Review Article

The Chronic Inflammatory Hypothesis for the Morbidity Associated with Morbid Obesity: Implications and Effects of Weight Loss

Daniel R. Cottam, MD[1,2]; Samer G. Mattar, MD[1,2]; Emma Barinas-Mitchell, PhD[1]; George Eid, MD[2]; Lewis Kuller, MD, DrPH[1]; David E. Kelley, MD[1]; Philip R. Schauer, MD[1,2]

[1]Obesity and Nutrition Research Center, and [2]Minimally Invasive Surgery Center, Department of Surgery, The University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Background: Obesity is a worldwide pandemic that causes a multitude of co-morbid conditions.However, there has been slow progress in understanding the basic pathophysiology that underlies co-morbid conditions associated with obesity. Recently, there has been intense interest in the role of inflammation in obesity. Using the inflammatory hypothesis, many of the mechanisms by which co-morbid conditions are associated with obesity are being elucidated.

Methods: We searched the literature and reviewed all relevant articles. We focused on hormones and cytokines that have been associated with other inflammatory conditions such as sepsis and systemic inflammatory response syndrome.

Findings: Angiotensinogen (AGT), transforming growth factor beta (TGFβ), tumor necrosis factor alpha (TNFα), and interleukin six (IL-6) are all elevated in obesity and correlate with several markers of adipocyte mass. These mediators have detrimental effects on hypertension, diabetes, dyslipidemia, thromboembolic phenomena, infections, and cancer. Weight loss results in a reduction of inflammatory mediators and a diminution of the associated co-morbid conditions.

Conclusions:The success of weight loss surgery in treating the complications associated with obesity is most probably related to the reduction of inflammatory mediators.While some aspects of bariatric physiology remain unclear, there appears to be a strong association between obesity and inflammation, thereby rendering obesity a chronic inflammatory state. A clearer understanding of the physiology of obesity will allow physicians who treat the obese to develop better strategies to promote weight loss and improve the well-being of millions of individuals.

Key words: Obesity, morbid obesity, inflammation, angiotensin, hypertension, leptin, tumor necrosis factor, transforming growth factor, interleukin, insulin resistance, infection, cancer, C-reactive protein, serum amyloid A

Reprint requests to: Samer G. Mattar, MD, Magee Women's Hospital, Suite 5500, 300 Halket Street, Pittsburgh, PA 15213, USA. Fax: 412-641-3680; e-mail:danamycottam@yahoo.com

Introduction

Obesity, defined as a BMI >30 kg/m^2, is a global epidemic that currently affects over 185 million adults in industrialized nations, 115 million in the developing world and over 18 million children under the age of five.[1,2] Patients who have a BMI >25 are considered overweight, while a BMI >30 is considered obese, and a BMI >40 is considered morbidly obese. In the US, >27% of the population is currently obese, with over half of the population being overweight. There are approximately 260,000 to 380,000 deaths a year from factors related to obesity in the US.[3] This exceeds the aggregate totals of lung (154,000), colon (48,000), breast (40,000) and prostate (30,200) cancer combined.[4] The BMI has

served as a useful clinical tool in the evaluation of obesity and the appropriateness of patients for surgery. However, as a measure of total fatness, the BMI measurement fails because it underestimates the total amount of fat in females (females have more fat mass then men at similar BMIs) and overestimates fat mass in muscular men.[5,6] A potentially useful addition to the appraisal of health risks of obesity would be biologic markers that assess the amount of excess inflammation.

Recently there has been rising interest in the role of inflammation in the morbidly obese. C-reactive protein (CRP), an acute phase reactant, has undergone intense investigation. Its elevation corresponds to the level of adiposity present in the body.[5,7,8] Additionally, this protein functions as a valuable tool to predict future cardiovascular events such as ischemic stroke, coronary heart disease, myocardial infarction, peripheral arterial disease, and mortality in men and women.[9-11] Yet, this protein plays only a small role in the acute phase response.[11] The acute phase response was associated with at least 45 different proteins and an extended list of associated phenomena.[11] We can draw meaningful conclusions from the data already present in the literature. Using a model of an increased adipocyte mass functioning as an endocrine organ, we can gain further insights into the dyslipidemic, oncologic, infectious, diabetic, hypertensive, and thromboembolic phenomena that plague morbidly obese patients. Additionally, we may gain insight as to why weight loss surgery is successful in reversing the complex metabolic phenomena associated with obesity.

Adipose Tissue as an Endocrine Organ

Until recently, it was accepted that the role of the adipocyte was the passive storage of energy in the form of white fat, or of brown fat for thermogenesis. The function of these cells was thought to be the release of fatty acids in times of starvation or the production of heat in times of cold, respectively. However, with the explosion of obesity-related research, it has become clear that fat cells actively monitor their environment, and vigorously respond to neural, paracrine, autocrine and endocrine inputs. These inputs include a wide array of steroids,

cytokines, prostaglandins, cholesterol, and fatty acids (Table 1).[12-36] It has also become clear that the adipocyte produces numerous secretions. While it is beyond the scope of this paper to investigate all secretions of the adipocyte, we can review those that are implicated in initiating the chronic inflammatory response that is associated with obesity (Table 2).[37-61] The most notable inflammatory mediators released by the adipocyte are angiotensinogen (AGT), transforming growth factor beta (TGFβ), tumor necrosis factor alpha (TNFα), and interleukin six (IL-6).

Angiotensinogen

AGT is a 60 Kd protein originally thought to be produced in significant amounts only in the liver.[62] This protein, which does not possess any independent biological activity, is the first step in the renin angiotensin system. Renin cleaves AGT to produce angiotensin I which has little biologic activity. Next, Angiotensin I is cleaved by angiotensin-converting enzyme (ACE) in the lung, to produce angiotensin II. Angiotensin II creates a system of biologic actions as will be described later. The main feature of this system is the regulation of blood pressure in the face of dehydration or hypovolemic shock.[63] One of the early responses to declining renal perfusion is the hepatic production of AGT.[64] The production of AGT in response to inflammation and shock has led to its recognition as an acute phase protein.[65,66] However, when the renin-angiotensin system becomes dysfunctional, as in renovascular occlusive disease, it manifests itself as hypertension.[63]

Recently, a significant elevation of angiotensinogen levels has been shown to correlate directly with leptin levels (a marker of adipocyte mass) and BMI.[67-71] These high levels are not caused by an overproduction of AGT from the liver, as indicated by the positive correlation between BMI and subcutaneous adipocyte angiotensinogen mRNA expression.[72] However, the overproduction of angiotensin is not, by itself, important, since it and its metabolite angiotensin I are both inactive proteins. These proteins are acted on by renin and angiotensin converting enzyme, which have both been shown, using

Table 1. Known endocrine hormones and secretions by adipose tissue

Molecule	Function/Effect	Reference
ASP	Promotes fat storage, inhibits lipolysis	12
Adipsin	Helps cleave the complement protein C3 into C3a and C3b ultimately to produce ASP	13
Adiponectin	Reduces hepatic glucose production while increasing muscle glucose utilization	12
Adipophilin	deposition and transport of cytosolic lipid droplets	14
Agouti protein	Regulation of energy homeostasis	15
Angiotensinogen	Regulator of blood pressure precursor of angiotensin II	16
Apo-E	Transport of cholesterol and other lipids between peripheral tissues and the liver	17
CETP	Facilitates the transfer of cholesteryl ester from HDL to apolipoprotein B-containing lipoproteins	18
FIAF	Regulation of metabolism, especially under fasting conditions	19
IL-1a	Regulation of fever and body heat	20
IL-6	Host defense, glucose and lipid metabolism	21
IL-6 sR	Augments the activity of IL-6	22
IGF-1	Stimulates cellular proliferation and mediates growth hormone	22,23
Leptin	Signals brain about adipose stores, energy expenditure	24
LPL	Hydrolyzes triglycerides VLDLs to free fatty acids for uptake into adipocytes	25
Metallothionein	Protection of fatty acids from oxidative damage	26
MIF	Immunoregulation and inflammation	27
NEFA	Elevated levels impair glucose uptake and increase liver gluconeogenesis	28
PAI-1	Regulation of the fibrinolytic system	29
PGI2	vasorelaxation and inflammation	
PGF2a	Smooth muscle constriction, adipocyte differentiation	30
Resistin	Unknown	31
Retinol	Adipocyte is storage depot for Vitamin A	32
Retinol BP	Carrier protein for retinol	33
Steroids	Metabolism and secretion of sex steroids and glucocorticoids	34
TGFb	Controls PAI-I synthesis, cell growth and differentiation	35
TNFa	Partially responsible for insulin resistance in diabetes	36
TNFa sR-I	Autocrine and paracrine mediator of TNF	36
TNFa sR-II	Autocrine and paracrine mediator of TNF	36

Acylation stimulating protein (ASP), Adipsin, Adiponectin, Adipophilin, AdipoQ, Agouti protein, Angiotensinogen, Angiotensin II, Apolipoprotein E (Apo-E), Cholesteryl ester transfer protein (CETP), Fasting-induced adipose factor (FIAF), IL-1a interleukin 1 alpha, IL-6 (interleukin 6), IL-6 sR (interleukin 6 soluble receptor), Insulin-like growth factor-1 (IGF-1), Leptin, Lipoprotein lipase (LPL), Metallothionein, Macrophage inhibitory factor (MIF), Non-esterified fatty acids (NEFA), Plasminogen activator inhibitor-1 (PAI-1), PGI2 prostacylin, PGF2a, Resistin, Retinol, Retinol binding protein (Retinol BP), Steroids, TGFb (Transforming growth factor-b), Tissue factor, TNFa (Tumor necrosis factor a), TNFa sR-I (Tumor necrosis factor soluble receptor I), TNFa sR-II (Tumor necrosis factor soluble receptor II)

mRNA expression techniques, to be active in human adipocytes. Additionally, the activity of these plasma mediators has been positively correlated with BMI and decline dramatically with moderate amounts of weight loss.[73-80] The end result is an overexpression of angiotensin II in obesity.

These findings would suggest that the metabolic effects of angiotensin II are important in obesity.

Several authors have demonstrated that overproduction of aldosterone in obesity positively correlates with BMI,[76,77,81,82] and that obesity is associated with volume expansion and sodium retention, even in moderate levels of obesity.[74,82-85] In addition, the direct effects of angiotensin II on the sympathetic nervous system could be a cause of essential hypertension.[86,87] Masuo et al[86] followed 1,897 lean men

Table 2. Acute Phase reactants and inflammatory mediators in obesity, trauma, and ARDS

Inflammatory Marker	ARDS/ Trauma	Obesity	Weight Loss	References
Cytokines				
IL-1α	↑	↑	?	37-39
IL-1β	↑	↑	↓	37, 40
IL-1RA	↑	↑	↓	37,40-41
IL-3	↑	↑	↓	37,42
IL-6	↑	↑	↓	37, 43
IL-8	↑	↑	↑	37, 44-45
TNF-	↑	↑	↓	37, 42
TNFsRA	↑	↑	?	37, 46
TGFbeta	↑	↑	?	37, 47
Acute Phase Proteins				
Compliment C3	↑	↑	↓	37,48
Haptoglobin	↑	↑	↓	37, 48
CRP	↑	↑	↓	37, 49-50
Fibrinogen	↑	↑	↓	37, 51-52
Serum amyloid A	↑	↑	↓	37, 53
Ceruloplasmin	↑	↑	?	37, 54
a1-anti-chymotrypsin	↑	↑	?	37, 55
LBP	↑	↑	?	56
AGP	↑	↑	?	56
PAI-1	↑	↑	↓	37, 51-52
Cell Surface Receptors				
CD14	↑	↑	↓	57-58
CD14/CD16*	↑	↑	↓	57-58
CD62	↓	↓	↑	58-59
CD95	↑	↑	↓	59
Other				
vWF	↑	↑	↓	62
FVIII	↑	↑	↓	62
ESR	↑	↑	↓	60, 61

Lipopolysaccharide binding protein (LBP), a-Acid glycoprotein (AGP), CD95 (Fas Antigen), Plasminogen activator inhibitor-1 (PAI-1), Transforming growth factor-b (TGFb), Tumor necrosis factor a (TNFa), Tumor necrosis factor soluble receptor (TNFsRA), Von Willebrands Factor vWF, Acute respiratory distress syndrome (ARDS)
*CD14/CD16 monocyte subset responsible for production of cytokines

over 10 years and found that plasma norepinephrine (NE) levels increased as BMI increased. The increase in NE levels directly correlated with rising blood pressure. The relative contribution between aldosterone-induced sodium retention and sympathetic over-activity in obese patients with hypertension still has to be elucidated (Figure 1).

Tumor Necrosis Factor Alpha and Transforming Growth Factor Beta

TNFα is one of the cardinal cytokines that mediate immune and inflammatory responses. It was origi-

nally thought to be produced only by macrophages and monocytes, and these cells continue to be heavily investigated.[88,89] This is partly due to the strong association of TNFα with trauma, acute respiratory distress syndrome, multiple organ system failure, systemic inflammatory response syndrome (SIRS), septic shock and death.[90-93] It has also been associated with apoptosis and the procoagulant state present in conditions of excess inflammation.[89,94,95] Large amounts of TNFα are also present in obesity.

TNFα in obesity is produced by adipocytes throughout the body as seen in mRNA studies, but more abundantly by adipocytes in the waist-hip region.[96] This is manifested as a mild correlation of serum TNFa with BMI, but strong correlation with
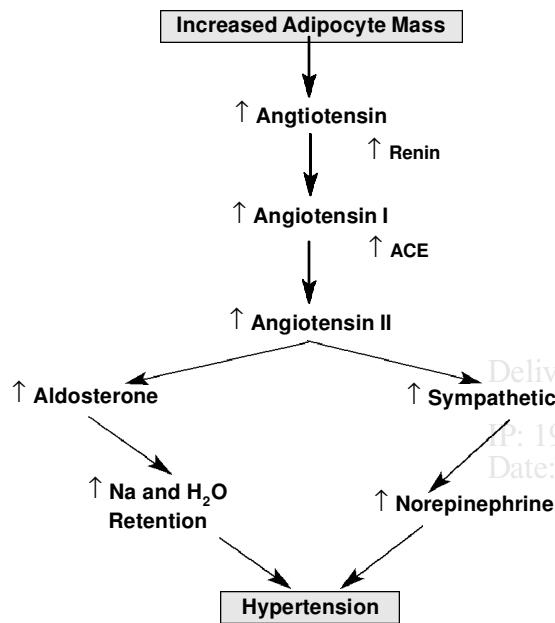
Figure 1. This figure illustrates the relationship between increased adipocyte mass, aldosterone and sympathetic tone as causes of hypertension in obesity.

waist-hip ratio. (The waist is measured at the narrowest point of the relaxed stomach while the hips are measured on the widest place).[96,97] Both the adipocyte mRNA expression and serum TNFα levels are elevated in obesity and concurrently decrease with weight loss.[96,100]

In trauma and other inflammatory conditions, TNFα is associated with several abnormalities in the hemolytic and fibrinolytic system. The abnormalities include increases in the serum levels of von Willebrand factor (vWF) and plasminogen activator inhibitor (PAI-1).[89,101-104] In obesity, vWF correlates with BMI and waist circumference and decreases with weight loss.[61,97,105] Levels of TNF expression also correlate with serum levels of vWF.[97] While the exact mechanism has yet to be elucidated, it may be presumed that TNFα mediates vFW expression in obesity, in keeping with other states of chronic inflammation.

Serum levels of PAI-1, as with vWF, have also been found to correlate with TNF.[29,47,97,106-109] Unlike vFW, which is produced in the liver, PAI-1 is produced by the adipocyte. TNF can directly induce the production of PAI-1,[106,107,110,112] or it can influence its production through a TGF-β mediated pathway.[47,107-109,112,113] TGFβ is elevated in acute inflam-

matory states,[89] and levels of TGFβ positively correlate with BMI.[47,107] With weight loss, both TGFβ and PAI-1 levels fall significantly.[50,61,105,114,115] This may explain why chronic inflammation in obesity predisposes morbidly obese individuals to higher rates of thromboembolic phenomena.

Another relationship seen in acute inflammation and obesity is insulin resistance secondary to TNFα. There are many lines of evidence to support this hypothesis. TNFα, has been shown to induce insulin resistance in isolated cells, animals, and humans.[116-119] Also, medication and dietary modifications improve insulin sensitivity, and this coincides with a decrease in TNFα and weight loss.[120-127] The precise mechanism is related to TNFα receptor expression, as obese mouse models lacking either TNFα or its receptors do not exhibit significant insulin resistance.[128-130] TNFα almost certainly plays a large part in obesity-associated insulin resistance (Figure 2). Future studies will investigate how much other insulin mediators that are elevated in obesity and decrease with weight loss such as enteroglucagon (glucagonlike peptide 1 [GLP-1]), and IL-1 (another acute phase reactant), interact with TNFα.[40,131-132]
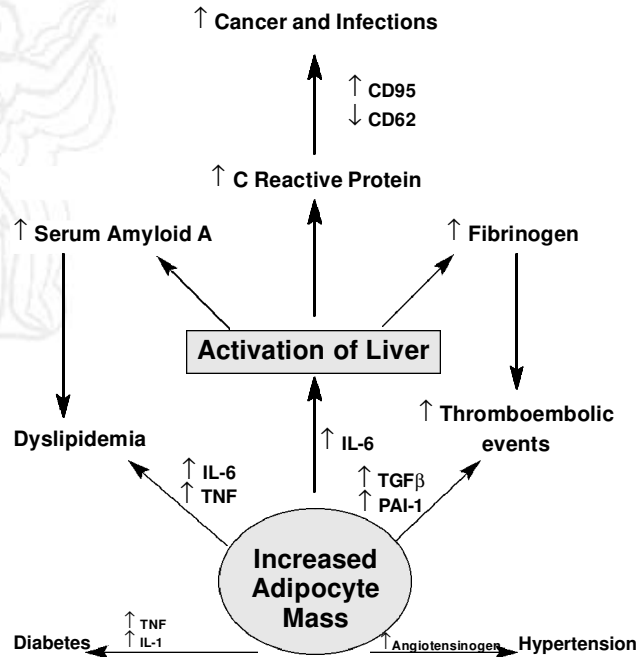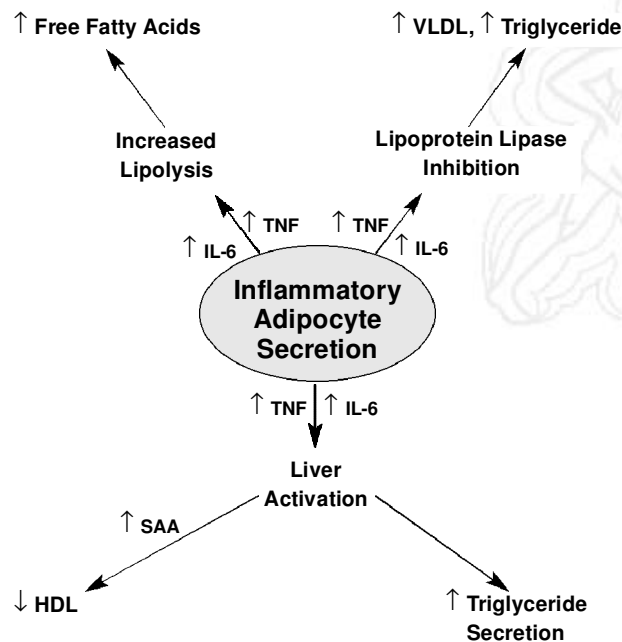

Figure 2. This figure demonstrates the effect of increased adipocyte mass in liver activation, as well as the possible mechanisms for increased cancer incidence, thrombotic events, hypertension, diabetes and dyslipidemia seen in obesity.

TNF and IL-6

In addition to inducing the production and secretion of TGFβ, TNFα also induces the secretion of IL-6.[89,133-135] IL-6 levels are elevated in obesity and correlate with the level of TNFα, waist-hip ratio (WHR) and BMI, and fall with weight loss.[43,97,136-138] These two cytokines, in conjunction, are responsible for the dyslipidemia that is common in morbid obesity. Specifically, both IL-6 and TNFα correlate with the level of dyslipidemia,[137,138] inhibit lipoprotein lipase (increasing VLDL and triglycerides),[96,133,139-141] increase triglyceride secretion from the liver,[139,142] and increase lipolysis (increasing free fatty acids),[139-142] while TNFα alone stimulates hormone sensitive lipase, and down-regulates fatty acid binding protein and fatty acid synthase.[133,140] All of these changes in lipid metabolism are reversible with weight loss (Figure 3).[96,137,143-145]

Perhaps the most important aspect of IL-6 physiology is its induction of the acute phase response by the liver. The liver is responsible for the production of many of the acute phase proteins seen in trauma and sepsis. The most studied of these proteins are C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen.

CRP is a member of the pentraxin family of proteins and is secreted by the liver in response to IL-6 production in trauma, sepsis and other inflammatory conditions.[146-148] It rises quickly in the face of inflammation and falls quickly with its resolution. It binds to Fc receptors to induce the secretion of pro- and anti-inflammatory cytokines, and to help the phagocytosis of bacteria. CRP activates complement, and down-regulates white blood cells adhesive molecules in response to sepsis and systemic inflammation.[149-152] In morbid obesity, the level of CRP is positively correlated with the waist ratios, hip-waist ratios, and BMI. This relationship is unchanged in both "healthy" obese patients and in general population studies of adults and children.[5,7-8,43,49] With exercise and weight loss, the levels of CRP fall dramatically.[8,43,49,138] Additionally, many of the same effects seen in trauma secondary to elevated levels of CRP, such as elevated cytokine levels, decreased expression of cell surface adhesive molecules, and increased expression of death receptors (apoptotic receptors), are seen in obesity.[56-58,149,150] The altered expression of adhesive molecules such as L-selectin (CD62) and the increased expression of death receptors such as the fas antigen (CD95) secondary to inflammation could play a role in the increased incidence of wound infections and cancer in obesity. As white blood cells are unable to migrate to target sites, those that arrive are more susceptible to apoptosis (Figure 2).[56-58]

IL-6 and TNF also promote the secretion of an additional sensitive acute phase protein elevated in trauma and sepsis, serum amyloid A (SAA) (Figure 3).[153,54] SAA, together with CRP, provides us the ability to compare the inflammation present in obesity with other inflammatory states. In trauma and infection, CRP and SAA levels can rise from 200 to 500 fold for CRP and 500 to 2000 fold for SAA, while in morbid obesity they rise 20 fold for CRP and 10 fold for SAA (when compared to lean individuals).[153] Furthermore, levels of SAA correlate with BMI, WHR, CRP and leptin.[92,52,55,156] Perhaps more importantly, in inflammatory conditions such as trauma, sepsis, and rheumatoid arthritis, SAA has been shown to be responsible for the drop in HDL by replacing apolipoproteins A-1 and A-11 with

Figure 3. In obesity, the inflammatory mediators TNF and IL-6 are thought to be responsible for many of the alterations in lipid metabolism. The decreased levels of HDL with elevated levels of triglycerides and VDL could contribute to the higher incidence of cardiovascular disease seen in obesity.

SAA.[157-161] This converts normal HDL (NHDL) into acute phase HDL (APHDL). APHDL is absorbed by macrophages more rapidly and is degraded faster.[153,162-63] Thus, lower levels of HDL are seen in inflammatory conditions. This effect could explain the lower levels of HDL seen in obesity and offers an explanation for increased macrophage lipid uptake in the pathogenesis of atherosclerosis.[52,156,164]

Fibrinogen, like CRP and SAA, is an acute phase reactant produced in the liver, the production of which is controlled by IL-6.[165-167] Fibrinogen is the main determinant of plasma viscosity and plays essential roles in blood rheology, platelet aggregation, and endothelial function.[168-170] Elevated levels have been found in obesity and correlate with CRP, SAA, BMI and WHR in most studies.[171-180] Furthermore, fibrinogen levels decline with weight loss greater than 10%.[50,173,178,180] Certainly, the higher levels of fibrinogen, von Willebrand factor and PAI outlined here, when combined with the elevated levels of Factor VII and Factor VIII, predispose obese patients to a higher risk of thromboembolic complications.[61]

Treatment of Obesity

The causes of obesity are multifactorial. Current treatment options for mild obesity (BMI<35) include diet and exercise. However, for the majority of patients with a BMI >35, durable non-surgical weight loss has proved unsuccessful for many individuals. It is for these reasons that the NIH recommended in 1991 and in 1998 that surgical treatment be considered for patients with a BMI >40 or for patients with BMI >35 and co-morbid conditions who have failed supervised weight loss attempts.[181,182] Weight loss surgery has been shown to eliminate between 85% and 95% of all co-morbid conditions associated with obesity with an acceptable low morbidity.[183-5] The success of weight loss surgery is related to the anti-inflammatory effects of sustained weight loss. Many of the above studies determined that weight loss was associated with resolution of clinical as well as physiologic phenomena. While many aspects of bariatric physiology remain unclear, there appears to be a strong association between obesity and inflammation, thereby rendering obesity a chronic inflammatory state. Chronic inflammation could account for many of the detrimental effects of obesity in these patients. Future studies should further investigate this critical relationship (whether it is in the causal pathway or merely associative) in order to increase our understanding of both the patterns of inflammatory response in the context of obesity and its effect on body physiology.

References

1. World Health Organization
http://www.who.int/nut/obs.htm
2. American Obesity Association
http://www.obesity.org./sub/fastfacts/obesity_US.shtml
3. Allison DB, Fontaine KR, Manson JE et al. Annual deaths attributable to obesity in the United States. JAMA 1999; 282: 1530-8.
4. Cancer Facts and Figures 2002. American Cancer Society
5. Visser M, Bouter LM, McQuillan GM et al. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999; 282: 2131-5.
6. Gallagher D, Visser M, Sepulveda D et al. How useful is body mass index for comparison of body fatness across age gender, and ethnic groups? Am J Epidemiol 1996; 143:228-39.
7. Visser M, Bouter LM, McQuillan GM et al. Low grade systemic inflammation in overweight children. Pediatrics. 2001; 107: 13-9.
8. Tchernof A, Nolan A, Sites C et al. Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation 2002; 105: 564-9.
9. Ridker PM, Buring JE, Shih J, et al. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 1998; 98: 731-3.
10. Koenig W, Sund M, Frohlich M et al. C reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle aged men. Circulation 1999; 99: 237-42.
11. Ridker PM, Cushman M, Stampfer MJ et al. Plasma concentration of c reactive protein and risk of developing peripheral vascular disease. Circulation 1998; 97: 425-8.
12. Havel PJ. Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. Curr Opin Lipidol 2002; 13: 51-9.
13. Maslowska M, Vu H, Phelis S et al. Plasma acylation stim-

ulating protein, adipsin and lipids in non-obese and obese populations. Eur J Clin Invest 1999; 29: 679-86.

14. Heid HW, Moll R, Schwetlick I et al. Adipophilin is a specific marker of lipid accumulation in diverse cell types and diseases. Cell Tissue Res 1998; 294: 309-21.

15. MacNeil DJ, Howard AD, Guan X et al. The role of melanocortins in body weight regulation: opportunities for the treatment of obesity. Eur J Pharmacol 2002; 440: 141-57.

16. Engeli S, Negrel R, Sharma A. Physiology and pathophysiology of the adipose tissue renin-angiotensin system. Hypertension 2000; 35: 1270-7.

17. Curtiss LK, Boisvert WA. Apolipoprotein E and atherosclerosis. Curr Opin Lipidol 2000; 11: 243-51.

18. Inazu AB, Koizumi J, Mabuchi H. Cholesteryl ester transfer protein and atherosclerosis. Curr Opin Lipidol 2000; 11: 389-96.

19. Kersten S, Mandard S, Tan NS et al. Characterization of the fasting-induced adipose factor FIAF, a novel peroxisome proliferator-activated receptor target gene J Biol Chem 2000; 275: 28488-93.

20. Cannon B, Houstek J, Nedergaard J et al. Brown adipose tissue: More than an effector of thermogenesis. Ann NY Acad Sci 1998; 856: 171-87.

21. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. Int J Obes 1998; 22: 1145-58.

22. Chen NX, Hausman GJ, Wright JT. Influence of thyroxin in vivo on preadipocyte development and insulin like growth factor-I and IGF binding protein secretion in fetal stromal vascular cell cultures. Obes Res 1996; 4: 357-66.

23. Schmidt W, Poll JG, Loffler G. Adipose conversion of 3T3-L1 cells in a serum free culture system depends on epidermal growth factor, insulin like growth factor, corticosterone and cyclic AMP. J Biol Chem 1990; 265: 15489-95.

24. Jequier E. Leptin signaling, adiposity, and energy balance. Ann NY Acad Sci 2002; 967: 379-88.

25. Eckel RH. Lipoprotein lipase: a multifunctional enzyme relevant to common metabolic diseases. N Engl J Med 1989; 320: 1060-8.

26. Trayhum P, Duncan JS, Wood AM et al. Metallothionein gene expression and secretion by white adipose tissue. Am J Physiol Regulatory Integrative Physiol Comp 2000; 279: R2329-35.

27. Sakaue S, Nishihira J, Hirokawa J. Regulation of macrophage migration inhibitory factor expression by glucose and insulin in adipocytes in vitro. Mol Med 1999; 5: 361-71.

28. Frayn KN. Role of non-esterified fatty acids in the metabolic changes of obesity. Int J Obes 1996; 20 (Suppl 4): S7-10.

29. Vague J, Alessi MC. Regulation of fibrinolysis in the development of atherothrombosis: Role of adipose tissue. Thromb Haem 1999; 82: 832-6.

30. Reginato MJ, Krakow SL, Bailey ST. Prostaglandins promote and block adipogenesis through opposing effects on peroxisome proliferator activated receptor y. J Biol Chem 1998; 273: 1855-58.

31. Smith U. Resistin - Resistant to defining its role. Obes Res 2002; 10: 61-2.

32. Wolf GD. Release of stored retinol from adipocytes. Nutr Rev 1998; 56: 29-30.

33. Tsutsumi C, Okuno M, Tannous L et al. Retinoids and retinoid binding protein expression in rat adipocytes. J Biol Chem 1992; 267: 1805-10.

34. Labrie F, Simard J, Luu The V et al. Expression of 3 beta hydroxysteroid dehydrogenase, delta 5-delta 4 isomerase and 17 beta-hydroxysteroid dehydrogenase in adipose tissue. Int J Obes 1991; 15: 91-9.

35. Birgel M, Gottschling-Zeller H, Rohrig K et al. Role of cytokines in the regulation of plasminogen activator inhibitor-1 expression and secretion in newly differentiated subcutaneous human adipocytes. Arterioscler Thromb Vasc Biol 2000; 20: 1682-7.

36. Hotamisligil GS. The role of TNF alpha and TNF receptors in obesity and insulin resistance. J Intern Med 1999; 245: 621-5.

37. Schuchert VD, Billiar TR. Inflammation. In: Greenfield LJ, ed. Surgery Scientific Principals and Practice, Third Edition. 2001: 134-78.

38. Messier SP, Loeser RF, Mitchell MN et al. Exercise and weight loss in obese older adults with knee osteoarthritis: a preliminary study. J Am Geriatr Soc 2000; 48: 1062-72.

39. Raymond NC, Dysken M, Bettin K et al. Cytokine production in patients with anorexia nervosa, bulimia nervosa and obesity. Int J Eat Disord 2000; 28: 293-302.

40. Cottam DR, Schaefer PA, Angus LDG et al. Cytokine response to surgically induced weight reduction. Obes Res 2000; 8 (Suppl): S8 (abst).

41. Meier CA, Bobbioni E, Gabay C et al. IL-1 receptor antagonist serum levels are increased in human obesity: A possible link to the resistance to leptin? J Clin Endocrin Metab 2002; 87: 1184-8.

42. Kyzer S, Binyamini J, Chaimoff C et al. The effect of surgically induced weight reduction on the serum levels of the cytokines: intereukin 3 and TNF. Obes Surg 1999; 9:229-34.

43. Bastard JP, Jardel C, Bruckert E. Elevated levels of IL-6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrin Metab 2000; 85: 3338-45.

44. Straczkowski M, Dzienis-Straczkowska S, Stepien A et al. Plasma Interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor system. J Clin Endocrin Metab 2002; 87: 4602-6.

45. Bruun JM, Pedersen SB, Kristensen K et al. Opposite regulation of interleukin-8 and tumor necrosis factor alpha by weight loss. Obes Res 2002; 10: 499-506.

46. Hube F, Lee Y, Birgel M et al. Expression pattern of tumour necrosis factor receptors in subcutaneous and omental human adipose tissue: role of obesity and non-insulin dependent diabetes mellitus. Eur J Clin Invest 1999; 29: 672-8.

47. Alessi MC, Bastelica D, Morange P. Plasminogen activator inhibitor 1, transforming growth factor beta and BMI are closely associated in human adipose tissue during morbid

obesity. Diabetes 2000; 49: 1374-80.

48. Scriba PC, Bauer M, Emmert D et al. Effects of obesity, total fasting and re alimentation on T4, TBG, cortisol, thyrotrophin, transferrin, alpha 2 haptoglobin and complement C3 in serum. Acta Endocrin 1979; 91: 629-43.

49. Laimer M, Ebenbichler CF, Kaser S et al. Markers of chronic inflammation and obesity: a prospective study on the reversibility of this association in middle aged women undergoing weight loss by surgical intervention. Int J Obes 2002; 26: 659-62.

50. Primrose JN, Davies JA, Prentice R et al. Reduction in factor VII, fibrinogen and plasminogen activator inhibitor-1 activity after surgical treatment of morbid obesity.Thrombosis and Haemostasis 1992; 68: 396-9.

51. Juhan-Vague I, Alessi MC, Morange PE. Hypofibrinolysis and increased PAI-1 are linked to atherothrobosis via insulin resistance and obesity. Ann Med 2000; 32: 78-84.

52. Danesh J, Muir J, Wong YK. Risk Factors for coronary heart disease and acute phase proteins. A population based study. Eur Heart J 1999; 20: 954-9.

53. Cignarelli M, DePergola G, Picca G et al. Relationship of obesity and body fat distribution with ceruloplasmin serum levels. Int J Obes 1996; 20: 809-13.

54. Hak AE, Pols HA, Stejpiwer DA et al. Markers of inflammation and cellular adhesion molecules in relation to insulin resistance in nondiabetic elderly: The Rotterdam study. J Clin Endocrinol Metab 2001; 86: 4398-405.

55. Dielen FMH, Veer CV, Schols AM et al. Increased leptin concentrations correlate with increased concentrations of inflammatory markers in morbidly obese individuals. Int J Obes 2001; 25: 1759-66.

56. Cottam DR, Schaefer PA, Shaftan GW et al. Effect of surgically-induced weight loss on leukocyte indicators of chronic inflammation in morbid obesity. Obes Surg 2002;12: 335-42.

57. Cottam DR, Schaefer PA, Angus LD et al. The effect of obesity on neutrophil Fc receptors and adhesion molecules (CD16, CD11b, CD62L). Obes Surg 2002; 12: 230-5.

58. Cottam DR, Schaefer PA, Angus LD et al. Dysfunctional immune-privilege in morbid obesity: implications and effect of gastric bypass surgery. Obes Surg 2003; 13: 49-57.

59. Pasulka P, Bistrian BR, Blackburn GL. Obesity and erythrocyte sedimentation rates (Letter). Ann Intern Med 1985; 103: 304.

60. Bacci V, Basso MS, Greco F et al. Modifications of metabolic and cardiovascular risk factors after weight loss induced by laparoscopic gastric banding. Obes Surg 2002; 12: 77-82.

61. Mertens I, Van Gaal LF. Obesity, haemostasis and the fibrinolytic system. Obes Rev 2002; 3: 85-101.

62. Takahashi D, Tamura K, Ushikubo T et al. Relationship between hepatic angiotensinogen mRNA expression and plasma angiotensinogen in patients with chronic hepatitis. Life Sci 1997; 60: 1623-33.

63. Stanley JC, Upchurch GR. Renal artery occlusive disease. In: Greenfield L, ed. Surgery Scientific Principals and Practices, Third Edition. 2001: 1709-24.

64. Kim PK, Deutschman CS. Inflammatory responses and mediators. Surg Clin North Am 2000; 80: 885-94.

65. Gabay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340: 448-54.

66. Hoj Nielsen A, Knudsen F. Angiotensinogen is an acute-phase protein n man. Scand J Clin Lab Invest 1987; 47: 175-8.

67. Tamura K, Umemura S, Yamakawa T et al. Modulation of tissue angiotensinogen gene expression in genetically obese hypertensive rats. Am J physiol 1997; 272: R1704-11.

68. Tamura K, Umemura S, Nyui N et al. Tissue specific regulation of angiotensinogen gene expression in SHR. Hypertension 1996; 27: 1216-23.

69. Schorr U, Blaschke K, Turan S et al. Relationship between angiotensinogen, leptin and blood pressure levels in young normotensive men. J Hypertens 1998; 16: 1475-80.

70. Bloen LJ, Manatunga AK, Tewdsbury DA et al. The serum angiotensinogen concentration and variants of the angiotensinogen gene in white and black children. J Clin Invest 1995; 95: 948-53.

71. Unemura S, Nyui N, Tamura K et al. Plasma angiotensinogen concentrations in obese patients. Am J Hypertens 1997; 10: 629-33.

72. Van Harmelen V, Ariapart P, Hoffstedt J et al. Increased adipose angiotensinogen gene expression in human obesity. Obes Res 2000; 337-41.

73. Hall JE, Brands MW, Dixon WN et al. Obesity induced hypertension: Renal function and systemic hemodynamics. Hypertension 1993; 22: 292-9.

74. Dobrian AD, Davies MJ, Prewitt RL et al. Development of hypertension in a rat model of diet induced obesity. Hypertension 2000; 35: 1009-15

75. Granger JP, West D, Scott J. Abnormal pressure natriuresis in the dog model of obesity induced hypertension. Hypertension 1994; 23 (Suppl): S18-21.

76. Egan BM, Stepniakowski K, Goodfriend TL. Renin and aldosterone are higher and the hyperinsulinemic effect of salt restriction greater in subjects with risk factors clustering. Am J Hypertens 1994; 7: 886-93.

77. Cooper R, McFarlane AN, Bennett FI et al. ACE, angiotensinogen, and obesity: a potential pathway leading to hypertension. J Hum Hypertens 1997; 11: 107-11.

78. Licata G, Scaglione R, Ganguzza A et al. Central obesity and hypertension: Relationship between fasting serum insulin, plasma renin activity and diastolic blood pressure in young obese subjects. Am J Hypertens 1994; 7: 314-20.

79. Giacchetti G, Faloia E, Sardu C et al. Gene expression of angiotensinogen in adipose tissue of obese patients. Int J Obes 2000; 24(Suppl 2): S142-3.

80. Harp JB, Henry SA, DiGirolamo M. Dietary weight loss decreases serum angiotensin-convertin enzyme activity in obese adults. Obes Res 2002; 10: 985-90.

81. Rocchini AP, Key J, Bondie D, Chico R et al. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. N Engl J Med 1989; 321: 580-5.

82. Goodfriend TL, Egan BM, Kelley DE. Aldosterone in obesity. Endocr Res 1998; 24:789-96.

83. Rocchini AP, Cardiovascular regulation in obesity induced

hypertension. Hypertension 1992; 19 (Suppl): S155-60.

84. Reisin E, Sodium and obesity in the pathogenesis of hypertension. Am J hypertens 1990; 3: 164-7.

85. Hall JE. Mechanisms of abnormal renal sodium handling in obesity hypertension Am J Hypertens 1997; 10 (Suppl): S49-55.

86. Masuo K, Mikami H, Ogihara T et al. Weight gain induced blood pressure elevation. Hypertension 2000; 35: 1135-40.

87. Masuo K, Mikami H, Ogihara T et al. Familial hypertension insulin, sympathetic activity, and blood pressure elevation. Hypertension 1998; 32: 96-100.

88. Schuchert VD, Billiar TR. Inflammation. In: Greenfeld LJ, Mulholland MW, eds. Surgery. Scientific Principles and Practice, Third Edition. 2001: 134-78.

89. Colletti LM. Cytokines. In: Greenfeld LJ ed. Surgery Scientific Principles and Practice, Third Edition. 2001: 111-34.

90. Strieter RM, Lynch JP, Basha MA et al. Host responses in mediating sepsis and the adult respiratory distress syndrome. Semin Respir Infect 1990; 5: 233-47.

91. Tracey KJ, Lowry SF, Cerami A. Cachectin/TNF in septic shock and septic adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138: 1377-9.

92. Schlag F, Redl H, Hallstrom S. The cell in shock: the origin of multiple organ failure. Resuscitation 1991; 21: 137-80.

93. Ksontini R, Mackay SL, Moldawer LL. Revistiing the role of tumor necrosis factor alpha and the response to surgical injury and inflammation. Arch Surg 1998; 133: 558-67.

94. Van Der Poll T, Buller HR, Ten Cate H et al. Activation of coagulation after administration of tumor necrosis factor to normal subjects. N Engl J Med 1990; 322: 1622-7.

95. Oberholzer C, Oberholzer A, Clare-Salzler M et al. Apoptosis in sepsis: a new target for therapeutic exploration. FASEB 2001; 15: 879-92.

96. Kern PA, Saghizadeh M, Ong JM et al. The expression of tumor necrosis factor in human adipose tissue: Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest 1995; 95: 2111-9.

97. Yudkin JS, Stehouwer CDA, Emeis JJ et al. C-Reactive protein in healthy subjects: Associations with obesity insulin resistance, and endothelial dysfunction: A potential role for cytokines originating from adipose tissue. Arterioscler Thromb Vasc Biol 1999; 19: 972-8.

98. Tsukui S, Kanda T, Nara M et al. Moderate intensity regular exercise decreases serum tumor necrosis factor alpha and HbA1c levels n healthy women. 2000; 9: 1207-11.

99. Zahorska-Markiewicz B, Janowska J, Olszanecka-Glinianowicz M, et al. Serum concentrations of TNF-alpha and soluble TNF-alpha receptors in obesity. Int J Obes 2000; 11: 1392-5.

100. Bruun JM, Pedersen SB, Kristensen K et al. Opposite regulation of interleukin-8 and tumor necrosis factor alpha by weight loss. Obes Res 2002; 10: 499-506.

101. Miller Cl, Graziano C, Lim RC et al. Generation of tissue factor by patient monocytes: correlation to thromboembolic complications. Thromb Haemost 1981; 42: 489-95.

102. Blakowski, SA, Zackarski LR, Beck JR. Postoperative elevation of human peripheral blood monocyte tissue factor coagulant activity. J Lab Clin Med 1986; 108: 117-20.

103. Ollivier V, Sheibani A, Chollet-Martin S et al. Monocyte procoagulant activity and membran associated D Dimer after knee replacement surgery. Thromb Res 1989; 55: 179-85.

104. Van Der Poll T, Van Deventer SHJ, Pasterkamp G et al. Tumor necrosis factor induces von Willebrand factor release in healthy humans. Thromb Haemost 1992; 67: 623-6.

105. De Pergola G, De Mitrio V, Giorgino F et al. Increase in both pro-thrombotic and anti-thrombotic factors in obese premenopausal women: relationship with body fat distribution. Int J Obes 1997; 21: 527-35.

106. Cigolini M, Tonoli M, Borgato L et al. Expression of plasminogen activator inhibitor-1 in human adipose tissue: a role for TNF-α. Atherosclerosis 1999; 143: 81-90.

107. Loskutoff D, Samad F. The adipocyte and hemostatic balance in obesity: studies of PAI-1. Arterioscler Thromb Biol 1998; 18: 1-6.

108. Alessi MC, Morange P, Juhan-Vague I. Fat cell function and fibrinolysis. Horm Metab Res 2000; 32: 504-8.

109. Birgel M, Bottschling-Zeller H, Rohrig K et al. Role of cytokines in the regulation of plasminogen activator inhibitor-1 expression and secretion in newly differentiated subcutaneous human adipocytes. Arterioscler Thromb Vasc Biol 2000; 20: 1682-7.

110. Samad F, Yamamoto K, Pandey M et al. Elevated expression of transforming growth factor beta in adipose tissue from obese mice. Mol Med 1997; 3: 37-40.

111. Agostino G, Tonoli M, Deorsola B et al. PAI-1 release from human adipose tissue is stimulated by TNF-alpha. Thromb Haemost 1997; 77 (Suppl): S749 (abst).

112. Samad F, Teoman K, Wiesbrock SM et al. Tumor necrosis factor alpha is a key component in the obesity-linked elevation of plasminogen activator inhibitor 1. Proc Natl Acad Sci 1999; 96: 6902-7.

113. Fruhbeck G, Gomez-Amrosi JG, Murazabal JF et al. The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. Am J Physiol Endorcrinol Metab 2001; 280: 827-47.

114. Folsom AR, Hekmat T, Qamhieh T et al. Impact of weight loss on plasminogen activator inhibitor, factor VII and other hemostatic factors in moderately overweight adults. Arterioscler Thromb. 1993; 13: 162-9.

115. Mavri A, Stegnar M, Krebs M et al. Impact of adipose tissue on plasma plasminogen activator inhibitor-1 in dieting obese women. Arterioscler Thromb Vasc Biol 1999; 19: 1582-7.

116. Hauner H, Petruschke T, Russ M et al. Effects of tumour necrosis factor alpha on glucose transport and lipid metabolism of newly differentiated human fat cells in culture. Diabetologia 1995; 38: 764-71.

117. Liu LS, Spelleken M, Rohrig K et al. Tumor necrosis factor alpha acutely inhibits insulin signaling in human adipocytes – implication of the P80 tumor necrosis factor receptor. Diabetes 1998; 47: 515-22.

118. Lang CH, Dobrescu C, Bagby GJ et al. Tumor necroisis factor impairs insulin action on peripheral glucose disposal

and hepatic glucose output. Endocrinolgy 1992; 130: 43-52.

119. Sethi JK, Hotamisligil GS. The role of TNFα in adipocyte metabolism. Semin Cell Dev Biol 1999; 10: 19-29.

120. Peraldi P, Xu M, Spiegelman BM et al. Thiazolidinediones block tumor necrosis factor alpha induced inhibition of insulin signaling. J Clin Invest 1997; 100: 1863-9.

121. Miles PD, Romeo OM, Higo K et al. TNF alpha induced insulin resistance in vivo and its prevention by troglitazone. Diabetes 1997: 46:1678-83.

122. Hoffmann C, Lorenz K, Braithwaite SS et al. Altered gene expression for tumor necrosis factor alpha and its receptors during drug and dietary modulation of insulin resistance. Endocrinology 1994; 134: 264-70.

123. Saghizadeh M, Ong HM, Garvey WT et al. The expression of TNFa by human muscle: Relationship to insulin resistance. J Clin Invest 1996; 97: 1111-6.

124. Gimble RF. Inflammatory status and insulin resistance. Curr Opin Clin Nutr Metab Care 2002; 5: 551-9.

125. Zahorska-Markiewicz B, Janowska J et al. Serum concentration of TNFα and soluble TNF receptors in obesity. Int J Obes 2000; 24: 1392-5.

126. Murase K, Odaka H, Suzuki M et al. Pioglitazone time dependently reduces tumour necrosis factor alpha level in muscle and improves metabolic abnormalities in wistar fatty rats. Diabetologia 1998; 41: 257-64.

127. Moller DE. Potential role of TNF alpha in the pathogenesis of insulin resistance and type 2 diabetes. Trends Endocrinol Metab. TEM 2000; 11: 212-17.

128. Uysal KT, Wiesbrock SM, Marino MW et al. Protection from obesity induced insulin resistance in mice lacking TNF alpha function. Nature 1997; 389: 610-4.

129. Ventre J, Doebber T, Wu M et al. Targeted disruption of the tumor necrosis factor alpha gene metabolic consequences in obese and non-obese mice. Diabetes 1997; 46:1526-31.

130. Uysal KT, Wiesbrock SM, Hotamisligil GS et al. Functional analysis of TNF receptors in TNF alpha mediated insulin resistance in genetic obesity. Endocrinology 1998; 139: 4832-8.

131. Greenway SE, Greenway FL, Klein S. Effects of obesity surgery on non-insulin-dependent diabetes mellitus. Arch Surg 2002; 137: 1109-17.

132. Raymond NC, Dysken M, Bettin K et al. Cytokine production in patients with anorexia nervosa, bulimia nervosa and obesity. Int J Eat Disord 2000; 28: 293-302.

133. Coppack SW. Pro inflammatory cytokines and adipose tissue. Proc Nutr Soc 2001; 60: 349-56.

134. Cesaris P, Starace D, Riccioli A et al. Tumor necrosis factor alpha induces interleukin 6 production and integrin ligand expression by distinct transduction pathways. J Biol Chem 1998; 273: 7566-71.

135. Stephens JM, Butts MD, Pekala PH. Regulation of transcription factor mRNA accumulation during 3T3-L1 preadipocyte differentiation by tumor necrosis factor alpha. J Mol Endocrin 1992; 9:61-72.

136. Yudkin JS, Kumari M, Humphries SE et al. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link. Atherosclerosis 2000; 148: 209-14.

137. Chan JC, Cheung JC, Stehouwer CD et al. The central roles of obesity associated dyslipidaemia, endothelial activation and cytokines in the metabolic syndrome – an analysis by structural equation modelling. Int J Obes 2002; 26: 994-1008.

138. Ziccardi P, Nappo F, Giugliano G et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. Circulation 2002; 105: 804-9.

139. Fruhbeck G, Gomez-Ambrosi J, Muruzabal FJ et al. The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. Am J Physiol Endocrinol Metab 2001; 280: E827-47.

140. Grunfeld C, Gulli R, Moser AH et al. Effect of tumor necrosis factor administration in vivo on lipoprotein lipase activity in various tissues of the rat. J Lipid Res 1989; 30: 579-85.

141. Bastard JP, Jardel C, Bruckert E et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipost tissue of obese women after weight loss. J Clin Endocrin Metab 2000; 85: 3338-45.

142. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. Int J Obes 1998; 22: 1145-58.

143. Ridker PM, Hemmekens CH, Buring JE et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836-43.

144. Tsukui S, Kanda T, Nara M et al. Moderate intensity regular exercise decreases serum tumor necrosis factor alpha and HbA1c levels in healthy women. Int J Obes 2000; 24: 1207-11.

145. Kern A, Saghizadeh M, Ong JM et al The expression of tumor necrosis factor in human adipose tissue regulation by obesity, weight loss and relationship to lipoprotein lipase. J Clin Invest 1995; 95: 2111-9.

146. Du Clos TW. Function of C-reactive protein. Ann Med 2000; 32: 274-8.

147. Das UN. Is obesity an inflammatory condition? Nutrition 2001; 17: 953-66.

148. Weinhold B, Ruther U. Interleukin-6 dependent and independent regulation of the human C-reactive protein gene. J Biochem 1997; 327: 425-29.

149. Arbones ML, Ord DC, Ley K et al. Lymphocyte homing and leukocyte rolling and migration are impaired in L-selectin deficient mice. Immunity 1994; 1: 247-60.

150. Zouki C, Beauchamp M, Baron C et al. Prevention of in vitro neutrophil adhesion to endothelial cells through shedding of l-selectin by C-reactive protein and peptides derived from C-reactive protein. J Clin Invest. 1997; 100; 522-9.

151. Vgontzas AN, Papanicolaou DA, Bixler EO et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000; 85: 1151-8.

152. Ford ES, Galuska DA, Gillespei C et al. C reactive protein and body mass index in children: Findings from the third national health and nutrition examination survey, 1988-94.

J Pediatr 2001; 138: 486-92.

153. Malle E, De Beer FC. Human serum amyloid A protein: a prominent acute phase reactant for clinical practice. Eur J Clin Invest 1996; 26: 427-35.

154. Jensen LE, Whitehead AS. Regulation of serum amyloid A protein expression during the acute phase response. J Biochem 1998; 334: 489-503.

155. Jousilahti P, Salomaa V, Rasi V et al. The association c-reactive protein, serum amyloid A and fibrinogen with prevalent coronary heart disease – baseline findings of the PAIS project. Atherosclerosis 2001; 156: 451-6.

156. Pruzanski W, Stefanski E, de Beer FC et al. Comparative analysis of lipid composition of normal and acute phase high density lipoproteins. J Lipid Res 2000; 41: 1035-47.

157. Coetzee GA, Strachan DR, van der Westhuyzen HC et al. Serum amyloid A containing human high-density lipoprotein 3. Density, size, and apolipoprotein composition. J Biol Chem 1986; 261: 9644-51.

158. Malle EA, Steinmetz A, Raynes JG. Serum amyloid A: an acute phase protein and apolipoprotein. Atherosclerosis 1993; 102: 131-46.

159. De Beer FC, Fagan GR, Gughes RK et al. Serum amyloid a protein concentrations in inflammatory diseases and its relationship to the incidence of reactive systemic amyloidosis. Lancet 1982; 2: 231-4.

160. Urieli-Shoval S, Linke R, Matzner Y. Expression and function of serum amyloid A, a major acute phase protein, In normal and disease states. Curr Opin Hematol 2000; 7: 64-9.

161. Baussermann LL, Herber PN. Degradation of serum amyloid A and apolipoproteins by serum proteases. Biochemistry 1984; 23: 2241-5.

162. Kisilevsky R,Subrahmanyan L. Serum amyloid A changes high-density lipoprotein's cellular affinity. A clue to serum amyloid A's principal function. Lab Invest 1992; 66: 778-85.

163. Liuzzo G, Biasucci LM, Gallimor JR et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. N Engl J Med 1994; 331: 417-24.

164. McCarty MF. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxifylline. Med Hypotheses 1999; 52: 465-77.

165. Amrani DL. Regulation of fibrinogen biosynthesis; glucocorticoid and interleukin-6 control. Blood Coagulation and Fibrinolysis 1990; 1: 443-6.

166. Kerr R, Stirling D, Ludlam C. Interleukin 6 and haemostasis. Br J Haematol 2001; 115: 3-12.

167. Cook NS, Ubben D. Fibrinogen as a major risk factor in cardiovascular disease. Trends Pharm Sci 1990; 11: 444-51.

168. Dormandy JA, Reid HL. Controlled defibrination in the treatment of peripheral vascular disease. Angiology 1978; 29: 80-8.

169. Meade TW, Vickers MV, Thompson SG. The effect of physiological levels of fibrinogen on platelet aggregation. Thromb Res 1985; 38: 527-34.

170. Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta analysis and review of the literature. Ann Intern Med 1993; 118: 956-63.

171. Rillaerts E, Van Gaal L, Xiang DZ. Blood viscosity in human obesity: relation to glucose tolerance and insulin status. Int J Obes 1989; 13: 7139-45.

172. Fanari P, Somazzi R, Nasrawi F et al. Haemorheological changes in obese adolescents after short-term diet. Int J Obes 1993; 17:487-94.

173. Avellone G, Di Garbo V, Cordova R et al. Evaluation of cardiovascular risk factors in overweight and obese subjects. Int Angiol 1994; 13: 25-9.

174. Licata G, Scaglione R, Avellone G et al. Hemostatic function in young subjects with central obesity: relationship with left ventricular function. Metabolism 1995; 44: 1417-21.

175. Landin K, Stigendal L, Eriksson E et al. Abdominal obesity is associated with an impaired fibrinolytic activity and elevated plasminogen activator inhibitor-1. Metabolism 1990; 10: 1044-48.

176. Avellone G, DiGarbo V, Cordova R et al. Coagulation, fibrinolysis and haemorheology in premenopausal obese women with different body fat distribution. Thromb Res 1994; 75: 223-31.

177. Dahlgren F, Janson PO, Johansson S et al. Hemostatic and metabolic variables in women with PCOS. Fertil Steril 1994; 61: 455-60.

178. Ditschuneit HH, Flechtner-Mors M, Adler G. Fibrinogen in obesity before and after weight reduction. Obes Res 1995; 3: 43-8.

179. Cigolini M, Targher G, Bergamo A et al. Visceral fat accumulation and its relation to plasma hemostatic factors in healthy men. Arterioscler Thromb Vasc Biol 1996; 16: 368-74.

180. Marckmann P, Toubro S, Astrup A. Sustained improvement in blood lipids, coagulation, and fibrinolysis after major weight loss in obese subjects. Eur J Clin Nutr 1998; 52: 329-33.

181. Gastrointestinal surgery for severe obesity. National Institues of Health Consensus Development Conference Draft Statement. Obes Surg 1991; 1: 257-66.

182. Executive Summary. Obes Res 1998; 6 (Suppl 2): S51S-63.

183. Stubbs RS, Wickremesekera SK. Insulin resistance in the severely obese and links with metabolic co-morbidities. Obes Surg 2002; 12: 343-8.

184. Pories WJ.Why does the gastric bypass control type 2 diabetes mellitus? Obes Surg 1992; 2: 303-11.

185. Schauer PR, Ikramuddin S, Gourash W. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg 2000; 232: 515-29.