Obesity –"An excuse or a blame"

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ABSTRACT

On a global scale, obesity has reached epidemic proportions and is a major contributor to the global burden of chronic disease and disability. At the moment, more than one billion adults worldwide are overweight and at least 300 million of them are clinically obese. Obesity is a rising worldwide problem affecting both the developed countries as well as the developing nations. Obesity is common but complex and multifactorial disorder with higher heritability. Obesity results because of body fat accumulated over a time because of chronic energy imbalance that is calories consumed exceed calories expended. There are many genetic and environmental factors that influence this balance. Obesity is an important public health problem because it increases the risk of developing diabetes, hypertension, heart disease and some type of cancers. The present article reviews role of genes that are identified in causing obesity.

Key Words: Obesity, genes, environment, pathology

Introduction

Is it nature or nurture, genes or environment, Grandma's genes or Grandma's homemade pork-and-beans? Just what is it that makes some people overweight, while others can seemingly eat forever without gaining a pound? (1). Obesity is defined as an abnormal increase in body fat (though not necessarily in body weight) (2). Obesity is a global pandemic and a major health concern because of the consequent morbidity and premature mortality; obesity predisposes to serious morbidities such as type 2 diabetes, hypertension and coronary heart disease.

Industrialisation and modernisation is rightly blamed for the increasing obesity prevalence all over the world, as it created an "obesogenic" environment with caloric abundance and ubiquitous automation which encouraged sedentary lifestyles, (3,4) resulting in energy intake and expenditure imbalance and favours the net deposition of calories as fat. Although this trend of increasing body girth is very much driven by the "obesogenic" environment, it is facilitated by the individual's genetic susceptibility to excessive weight gain (5). Obesity is a common but complex, multifactorial disorder with high heritability. While it is well established that obesity runs in families, the familial clustering is not just due to a common lifestyle and shared environment (6).

Classification of obesity

The body mass index (BMI), also known as the Quetelet index, is used far more commonly than body fat percentage to define obesity. BMI is closely correlated with the degree of body fat in most settings. $BMI = weight/height^2$, where, weight is in kilograms and height is in meters (7). The most commonly used definitions, established by the World Health Organization (WHO) in 1997 and published in 2000, provided the values listed in the table 1 (8).

Table 1. Classification of Obesity (8)

BMI	Classification
< 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.9	Class I obesity
35.0–39.9	Class II obesity
≥ 40.0	Class III obesity

[*]BMI=Body Mass Index

Pathophysiology of obesity

A complex feedback control system consisting of a central processing unit which receives afferent signals and generates appropriate efferent stimuli in response controls food intake, satiety and

subsequently weight. Age and gender differences in food intake have been identified with an increase in adolescence, peaking in the second decade after which it declines (9). Gastric distension via activation of vagal afferents is a signal for satiety, with gastric contractions signalling for hunger. Nutrients, neural impulses and hormones themselves act as afferent signals in the regulation of energy intake and expenditure. Nutrient absorption, e.g. which of glucose initiates a sensation of satiety whereas a fall in glucose promotes hunger. This effect is itself mediated by different neurotransmitters, hormones and peptides (10).

Leptin is a peptide produced by adipocytes which has been closely correlated with fat mass, with secretion increasing as fat deposition increases (11). It acts to reduce food intake and is believed to increase sympathetic nervous system activity (12). This peptide has found use in a small number of individuals who have been shown to be deficient in the leptin gene. Another important peptide is Growth Hormone (GH) relin which is secreted by the stomach and duodenum and has been shown to stimulate GH secretion. It is an endogenous ligand for the GH receptor. GH relin increases food intake and its secretion is in turn suppressed by food intake (13, 14, 15). Serum concentrations increase in anticipation of a meal. Its secretion has been shown to increase after diet- and exercise-induced weight loss and is believed to be one of the reasons why lifestyle modification does not lead to permanent weight loss. Other peptides that have been shown to reduce food intake are cholecystokinin (CCK) (16), enterostatin (17) and polypeptide Y 3-36 (18). The list of peptides is ever on the increase but the precise interaction between them and their relevance in humans awaits the outcome of further research. Afferent impulses proceed centrally to the hindbrain and the hypothalamus for integration and processing. A number of specific anatomical sites have been implicated as a result of *in vivo* studies generally involving destruction of the said area and observation of outcomes (19).

According to Josanne (2007), (20) the nucleus of the tractus solitarius in the hindbrain is the site where vagal and other neural input is integrated. The arcuatenuceus at the base of the hypothalamus receives signals from leptin and in turn increases both production and secretion of neuropeptide Y (NPY) and Agouti-related peptide (AgRP) thereby increasing food intake. On the other hand, cocaine-amphetamine-related transcript (CART) and pro opiomelanocortin (POMC) decrease food intake. The paraventricular nucleus of the hypothalamus is itself stimulated by peptides from arcuate nucleus and relays signals further. Destruction of the ventromedial hypothalamus has been shown to lead to increased food intake and subsequently obesity in animals treated experimentally. The lateral hypothalamic nucleus in turn exerts opposite effects such as decreased feeding and lowering body weight. Furthermore specific areas of the amygdala can affect feeding partially through the ventromedial hypothalamus (20).

Amongst the hormones that interact at the efferent end of the regulatory system, glucocorticoids are believed to play an important permissive role these effects possibly mediated via the sympathetic nervous system. For example, it has been noted that leptin deficiency does not result in obesity in the absence of glucocorticoids (21).

Genetics of obesity

In the past, people have often thought of obesity as a disease that is caused by too much food, too little exercise, and no self-control. Although this may be true in some cases, obesity is a multi-factorial disease; environmental and genetic factors interact resulting in a disorder of energy balance. Genes are activated by a person's environment, in other words "genetics loads the gun, but environment pulls the trigger" (22). Knowledge about the role genetics plays in bodyweight is still limited, but it is known that obesity has a polygenetic cause; there is not one specific "obesity gene." In fact, more than 250 genes have been found that relate to some cause of human obesity. These genes have been linked to variable biological functions that are related to fat store in adipocytes. Some have relation to food intake and others have to do with energy expenditure. There are certain genes that are linked to lipid and glucose metabolism and others have a role in adipose tissue development (23).

One of the earliest theories connecting genetics and obesity was proposed by James in 1962. His thrifty gene hypothesis aimed to explain the tendency of various ethnic groups towards obesity and diabetes (24). In essence, the theory proposes that our ancestors possessed a gene (or set of genes) that allowed them to increase rates of fat storage in times of prosperity so that they could store energy during times of famine and therefore would not starve. Additionally, he proposed that

this gene is still active in humans, conversely does not serve to advantage in current times because we rarely experience times of extreme famine (25). Instead, the thrifty gene continues to allow storing excess amounts of fat which, paired with a lower activity level, leads to obesity and other chronic diseases.

Obesity can be either monogenic or polygenic in inheritance. Five single gene defects have been identified;

Agouti gene: The protein binds to melanocortin-4 receptor in the hypothalamus thereby modulating food intake. Concentrations have been found to be higher in obese than non-obese men and correlate well with basal metabolic index (BMI) (26). A related gene which has been identified is the mahogany gene (27).

Leptin gene: Leptin is produced in fat cells, gut, and placenta, which signals the brain about the amount of stored fat (28, 29). Deficient mice have hyperphagia, insulin resistance and infertility. In humans leptin may act on the arcuate nucleus to decrease neuropeptide Y (NPY) production which usually stimulates food intake. Obesity due to leptin deficiency has been reported in two families, affected subjects responding well to leptin therapy (30, 31). In contrast the majority of obese subjects have a high level of circulating leptin level suggesting a level of leptin resistance (32).

Leptin receptor gene: Leptin receptor deficiency secondary to mutations in the leptin receptor gene has been reported in humans (33).

Melanocortin-428 (34) and melanocortin-3 receptor gene defects (35): Transgenic mice with mutations in these genes exhibit hyperphagia and severe obesity. Observations in these mice suggest that receptors for MSH normally inhibit food intake and fat accumulation.

Serotonin: Subtype receptor elimination in transgenic mice results in similar manifestations (36).

The heritability of weight, metabolic rate, thermic responses to food and spontaneous physical activity has been studied in families which included twins or adoptees. Twins separated at birth maintained the same characteristics regarding weight control despite different environmental backgrounds. Similarly studies in adopted children showed that regulation of weight and body composition was similar to that of biological parents and differed from that of the adoptive parents (37).

Numbers of variant genes associated with obesity have been reported (Table 2). Leptin is an adipocyte-derived hormone that is essential for normal body weight regulation. Its main physiological role may be to coordinate the metabolic, endocrine and behavioural responses to starvation. Leptin is taken up into the central nervous system (CNS) by a saturable transport mechanism and binds to the long form of the leptin receptor (Ob Rb), which is principally located in the arcuate nucleus of the hypothalamus (39). Within the arcuate nucleus, leptin is able to directly inhibit the expression of NPY and Agouti-related peptide (AGRP), peptides that increase food intake and decrease energy expenditure (40, 41). In contrast, expression of peptides that decrease food intake, such as cocaine and amphetamine regulated transcript (CART) and pro-opiomelanocortin (POMC) are increased (42).

Table 2. Selected genes with variants that have been associated with obesity (38)

Gene symbol	Gene name	Gene product's role in energy balance
LEP	Leptin	Produced by fat cells
LEPR	Leptin receptor	When bound by leptin, inhibits appetite
INS	Insulin	Produced by pancreas
INSR	Insulin receptor	Induces uptake and storage of glucose
GHRL	Ghrelin	Produced by stomach
GHSR	Growth hormone secretagogue receptor	When bound by Ghrelin, stimulates appetite
MC4R	Melanocortin 4 receptor	When bound by alpha-melanocyte stimulating hormone, stimulates appetite
FTO	Fat mass- and obesity-associated gene	Promotes food intake
PPARG	Peroxisome proliferator-activated receptor gamma	Stimulates lipid uptake and development of fat tissue
ADIPOQ	Adipocyte-, C1q-, and collagen domain-containing	Produced by fat cells, adiponectin promotes energy expenditure

*C1q = complement component 1, q subcomponent, A chain

Pathologies associated with obesity

In addition to mechanically affecting the body, i.e. by exacerbating osteoarthritis and back pain (43,44) because of extra weight placed on a skeleton, obesity is associated with higher incidence of several severe pathologies.

Diabetes mellitus: Accumulated data demonstrate the association between obesity, non insulin dependent diabetes mellitus-the most common primary form of diabetes-and impaired glucose tolerance (45). In obese individuals, the adipose tissue releases high amount of non esterified fatty acids, glycerol, pro-inflammatory cytokines, and hormones that are linked with the development of insulin resistance. Insulin resistance generates compensatory hyperinsulinemia, with over stimulation of pancreatic ß-cells and reduction of insulin receptors (46).

Hypertension: Insulin in excess alters Na+ and Ca++ retention rates, in turn altering vascular reactivity and increase in cardiac output and peripheral resistance, which are the main components of blood pressure regulators. Epidemiological studies have demonstrated that between 65-75% of the risk for hypertension is accounted for by obesity (47, 48). Recently, endocrinological studies of adipose tissue revealed tight links between obesity and hypertension, likely consequent to the facts that the adipose tissue secretes bioactive molecules and immunomodulators (49,50). Out of these, leptin is endowed with significant pleiotropic actions on several organic systems (51,52). In chronic hyperlipidemia and in obesity, (53) saw the development of hypertension, and renal, vascular, and cardiac damage.

Dislipidemia: Obesity is the most common cause of Dislipidemia. Lipid over supply in a state of obesity, hyperinsulinemia, and/or insulin resistance results in increased non esterified fatty acid availability and, in turn, higher Triglycerides (TG) stores (54,55) in non adipose tissues, e.g. muscle, liver, pancreas. Fatty acid metabolites also accumulate and cause activation of signal transduction pathways that further induce inflammation and impair insulin secretion. Frequently, these fatty acid induced disorders are referred to as "lipotoxicity". Thus evaluated TG level is often accompanied by a slight increase in total cholesterol and a marked drop in high density lipoprotein (HDL) cholesterol. Moreover low density lipoprotein (LDL) rich in TG partially metabolised by hepatic lipase, are converted into small LDL, with higher atherogenic potential (56,57). This may be due to a higher prevalence of hypertension and pro-inflamatory/prothrombotic states associated with adipose tissue accumulation.

Cardiac alterations: In general, obesity is an imperative determinant of cardiovascular diseases (CVD) (58,59) and increases the risk for heart failure, sudden cardiac death and angina or chest pain, and abnormal heart rhythm. All the heart failure is the most common cause of death in obese people; cardiomayopathy and sudden cardiac death also increase in healthy obese patients (60). In the Framingham heart study (61), the annual sudden cardiac death rate was nearly 40 times higher in obese people than in non obese population patients (60).

Metabolic Syndrome: Obesity is regarded as the major component of metabolic syndrome (62). This syndrome is characterized by co-occurrence of multiple metabolic disorders, namely overall and abdominal obesity, insulin resistance, hypertension, hyperglycemia, impaired glucose tolerance, and the combination of low HDL cholesterol and elevated TG level (63). The metabolic syndrome is also characterised by prothrombotic and proinflammatory states (64).

Lung diseases: Obesity is allied with an increased risk for chronic respiratory disorders, including chronic obstructive pulmonary disease, asthma, hypoventilation syndrome, and sleep apnea. In view of that, weight loss often leads to symptomatic improvement (65, 66). Respiratory disorders contribute to increased risk of hypertension, dysrhythmias, heart failure, stroke, myocardial infarction, and increased inflammation (67) hence, weight loss programs are mandatory in obese lung patients.

Cancer: In contrast with cardiovascular disease and diabetes, obesity is less often indicated as a risk factor for many cancers. Even so the international agency for research on cancer classified the evidence of a causal link as sufficient for cancers of breast, endometrial, colon, kidney, prostate, gall bladder and esophagus although the biological mechanisms that explain this link are not known for any of these cancers (68). The link between diet, obesity, and cancer is still not completely understood but the rising worldwide trend in obesity and cancer might be- at least in part- causal. Undeniably, overeating may be the largest avoidable cause of cancer in non smokers. While the putative cause of this obesity related cancer has been primarily ascribed to excess estrogen production by adipose tissue, inflammation due to adipocytokines secreted by

adipocytes, infiltrating macrophages or associated stromal cells might also play an important role (69). Higher adipocytokines (leptin, hepatocyte growth factor, adiponectin) levels can negatively affect cell proliferation, apoptosis, invasive growth, and angiogenesis. Obesity is associated with increased tumorigenesis that might explain the greater prevalence of neoplasis in obese individuals, who also have higher concentrations of inflammatory tumor growth factors (70).

Neurological Disorders: Psychological damage caused by overweight and obesity carries a large health burden (71). This disorder can range from lowered self esteem to frank clinical depression. Certainly, rates of anxiety and depression are 3 to 4 times higher among obese individual (72). Obesity significantly increases the risk of contracting Alzheimer's disease. A strong correlation exist between BMI and high level of ß amyloid, i.e. the protein that accumulates in Alzheimer's brain, destroying nerve cells and producing cognitive and behavioural problems. While the precise nature of association remains obscure, physiological changes, obesity may promote Alzheimer disease and dementia (73, 74). As an example, the FTO gene has a small but relevant effect on BMI and increases the risk for diabetes (75).

Present to Future phase

According to Nicole (2009), Research on the genetic components of obesity is extremely important. The more is known about the causes for this chronic disease the more efficiently it can be worked to prevent it. Although obesity has both genetic and environmental influences, it is believed that environment activates (or deactivates) certain genes. If these genes can be identified, then it will be able to avoid environmental influences which may cause them to be expressed. In the future when people are able to know for certain that they have a genetic predisposition for obesity, not only that it seems to run in their family, they will be able to have an individualized plan in order to maintain a healthy weight. Recognizing a genetic inclination is the first step in preventing a phenotypic expression of obesity. Genes are not our destiny. They may predispose for certain conditions or phenotypes, but in the case of obesity especially they are not the end-all-be-all. Obesity is a multi-factorial disease which is not caused by nature or nurture, but rather an interaction of the two. This means

that even if it is in DNA to be obese there are ways to avoid it with the use of diet and exercise.

Many researchers and doctors alike are excited about the identification of obesity influencing genes because it will allow them to develop new medications and supplements to promote weight loss; however this is not the healthiest approach to take. Instead, health professionals should use the knowledge of a patient's genetic predispositions in order to recommend effective dietary and lifestyle changes. Certain conditions or genes influence how an individual's body will respond to the food that they consume, so in knowing a patient's genetic makeup a health professional would be able to better advise them on what to avoid or what to focus on. The link between genetics and obesity should not be used as an excuse or as somewhere to put the blame, but rather as an opportunity for healthy approaches towards prevention as well as treatment (76).

References

1. Quinn P. Stein, MS, CGC; Amelia R. Mroch, MS, CGC; Kristen L De Berg, MS; Jason D. Flanagan, MS, CGC. The Influential Role of Genes in Obesity 2011.
2. Deurenberg P, Weststrate JA, Seidell JC. Body mass index as a measure of body fatness: age-and sex-specific prediction formulas. Br J Nutrition 1991; 65: 105-114.
3. French SA, Story M, Jeffery RW. Environmental influences on eating and physical activity. Annu Rev Public Health 2001; 22: 309-335.
4. Bell CG, Walley AJ, Froguel P. The genetics of human obesity. Nat Rev Genet 2005; 6: 221-234.
5. Bouchard C. Current understanding of the etiology of obesity: genetic and nongenetic factors. Am J Clin Nutr 1991; 53: 1561-1565.
6. Allison DB, Faith MS, Nathan JS. Risch's lambda values for human obesity. Int J Obes Relat Metab Disord 1996; 20: 990-999.
7. Gallagher D, Heymsfield SB, Heo M, et al. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 2000; 72: 694-701.
8. WHO 2000 p.9 http://en.wikipedia.org/wiki/Classification_of_obesity#cite_note-13)
9. Bray GA. Contemporary diagnosis and management of obesity. Handbooks in Health Care Co, Newtown, PA 1998.
10. Campfield, LA, Brandon P, Smith FJ. On-line continuous measurement of blood glucose and meal pattern in free-feeding rats; the role of

glucose in meal initiation. Brain Res Bull 1985; 14: 605.

11. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normalweight and obese humans. N Engl J Med 1996; 344: 292.

12. Bray GA, York DA. Leptin and clinical medicine: a new piece in the puzzle of obesity. J Clin Endocrinol Metab 1997; 82: 2771.

13. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002; 346: 1623.

14. Wren AM, Seal LJ, Cohen MA, et al. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab 2001; 86: 5992.

15. Druce MR, Wren AM, Park AJ, et al. Ghrelin increases food intake in obese as well as lean subjects. Int J Obes Relat Metab Disord 2005; 29: 1130.

16. Barrachina MD, Martinez V, Wang L, et al. Synergistic interaction between leptin and cholecystokinin to reduce short-term food intake in lean mice. Proc Natl Acad Sci USA 1997; 94: 10455.

17. Erlanson-Albertsson C, York D. Enterostatin a peptide regulating fat intake. Obes Res 1997; 5: 360.

18. Batterham RL, Cohen MA, Ellis SM, et al. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med 2003; 349: 941.

19. Berthoud HR. Multiple neural systems controlling food intake and body weight. Neurosci Biobehav Rev 2002; 26: 393.

20. Vassallo J, Pathogenesis of obesity. Journal of the Malta College of Pharmacy Practice 2007.

21. Tataranni PA, Young JB, Bogardus C, Ravussin E. A low sympathoadrenal activity is associated with body weight gain and development of central adiposity in Pima Indian men. Obes Res 1997; 5: 341.

22. Kelly Evelyn KB. Obesity. Wesport, Connecticut: Greenwood Press (2006).

23. Al Rubeaan K. New candidate obesity genes. In K. Keller (Ed.), Encyclopedia of obesity. Thousand Oaks, CA: SAGE Publications, (2008) pp. 496-497.

24. Neel JV. Diabetes mellitus: a „thrifty" genotype rendered detrimental by "progress". Am J Hum Genet 1962; 14: 353-362.

25. Harsch I. (ed.). The various types and treatments for obesity. New York: Nova Science Publishers (2006).

26. Katsuki A, Sumida Y, Gabazza EC, et al. Plasma levels of agouti-related protein are increased in obese men. J Clin Endocrinol Metab 2001; 86: 1921.

27. Nagle DL, McGrail SH, Vitale J, et al. The mahogany protein is a receptor involved in suppression of obesity. Nature 1999; 398: 148.

28. Zhang YY, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homolog. Nature 1994; 372: 425.

29. Campfield LA, Smith FJ, Burn P. The OB protein (leptin) pathway a link between adipose tissue mass and central neural networks. Horm Metab Res 1996; 28: 619.

30. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997; 387: 903.

31. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999; 341: 879.

32. Considine RV, Considine EL, Williams CJ, et al. Evidence against either a premature stop codon or the absence of obese gene mRNA in human obesity. J Clin Invest 1995; 95: 2986.

33. Clement K, Vaisse C, Lahlou N, et al. A mutation in the leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998; 392: 398.

34. Huszar D, Lynch CA, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell 1997; 88: 131.

35. Chen AS, Marsh DJ, Trumbauer ME, et al. Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass. Nat Genet 2000; 26: 97.

36. Lucas JJ, Yamamoto A, Scearce-Levie K, et al. Absence of fenfluramine-induced anorexia and reduced c-fos induction in the hypothalamus and central amygdaloid complex of serotonin 1B receptor knock-out mice. J Neurosci 1998; 18: 5537.

37. Stunkard AJ, Harris JR, Pedersen NL, McLearn GE. The body-mass index of twins who have been reared apart. N Engl J Med 1990; 322: 1483.

38. Centers for Disease Control and Prevention CDC 24/7: Saving Lives Protecting People.™ Genomics and Health http://www.cdc.gov/genomics/resources/diseases/obesity/obesedit.htm

39. Banks WA, Kastin AJ, Huang WT, Jaspan JB, Maness LM. Leptin enters the brain by a saturable system independent of insulin. Peptides 1996; 17: 305-311.

40. Wang Q, Bing C, Al-Barazanji K, et al. Interactions between leptin and hypothalamic neuropeptide Y neurons in the control of food intake and energy homeostasis in the rat. Diabetes 1997; 46: 335-341.

41. Claycombe KJ, Xue BZ, Mynatt RL, Zemel MB, Moustaid-Moussa N. Regulation of leptin by agouti. Physiol Genomics 2000; 2: 101-105.

42. Cowley MA, Smart JL, Rubinstein M, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature 2001; 411: 480-484.

43. Roffey DM, Ashdown LC, Dornan HD, et al. Pilot evaluation of multidisciplinary,medically supervised,non surgrical weight loss programme on the severity of low back pain in obese adults. Spine J 2011; 11: 197-204.

44. Jiang L, Rong J, Wang Y, et al. The relationship between body mass index and hip osteoarthritis: A systematic review and meta analysis. Joint bone spine 2011; 78: 150-155.

45. Malnick SD, Knobler H. The medical complications of obesity. QJM 2006; 99: 565-579.

46. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: Pathogenesis and treatment. Lancet 2008; 371: 2153-2156.

47. Wofford MR, Hall JE. Pathophysiology and treatment of obesity hypertension. Currpharm Des 2004; 10: 3621-2637.

48. Alpert ME. Obesity cardiomayopathy: Pathophysiology and evolution of clinical syndrome. Am J Med Sci 2001; 321: 225-236.

49. Hajer GR, van Haften TW, Visseren FLJ. Adipose tissue dysfunction in obesity, diabetes and vascular disease. Eur Heart J 2008; 29: 2959-2971.

50. Hatley L, Pris JB. Fat as an endocrine organ: relationship to the metabolic syndrome Am J Med Sci 2005; 330: 280-289.

51. Sharma V, McNeill JH. The emerging roles of leptin and Ghrelin in cardiovascular physiology and pathophysiology. Curr Vasc Pharmacol 2005; 3: 169-180.

52. Guha PK, Villarreal D, Reams GP, Freeman RH. Role of leptin in regulation of body fluid volume and pressure. Am J Ther 2003; 10: 211-218.

53. Kshatriya S, Liu K, Salah A, et al. Obesity hypetension: the regulatory role of leptin. Int J Hypertens 2011.

54. Boden G, Lebed B, Schatz M, Homko C, Lemieux S. Effects of acute changes of plasma free fatty acid on intramyocellular fat content and insulin resistance in healthy subjects. Diabetes 2001; 50: 1612-1617.

55. Marchesini G, Brizi M, Bianchi G, et al. Noon alcoholic fatty liver disease: A feature of the metabolic syndrome. Diabetes 2001; 50: 1844-1850.

56. Ravussin E, Smith SR. Increased fat intake, impaired fat oxidation, and failure of fat cell proliferation result in ectopic fat storage, insukin resistance, Type 2 diabetes mellitus. Ann N Y Acad Sci 2002; 967: 363-378.

57. Schaffer JE. Lipotoxicity when tissue over eat. Curr Opin Lipidol 2003; 14: 281-287.

58. Marinou K, Tousoulis D, Antonopoulos AS, Stefanadi E, Stefanadis C. Obesity and cardiovascular disease: from pathophysiology to risk stratification. Int J Cardiol 2010; 1: 76-88.

59. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss J Am College Cardiol 2009; 53: 1925-1932.

60. Messereli FH, Nunez BD, Ventura HO, Snyder DW. Over weight and sudden death: increased ventricular ectopy in cardiomayopathy of obesity. Arch Intern Med 1987; 147: 1725-1728.

61. Kannel WB, Plehn JF, Cupples LA. Cardiac failure and sudden death in the framinghan study. Am Heart J 1988; 115: 869-875.

62. Reaven GM. The metabolic syndrome: time to get off the merry-go-round? J Intern Med 2011; 269: 127-136.

63. Visioli F. Metabolic syndrome: When nutrition helps pharma. Eur J Pharmacol 2011; 668: 5.

64. Bethesda MD. Third report of National cholesterol education programme (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatmen panel III). Ntional institutes of health; 2002.

65. Piper AJ. Obesity hypoventilation syndrome – the big and the breathless. Sleep Med Rev 2011; 15: 79-89.

66. Poulain M, Doucet M, Major GC, et al. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. CMAJ 2006; 174: 1293-1299.

67. Kuo LC, Polson AM, Kang T. Associations between periodontal diseases and systemic diseases: a review of the inter-relationships and interactions with diabetes, respiratory diseases, cardiovascular diseases and osteoporosis. Public Health 2008; 122: 417-433.

68. World Health Report. Reducing risks,promoting healthy life; 2002.

69. Vona-Davis L, Rose DP. Adipokines as endocrine, paracrine, and autocrine factors in breast cancerrisk and progression. Endocr Relat Cancer 2007; 14: 189-206.

70. Cottam D, Fisher D, Ziemba A, et al. Tumor growth factor expression in obesity and changes in expression with weight loss: another cause of increased virulence and incidents of cancer in obesity. Surg Obes Relat Dis 2010; 6: 538-541.

71. Xu Q, Anderson D, Lurie-Beck J. The relationship between abdominal obesity and depression in the general population; systematic review and meta analysis. Obes Res Clin Pract 2011; 5: 267-278.

72. International Obesity Task Force (IOTF) http://www.iotf.org/.

73. Profenno LA, Porsteinsson AP, Faraone SV. Meta analysis of alzhimers's disease risk with obesity, diabetes, and related disorders. Biol Psychiatry 2011; 67: 505-512.

74. Mazza M, Marano G, Traversi G, Briap, Mazza S. Primary cerebral blood flow deficiency and alzhi,er;s disease: shadows and lights. J Alzhimer Dis 2011; 23: 375-389.

75. Kellen L, Xu W, Wang HX, Winbald B, Fratiglioni L, Graff C. The obesity related gene, FTO, interacts with APOE, and is associated with alzhimer's disease risk: a prospective cohort study. J Alzhimer Dis 2011; 23: 461-469.

76. Nicole Lopes, "Current Connections between Genetics and Obesity" (April 7, 2009). Undergraduate Library Research Award. Paper 2. http://digitalcommons.lmu.edu/ulra/awards/2009/2