of triglycerides together with normal triglyceride removal[22] or hypersecretion of triglyceride and decreased removal[23]. Based on these results, we suggest that a heterogenerous mechanism of hypertgriglyceridemia exists in obese humans.

A reduced HDL-cholesterol level in the serum obese humans is presumed to be explained by the disturbed metaboric pathway of VLDL to HDL as a result of impaired lipoprotein lipase in the serum[24]. In this situation, lipoprotein lipase is presumed to become less sensitive to insulin stimulation since the majority of obese humans have hyperinsulinemia.

4) Obesity and Atherosclerosis

Among the many risk factors for coronary heart disease (CHD), diabetes (impaired glucose tolerance), hypertension and hyperlipidemia are presumed to be major risk factors. The increased incidence of CHD in obese individuals has been explained as an increasing number of major risk factors accumulating by chance. It is now also believed that there exists a clustering syndrome of major risk factors for CHD. Reaven is a proponent of Syndrome X″[25]. He suggests that the central feature of this clustering syndrome is insulin resistance. Insulin resistance results in diabetes; hyperinsulinemia associated with insulin resistance produces a large volume of blood, which results in hypertension; and hyperinsulinemia enhances hepatic lipid synthesis, resulting in hypertriglyceridemia followed by low HDL-cholesterol. All of these disorders cooperatively contribute to the development of CHD. Thereafter, Kaplan[26], Tokunaga and Matsuzawa, et al.[27] and DeFronzo, et al.[28] became proponents of ″Deadly Quartet″ ″Visceral Syndrome″ and ″Insulin Resistance Syndrome″ respectively. The main cause of these clustering syndromes is presumed to be obesity-induce insulin resistance associated with hyperinsulinemia (Fig. 7).

5) Obesity and Cancer

Recently, it has been found that certain types of cancer are more often associated with obesity such

as uterine, breast, prostrate and colon cancers. The principal estrogen formed in postmenopausal women is estrone, which is derived from the extraglandular aromatization of circulating androstenedione in adipose tissue. The results of in vivo studies indicate that the fractional conversion of androstenedione to estrone increases with obesity as well as aging[29,30]. The incidence of endometrial and breast cancers is also known to increase with obesity[31]. The estrogen produced in adipose tissue, is therefore believed to play an important role in the pathogenesis of endometrial and breast cancers, since endometrial and mammary gland cells have estrone receptors. However, a positive relation between obesity and these cancers has not been clearly observed in Japan. It may play some role that the degree of obesity is smaller in Japanese than in Caucasians.

We observed impaired immunity in obesity[32]. This may also contribute to an increase in the incidence of certain typed of cancer in obesity.

REFERANCES

1. Matsuki S: *Judgement of obesity. Nihon Ishikai Zashi, 68:916, 1972*
2. Minowa S: *Judgement of obesity. Koushueisei 46:520, 1980*
3. Japan Ministry of Public Welfare: *Tables and figures for judgement of obesity and leanness. Dai-ichi Pubhshing Co., Tokyo, 1986*
4. Tsukamoto H, Tamura M: *Physical constitution from a view of mortanity rate. Tables of Meiji Life Insurance Company's Standard Body Weight. Kosei no Shihyo 33:3, 1986*
5. Tokunaga K, et al: *Ideal body weight estimated from the body mass index with the lowest morbidity. Int J Obes 15:1-5, 1991*
6. Japan Society for the Study of Obesity: *Obesity-guideline for dialognosis, treatment and management. Ishiyaku publishuing Co, Tokyo 1993*
7. Yoshiike N, et al: *Relation between body mass index and risk for diabetes, hypertension, hyperlipidemia-A epidemiological study by multi-center cooperative study-. Himan kenkyu 6:4, 2000*
8. Kissebah AH, et al: *Relation of body fat distribution to metabolic complications of obesity. J Clin Endocri Metab 54:254, 1982*
9. Fujioka S, et al: *Contribution of intraabdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 36:54, 1987*
10. Matsuzawa Y, et al: *New criteria for obesity judgemant and diagnosis of pathological obesity. Himan kenkyu 6:18, 2000*
11. Olefsky JM, et al: *Insulin action and resistance in obesity and non insulindepandent type-Ⅱ diabetes mellitus. Am J Physiol 243:E-15, 1982*
12. Bjorntorp P, Sjostrom L: *Carbohydrate storage in man: speculations and some quantitative considerations. Metabolism 27:1853, 1978*
13. Okuno A. et al: *Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker fatty rats. J Clin Invest 101:1354, 1998*
14. Paulsan EP, et al: *Plasma glucose, free fatty acids and immunoreactive insulin in 66 obese children. Diabetes 17:261, 1968*
15. Chiang BN, et al: *Overweight and hypertension. Circulation 39:403, 1969*
16. Kannel WB, et al: *Left ventricular hypertrophy by electrocardiogram: prevalence, incidence mortality in the Framingham study. Ann Int Med 71:89, 1969*
17. Deflronzo M, et al: *The effect of insulin on renal handing of sodium, potassium, calcium and*

phosphate in man. J Clin Invest 55:845, 1975

18. Well S, et al: *Increased plasma norepinaphrine concentrations and metabolic rates following glucose ingestion in man. Acta Endocrinol 29:806, 1982*
19. Landsberg L, Young JB: *Fasting, feeding and sympathetic nervous system. New Eng J Med 298:1295, 1978*
20. Carlson LA, Erickson M: *Quanitative, qualitative and serum lipoprotein analysis in obesity. Atherosclerosis 21:417, 1975*
21. Inoue S, et al: *Determinants of fasting hypertriglyceridemia in ventromedial hypothalamic obesity in rats. Am J Physiol 265:786, 1993*
22. Russel JC, et al: *Plasma lipid secretion and clearance in hyperlipidemic JCR: LA-corpulent rats. Arteriosclerosis 9:869, 1989*
23. *Yamazaki Y, et al: JTT-50lT a new oral hypoglycemic agent, reverses hypertriglyceridemia in Zucker fatty and ventromedial hypothalamus-lesioned obese rats. Metabolism 49:574, 2000*
24. Tsutsumi K, et al: *The novel compound, NO-1886 increases lipoprotein lipase activity with resulting elevation of high-density lipoprotein cholesterol and long-term administration inhibits atherogenesis in the coronary arterries of rats with experimental atheroscierosis. J Clin Invest 92:411, 1993*
25. Reaven GM: *Role of insulin resistance in human disease. Diabetes 37:1595, 1988*
26. *Kaplan NM: The deadly quartet: upper body obesity, glucose intorerance, hypertriglyceridemia and hypertension. Arch Int Med 14:1514, 1989*
27. Tokunaga K, et al: *Visceral fat syndrome. Jap J Int Med 81:81, 1992*
28. DeFronzo RA, Ferrannini E: *Insulin resistance: a multifaced syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disesase. Diabetes Care 14:173, 1991*
29. Grotin JM, et al: *Source of estron production in postmenopausal women. Clin Endocri 36:207, 1973*
30. Edman CD, MacDonald PC: *Effect of obesity on conversion of plasma androstenedione to estrone in ovulatory and anovulatory young women. Am J Obstet Glynecol 130:456, 1978*
31. MacDonald PC, et al: *Effect of obesity of conversion of plasma androstenedione to estronein postmenopausal women with and without endometrial cancer. Am J Obstet Glynecol 130:448, 1978*
32. Tanaka S, et al: *Impaired immunity in obesity: suppressed but reversible limphocyte responsiveness. Int J Obes 17:631, 1993*