2

Effect of Obesity on Circulating Adipokines and Their Expression in Omental Adipose Tissue of Female Bariatric Surgery Patients

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1. Introduction

This chapter is a review of the effects of excessive, formerly known as morbid, obesity on circulating levels and gene expression of adipokines and related factors in the visceral omental adipose tissue of women undergoing bariatric surgery. The current paradigm is that most of the deleterious metabolic effects of excessive obesity are due to Type 2 diabetes and/or hypertension secondary to the mild inflammatory process resulting from visceral adiposity. The visceral adipose tissue, which is primarily omental fat, acts as an endocrine tumor secreting adipokines that result in hypertension and diabetes. These deleterious effects are reversible after bariatric surgery due to a massive reduction in adipose tissue mass.

The circulating levels and gene expression in fat of many adipokines are affected by excessive obesity. However, a major problem is determining which adipokine alterations are causally related and which are secondary effects of the inflammatory state seen in obesity. Many reports have focused on only one adipokine and suggested that it has a causal relationship but at least 40 adipokines have been linked to excessive obesity by one or more investigators. The relative role of each of these adipokines in human obesity is discussed in this review. It should be noted that the term adipokine refers to any factor, including cytokines, whose circulating levels are affected by release from either the fat or nonfat cells of human adipose tissue.

2. The deleterious effects of human obesity are secondary to enhanced accumulation of visceral adipose tissue

The visceral omental fat of women is important because

i. it plays a key role in the pathogenesis of the deleterious metabolic consequences of obesity and
ii. women comprise 80 to 90% of bariatric surgery patients and
iii. most intra-abdominal fat is omental fat. The omentum also has a central role in an inflammatory response that involves macrophages in defending against peritonitis

(Platell et al., 2000). In obesity per se, this macrophage infiltration into the omentum may result in an enhanced inflammatory response that promotes insulin resistance and ultimately diabetes/hypertension and it has been reported that omentectomy in connection with open bariatric surgery resulted in an enhanced insulin sensitivity as compared to patients undergoing open bariatric surgery without omentectomy (Thorne et al., 2002).

Extreme obesity results in increased risk for hypertension and/or diabetes (Cottam et al., 2004, Pories, 2008, Sugerman et al., 2003). The type 2 diabetes is reversible since, after weight loss of approximately 40 kg or more due to bariatric surgery, the diabetes disappears in over 80% of humans (Pories, 2008; Sugerman et al., 2003). Not all extremely obese individuals develop diabetes or hypertension and for these individuals there is no increased risk of morbidity (Livingston & Ko, 2005). However, there is increasing evidence that the accumulation of visceral omental fat is associated with the development of diabetes/hypertension (Despres & Lemieux, 2006). It is recognized that waist circumference is an effective and inexpensive measure of visceral fat accumulation (Scherzer et al., 2008; Shen et al., 2006) and is a better predictor of coronary heart disease than is BMI (Canoy et al., 2007; Despres et al., 2008; Pischon et al, 2008). Waist circumference correlates with visceral fat accumulation as measured by MRI (Scherzer et al., 2008), DEXA (Shen et al., 2006) or fat mass as measured by bioelectrical impedance (Madan et al., 2006).

3. Most release of adipokines is by the nonfat cells in human adipose tissue except for leptin

Originally it was postulated that most of the adipokine release by adipose tissue was due to the fat cells but it is now clear that leptin is the only adipokine released exclusively by the fat cells. In fact, over a 48h incubation, the release of leptin was 1800% of that by the nonfat cells derived from the same amount of human adipose tissue, while that of adiponectin, amyloid proteins 1&2, haptoglobin and NGF was only 64, 144, 75 and 72% respectively of that by nonfat cells (Fain, 2006). Release of MIF and PAI-1 by fat cells was 37 and 23% of that by nonfat cells while that of cathepsin S, HGF, IL-1β, IL-1Ra, IL-6, IL-8, IL-10 MCP-1, TGF-β1, VCAM-1 and VEGF was 12% or less of that by nonfat cells (Fain, 2006). Clearly, the majority of the inflammatory adipokines are released by the nonfat cells of human adipose tissue, which is hardly surprising since per g of fat in obese women two-thirds of the cells are nonfat cells (Fain, et al., 2006) and it is established that obesity is accompanied by macrophage infiltration into human adipose tissue (Weisberg et al., 2003; Xu et al., 2003).

4. Relationship between circulating levels of adipokines and obesity

There is evidence that the circulating levels of many adipokines are elevated in obesity (Fain, 2010). Since the deleterious effects of obesity on diabetes is reversed in over 80% of the patients after bariatric surgery which reduced the BMI from above 45 to 35 or less (Pories, 2008), it is clear that the appropriate criteria for correlating decreases or increases in circulating adipokines is what happens over the range of BMI values from 30 to 70. Another way of assessing effects of obesity is to examine which adipokines show decreases in their circulating levels after bariatric surgery. An additional problem with regard to circulating adipokines is that the circulating levels of some are either at or below the limits of sensitivity

for their assay and this is a special problem with regard to TNFα and IL-1β. These adipokines may be very important in the inflammatory response seen in obesity but they primarily act as local autocrine or paracrine mediators of inflammation rather than as circulating hormones.

The effects of obesity and coronary artery disease on circulating levels of 16 adipokines are summarized in Table 1. The coronary artery disease patients were 16 individuals undergoing coronary artery bypass surgery. They had an average BMI of 30.1 and were compared with 12 controls undergoing open heart surgery for other reasons. The controls had a BMI of 27.3 and were younger than the coronary artery disease patients. The data were adjusted for age which eliminated effect of CAD on circulating levels of IL-8 and osteoprotegerin leaving only CD14 and adipsin as adipokines affected by coronary artery disease (Sacks et al., 2011). In contrast, obesity over the BMI range of 38 to 66 [mean was 50], in women undergoing bariatric surgery increased the circulating levels of adipsin, FABP4, and secretory phospholipase A_2 [PLA_2] (Table 1).

Circulating levels are elevated in obesity	**Circulating levels are elevated in CAD**	**Circulating levels are not elevated by excessive obesity or CAD**		
Adipsin	Adipsin	CD-163	IL-8	βNGF
FABP4	CD14	sFLT1	Lipocalin-2	RANTES
IL-1Ra		GPX-3	MCP-1	IL-10
$sPLA_2$		ZAG	Osteoprotegerin	

Table 1. Comparison of effects of obesity versus CAD on circulating levels of 17 adipokines. The effects of severe coronary artery disease (CAD) are taken from the report by (Sacks et al., 2011) while the data for obese women is for the same circulating adipokines with significant positive correlation coefficients [Pearson r of ≥ 0.51] between waist circumference and circulating levels in 12-23 bariatric surgery patients not taking drugs for hypertension with BMI values ranging from 38 to 66 and waist circumference from 107 to 168 cm (Fain, 2011).

Only with IL-1Ra was a significant positive correlation seen between waist circumference and circulating levels as well as mRNA expression in omental fat of severely obese female bariatric patients (Fain, 2011). There was no significant correlation between waist circumference and mRNA level for FABP4, adipsin, & PLA_2 in omental fat (Fain, 2011). Circulating levels of adipsin, FABP4 & PLA2 correlated with waist circumference but not with mRNA levels in omental fat. These data suggest that if mRNA levels in omental fat are equivalent to protein expression, then the circulating levels are not regulated solely by omental fat mRNA expression. It may well be that the source of these adipokines is other fat depots. Alternatively the data could be interpreted as compatible with the hypothesis that protein expression is not equivalent to gene expression.

I have examined the effects of obesity in women on gene expression of almost all the putative adipokines discussed in the next section, except for CRP, which is not released by human fat (Fain, 2006). I found significant positive correlations between waist circumference and mRNA levels in human omental fat for 4 of the 40 proteins: amyloid A [r = 0.57], PAI-1 [r = 0.53], IL-1Ra [r = 0.45] and leptin [r = 0.48] (Fain, 2011). Of these proteins only amyloid A and leptin are preferentially expressed in the fat cells of human omental fat (Fain, 2010).

5. Individual adipokines

The following sections discuss 40 putative adipokines listed in alphabetical order that have been linked to obesity and inflammation. It should be noted that correlations between waist circumference or BMI and circulating levels of any protein indicate only that the protein is a marker molecule rather than the maker of obesity. In view of the many known circulating marker molecules for obesity, caution should be exercised and direct proof demanded before any causal relationship is established. Furthermore, most reports are linked to a particular molecule and the professional careers of the authors are directly linked to their ability to persuade others that the particular marker of interest to them is causally linked to obesity.

5.1 Adiponectin

Adiponectin is a protein that circulates at relatively high levels in humans and is related to the C1q complement factor. Adiponectin, unlike leptin, is not produced solely by fat cells in humans (Fain et al., 2008c). Within 10 years of its discovery adiponectin was accepted as an anti-diabetic, anti-atherosclerotic and anti-inflammatory agent secreted by adipocytes whose low levels in obesity were related to the insulin-resistance in obesity (Trujillo & Scherer, 2005). While the circulating levels of most adipokines are elevated in obesity, this is not the case for adiponectin whose circulating levels negatively correlate with BMI values between 18 and 30, but in males there was no further drop in circulating adiponectin at BMI values above 32 (Arita et al., 1999). Negative effects of obesity on circulating adiponectin have been reported comparing individuals with mean BMI values of 27 versus 35 by Engeli et al., (2003) and by Hoffstedt et al., (2004) comparing humans with BMI values of 24 versus 37. One complexity with regard to circulating levels of adiponectin (Hung et al., 2008) and leptin (Thomas et al., 2000) is that they are both higher in women than in men but the significance of this is not yet understood.

Elevated concentrations of circulating adiponectin have been associated with a lower incidence of type 2 diabetes (Li et al., 2009; Zhu et al., 2010). However, circulating adiponectin is actually positively correlated with all cause mortality as well as cardiovascular mortality in type 2 diabetics (Forsblom et al., 2011). In another study Luc et al., (2010) found no correlation between total circulating adiponectin and cardiovascular disease in men enrolled in the PRIME study. Elevated levels of adiponectin have also been associated with stroke mortality (Nagasawa et al, 2011). Clearly low adiponectin levels in plasma of obese individuals may not necessarily be linked to increased mortality or development of type 2 diabetes and are not consistently seen. I conclude that adiponectin is not produced solely by fat cells and the function of adiponectin remains to be elucidated as well as whether it is causally linked to the development of type 2 diabetes in obesity. It may just be a unique marker of obesity whose levels are sometimes, but not always, lower in obesity.

5.2 Adipsin/complement D

Adipsin is another name for complement factor D that is a novel serine protease whose only known substrate is another complement serine protease known as factor B (Volanakis and Narayan, 1996). Complement factor D was re-discovered and named adipsin since it was

found in murine adipocytes and circulating levels were lower in several animal models of obesity (Rosen et al., 1989). However, Napolitano et al., (1994) found that in humans just the opposite was seen in that circulating levels of adipsin positively correlated with the extent of obesity. I found a similar correlation between circulating adipsin and BMI but there was no effect of obesity on the gene expression of adipsin in omental adipose tissue of obese women (Fain, 2011). The complement system is an essential element in our innate defense system and it is possible that the increase in adipsin/complement D seen in human obesity is a reflection of an enhanced inflammatory response to obesity. What accounts for the elevations in circulating adipsin/complement D in obesity is unclear, but it is an obesity marker.

5.3 Amyloid A

The serum amyloid A proteins are major acute-phase reactants released by the liver whose circulating levels increase dramatically in inflammation and obesity (Poitou et al., 2005; 2006; Yang et al., 2006a). Circulating levels of amyloid A (Yang et al., 2006a) as well as gene expression in adipose tissue (Yang et al., 2006a; Fain, 2011) correlated with BMI. In fact of over 100 genes whose expression was correlated in omental adipose tissue with BMI, the highest positive correlation was seen for amyloid A (Fain 2011). A major expression site of Amyloid A is adipose tissue, which is postulated to contribute to circulating levels (Poitou et al., 2005; Sjoholm et al., 2005) and Yang et al (2006a) have suggested that amyloid A is both a proinflammatory and lipolytic adipokine in humans. Whether this is the case remains to be demonstrated but these are intriguing possibilities.

5.4 Angiotensin converting enzyme (ACE)

ACE is a zinc metallopeptidase that cleaves the C-terminal dipeptide from angiotensin I to form Angiotensin II. The presence of the major components of the renin-angiotensin system in human adipose tissue has led to the suggestion that its regulation and function are involved in the hypertension linked to visceral adiposity (Giacchetti et al., 2002). The circulating levels of ACE are unchanged in obesity as is its gene expression in adipose tissue of humans but there is a positive correlation with blood pressure (Gorzelniak et al, 2002). It has been difficult to get evidence for a key role of ACE but recently it was reported that ACE inhibition using captopril treatment of mice on a high fat diet reduced the extent of obesity and the expression of markers of inflammation in murine adipose tissue (Premaratna et al. 2011). Lee at al (2008a) reported that in obese rats, angiotensin receptor blockade reduced insulin resistance by modification of adipose tissue metabolism. Abuissa et al (2005) demonstrated that anti-hypertensive agents such as ACE inhibitors or angiotensin receptor blockers can reduce the onset of diabetes in humans by approximately 25%. However, there is no evidence that circulating levels of ACE are altered in obesity.

5.5 Angiotensinogen

This protein is made in large quantities by the liver and secreted into the circulation where it can be cleaved by renin and/or cathepsin D to form angiotensin I. Karlsson et al (1998) demonstrated that angiotensinogen is also made in adipose tissue and is enriched in adipocytes, which was confirmed by Fain et al., (2008a). The reason for this is still not well understood but it could be a link between obesity and hypertension. Gorzelniak et al (2002) reported that angiotensinogen gene expression in human subcutaneous adipocytes was

negatively correlated with the BMI of the adipocyte donors and this may be an adaptive response to reduce angiotensin II formation in obesity. Angiotensinogen gene expression has consistently been reported to be lower in subcutaneous than in omental adipose tissue of humans (Giacchetti et al., 2002, van Harmelen et al., 2000; Fain, 2010) but the significance of this is also unknown. However, this might be linked to the deleterious effects of visceral obesity on the development of hypertension and diabetes in obese humans but the role of angiotensinogen made in fat is unclear.

5.6 Apelin

Apelin is a novel bioactive peptide that is the endogenous ligand of the orphan G protein-coupled receptor AJP (Masri et al., 2005; Castan-Laurell et al., 2011). The circulating levels of apelin and leptin are elevated in obesity but unlike leptin, the gene expression of apelin is found to the same extent in both nonfat and fat cells of human adipose tissue (Boucher et al., 2005; Heinonen et al., 2005). The apelin receptor is expressed on the surface of T lymphocytes and endothelial cells (Masri et al., 2005) and the enhanced levels seen in obesity may reflect release by nonfat cells of fat. A null mutation of the apelin receptor in mice had little effect except for an enhanced vasopressor response to apelin (Ishida et al., 2004). Hung et al (2011) found that inhibitors of the renin-angiotensin system enhanced the secretion of apelin by adipocytes. Fain (2011) found that extremely obese women taking anti-hypertensive agents had decreased expression of apelin in their omental adipose tissue that was accompanied by an enhanced expression of the renin receptor and CD150/SLAMF-1. These data suggest a counter regulatory role of apelin signaling to that of the angiotensin with regard to blood pressure regulation in humans.

5.7 Cathepsin S

Cathepsins are endopeptidase cysteine proteases that are secreted by inflammatory cells. Lafarge et al., (2010) suggested that cathepsin S is one of the most dysregulated genes in adipose tissue of obese subjects since its expression and circulating levels positively correlated with BMI. While in humans there are other cathepsins, it is cathepsin S that is more influenced by obesity (Naour et al., Lafarge et al., 2010). It has been suggested that cathepsin S is the link between obesity and inflammation in obesity (Taleb and Clement, 2007) but all the studies to date are correlative. For example Jobs et al., (2010) found a high correlation between circulating cathepsin S and c-reactive protein [CRP] but what this means is unclear since both are inflammatory response proteins made by the liver. It is perhaps better to describe the elevations in cathepsin S seen in obesity as a response to the inflammation with no proof yet for any type of causal relationship.

5.8 CD14

CD14 is a glycolipid-anchored membrane protein that functions as a receptor for the complex of lipopolysaccharide binding protein plus lipopolysaccharide and is also released into the circulation. In knockout mice lacking CD14 there is less diet-induced obesity and macrophage accumulation in adipose tissue (Cani et al., 2007; Roncon-Albuquerque et al., 2008). CD 14 is a co-receptor with toll-like receptor 4 [TLR4] for activation of macrophages by lipopolysaccharide and by free fatty acids, which Fessler et al (2009) have postulated to be the link between obesity and inflammation. However, there is no evidence that obesity affects the

circulating levels of CD 14 (Fain, 2011; Manco et al., 2007) despite the fact that release of CD14 by explants of human omental adipose tissue was enhanced in fat from obese individuals (Fain et al., 2010). I conclude that circulating CD 14 is not an obesity marker.

5.9 C reactive protein [CRP]

CRP is a prototypical acute phase protein released by the liver and its circulating levels can increase by 10,000-fold within hours of infection or injury. Recently CRP has been proposed as a predictive biomarker for cardiovascular disease risk although it has poor predictive value in humans (Levinson et al., 2004). Yudkin et al., (1999) originally reported that obesity is associated with elevated release of IL-6 by human adipose tissue and enhanced circulating levels of IL-6 and CRP. These results have been confirmed by Festa et al., (2001), Hanusch-Enserer et al., (2003) and Maachi et al., (2004). There is virtually no synthesis of CRP by adipose tissue and the small amount of release seen in vitro could be due to release of CRP taken up from the circulation (Fain, 2006). CRP levels in humans correlate with those of serum amyloid (Larsson and Hansson, 2003) suggesting that both are inflammatory markers released by the liver in response to the low-grade inflammation induced by obesity. At least for CRP in mice there is direct evidence that it is not involved in the development of atherosclerosis, clearly indicating that it is a marker not a maker of atherosclerosis (Nilsson, 2005).

5.10 Endothelin-1

Endothelin is a potent vasoconstrictor peptide that is released by endothelial cells. Yudkin (2007) pointed out that obese humans show endothelial dysfunction that may be due to vascular insulin resistance. Takahashi et al., (1990) had earlier reported that circulating levels of endothelin-1 are 3-fold higher in diabetics than in non-diabetic humans. Van Harmelen et al., (2008) reported that the release of endothelin-1 by subcutaneous adipose tissue in vivo was greater in obese individuals and that endothelin blocked the anti-lipolytic action of insulin in omental but not subcutaneous adipocytes. Gogg et al., (2009) subsequently reported that in microvascular endothelial cells isolated from subcutaneous adipose tissue of type 2 diabetics, insulin action was impaired at the level of IRS-1 and the PI 3-kinase pathways. They suggested that enhanced endothelin-1 was responsible for this impairment. These results suggest that studies should be designed to test the hypothesis that impaired insulin action in obesity is secondary to enhanced endothelin-1 release by endothelial cells.

5.11 Fatty acid binding protein 4 [FABP-4]

FABP4 is a member of a family of lipid chaperone proteins that bind with high affinity hydrophobic ligands such as long chain fatty acids (Furuhashi et al., 2008). FABP4 is also known as aP2 and appears to be involved in the movement of fatty acid out of the fat cell during lipolysis (Coe et al., 1999). In the absence of FABP4 there is enhanced accumulation of fatty acids in fat cells (Coe et al., 1999) and reduced expression of inflammatory cytokines in macrophages (Furahashi et al, 2008). Hotamisligil et al., (1996) reported that in FABP4-knockout mice, obesity still developed on a high-fat diet but insulin resistance or diabetes was not seen. These data support the hypothesis that the link between obesity and inflammation in adipose tissue is enhanced lipolysis and free fatty acid release seen in the enlarged fat cells that accumulate in obese animals. In the absence of FABP4 the release of

fatty acids by fat cells is impaired which results in reduced lipolysis. In obesity the circulating levels of FABP4 show a positive correlation with BMI (Xu et al., 2007; Terra et al., 2011; Fain, 2011). This suggests that the levels of FABP4 are elevated in obesity ensuring that fatty acid release is enhanced and the TLR4 receptors are activated in the monocytes and neutrophils surrounding the fat cells. This results in inflammatory adipokine release and recruitment of macrophages (Fessler et al., 2009). An alternative hypothesis is that the TLR4 receptors are less important in transmitting free fatty acid effects and that the role of FABP4 in macrophages is to move toxic free fatty acids into the macrophages. Furuhashi et al., (2007) have pointed out that inhibition of this protein with small molecules might be an effective way to prevent the development of diabetes in obesity. However, Lan et al., (2011) reported that such a drug ameliorated dyslipidemia but not the insulin resistance due to diet-induced obesity in mice.

5.12 Glutathione peroxidase 3 [GPX-3]

GPX-3 along with glutathione reductase are enzymes involved in the removal of hydrogen peroxide formed in mitochondria and are thus able to reduce the level of reactive oxygen species in cells (Haddad and Harb, 2005). Circulating levels of GPX-3 are down in patients with coronary atherosclerosis but by only 14% (Dogru-Abbasoglu et al., 1999) and slightly lower in obese humans as well (Lee et al, 2008b). However, negative effects of GPX-3 knockout studies in mice on the development of obesity (Yang et al, 2009) and of obesity in women on circulating levels of GPX-3 (Fain, 2011) suggest that the role of this enzyme in obesity is unclear. In conclusion, the general consensus is that obesity does not result in enhanced circulating levels of GPX-3.

5.13 Haptoglobin

Haptoglobin is an acute phase protein primarily synthesized in the liver of humans that binds hemoglobin (Quaye, 2008). Obesity is associated with elevated circulating levels of haptoglobin (Scriba et al., 1979; Chiellini et al., 2004). In murine in vitro differentiated adipocytes a proteomic approach identified haptoglobin as the most abundant protein secreted by these cells (Kratchmarova et al., 2002). However, in human adipose tissue haptoglobin release in vitro by both the nonfat and the fat cells was 1 to 5% of that for IL-8, IL-6 or adiponectin (Fain et al., 2004b). They concluded that adipose tissue release of haptoglobin probably contributed very little to circulating levels as did Taes et al., (2005). In contrast, Chiellini et al., (2004) concluded that haptoglobin was a novel marker of adiposity and that adipose tissue contributes to circulating levels in humans was important. Unfortunately haptoglobin does not appear to be a novel or unique marker for adiposity but a member of the acute phase response family released by liver whose circulating levels are elevated in mild inflammatory states such as those seen in obesity.

5.14 Interleukin-1β [IL-1β] and IL-1 receptor antagonist [IL-1 Ra]

IL-1β and TNFα are generally thought of as prototypical pro-inflammatory cytokines. Blockade of both pathways, but neither one alone, inhibited the inflammatory response based on IL-8 and IL-6 release by 40 to 50% when explants of human visceral omental adipose tissue are incubated for 48 h (Fain et al., 2005a). In interleukin-1 receptor knockout mice the insulin resistance and adipose tissue inflammation induced by a high fat diet is

abolished suggesting a key role for IL-1β in the inflammatory response due to obesity (McGillicuddy et al., 2011). IL-1β is primarily paracrine factor acting locally since circulating levels are below the sensitivity of available assays (Jung et al., 2010). However, IL-1β gene expression in both adipose tissue and liver decreases 6 months after bariatric surgery indicating a reduction in the chronic inflammatory state (Moschen et al., 2011).

In contrast, the circulating levels of IL-1 Ra are elevated in obesity (Fain, 2011; Juge-Aubry et al., 2003: Jung et al., 2010; Meier et al., 2002). Furthermore the gene expression of this protein, unlike that of IL-1β, in omental adipose tissue of humans correlates with waist circumference or BMI of obese women (Fain, 2011). IL-1Ra is a physiological antagonist of IL-1β since it competes with the IL-1 receptors for the available IL-1β and is sold as an injectable drug [anakinra] for the reduction of immune-mediated inflammatory conditions (Goldbach-Mansky, 2009). The elevated circulating levels of IL-1Ra that are seen in obesity as well as enhanced formation in adipose tissue in obesity are perhaps the best evidence that IL-1β formation is enhanced in obesity. Fain (2011) found that the mRNA expression in omental fat of IL-1Ra was the only one showing a positive correlation between waist circumference and mRNA levels in massively obese women taking anti-hypertensive drugs. In contrast, a positive correlation was seen for p67 phox, PAI-1 and 11β HSD1 mRNA expressions only in women not taking anti-hypertensive drugs. What this means is unclear but suggests that unexpected interactions exist between obesity and hypertension with regard to mRNA expression in omental fat.

5.15 Interleukin-6 [IL-6]

IL-6 is a well-established stimulator of acute-phase protein secretion by liver that can produce dramatic increases in circulating CRP, amyloid protein and haptoglobin (Heinrich et al., 1990). Yudkin et al., (2000) postulated that enhanced formation of IL-6 is important in the development of coronary heart disease based on the assumption that IL-6 is the most important mediator of an inflammatory response. It is established that obesity results in elevations in circulating IL-6 (Khaodhiar et al., 2004; Vozarova et al., 2001). While in adipose tissue the IL-6 content positively relates to an enhanced insulin resistance (Bastard et al., 2002) there is evidence that IL-6 is beneficial for insulin action on muscle (Carey and Febbraio, 2004; Kim et al., 2009). Furthermore IL-6 knockout mice develop obesity indicating complexities in IL-6 action in rodents (Wallenius, et al., 2002). Whatever its function, the circulating levels of IL-6 are clearly elevated in obesity.

5.16 Interleukin-8 [IL-8]

IL-8 is the prototypical human chemokine that is involved in the recruitment of circulating neutrophils to its site of release (Reape and Groot, 1999). Circulating levels of IL-8 are elevated in obesity (Bruun et al., 2003; Straczkowski et al., 2002). Release by adipose tissue explants, but not by adipocytes, of women with an average BMI of 42, was elevated as compared to those with a BMI of 32 (Fain et al., 2004a). IL-8 release was primarily by the nonfat cells of adipose tissue and release by omental was greater than that by subcutaneous adipose tissue explants incubated in vitro for 48 h (Bruun et al., 2004). It is possible that IL-8 is more important than any other adipokine in the inflammatory response to obesity especially with regard to recruitment of neutrophils and conversion to macrophages in adipose tissue.

5.17 Interleukin-10 [IL-10]

IL-10 is a cytokine commonly thought to have anti-inflammatory properties whose secretion by macrophages is coordinated with that of pro-inflammatory cytokines in that lipopolysaccharide will increase the release of IL-10 as well as inflammatory cytokines (Mocellin et al., 2003). In vitro studies with human adipose tissue indicated that IL-10 release is predominantly by the nonfat cells such as macrophages and is enhanced in adipose tissue from obese women (Fain, 2010). While adipose tissue macrophages are predominately of the classic-anti-inflammatory M2 phenotype, based on surface markers expression, they secrete higher amounts of pro-inflammatory adipokines such as TNF-α, IL-6, Il-1β and MCP-1 than the M1 macrophages (Zeyda et al., 2007). Esposito et al., (2003) reported that circulating levels of IL-10 were elevated in obesity in women and reduced, along with those of IL-6 and CRP, in obese women without the metabolic syndrome after a significant [11 kg] loss of weight. However, Fain (2011) reported no effect of BMI on circulating levels of IL-10 and Manigrasso et al., (2005) reported that after body weight reduction of 8 kg in android obese women there was no significant change in circulating levels of adiponectin or IL-10 while low adiponectin correlated with low IL-10 levels. Apparently, there is no large or reproducible effect of obesity on circulating levels of IL-10 and whether it is always an anti-inflammatory adipokine is unclear (Mocellin et al., 2003).

5.18 Leptin

Leptin was discovered in 1994 through positional cloning of the mouse *ob* gene (Zhang et al., 1994) and its absence leads to massive obesity in mice and men as well as delayed sexual maturation and immune defects (Dagogo-Jack, 2001; Gautron and Elmquist, 2011). However, few cases of human obesity are due to an absence of leptin since the vast majority of obese humans have elevated levels of leptin that correlate with BMI (Considine et al., 1996). There are sex differences as well since the circulating levels of leptin are higher in women than in men at all BMI values (Smirnoff et al., 2001). Furthermore, similar correlations of circulating values with BMI were soon reported for acute phase proteins such as amyloid and CRP as well as with soluble TNF receptors and PAI (van Dielen et al., 2001). Their report and many others have amply demonstrated that elevated body fat content is associated with a pro-inflammatory state and enhanced circulating levels of leptin. Furthermore, Kshatriya, et al., (2011) recently suggested that leptin might have a pathophysiological role in the development of hypertension and vascular heart disease in obesity.

Whether leptin is a pro-inflammatory hormone in obese humans is unclear but unlike all the known inflammatory factors it is released only by fat cells. The in vitro release of leptin is almost exclusively by fat cells as compared to the nonfat cells derived from human visceral omental adipose tissue while release of LPL is about 80%, amyloid about 60 % and adiponectin about 40% of total release by fat cells plus nonfat cells (Fain, 2010). To date, leptin appears to be the only protein made exclusively by fat cells and its formation apparently reflects fat cell size as reviewed by Fain and Bahouth (2000). In incubated fat cells or adipose tissue explants the greatest stimulation of leptin release is due to glucocorticoids which may be secondary to their anti-inflammatory effect (Fain et al., 2008d) and in vivo administration of glucocorticoids elevated circulating levels of leptin (Dagogo-jack, 2001). However, the link between fat cell size and enhanced leptin release remains to be demonstrated but one theoretical possibility is stretch receptors within fat cells.

5.19 Lipocalin-2

This protein was originally found as a protein secreted by human neutrophils. All lipocalins have an eight-stranded continuously hydrogen-bonded antiparallel β-barrel that can bind and transport a wide variety of small hydrophobic molecules such as fatty acids (Zhang et al., 2008). Based on studies in rodents, Yan et al., (2007) and Wang et al., (2007) concluded that lipocalin-2 was an inflammatory marker released by adipocytes whose release was enhanced by obesity. However, Jun et al., (2011) found no effect of global ablation of lipocalin-2 on obesity-mediated insulin resistance in vivo. In obese humans no statistically significant effect of BMI was found on circulating levels of lipocalin-2 (Stejskal et al., 2008) and this was confirmed by Fain (2011). Furthermore lipocalin-2 was found in and released almost exclusively by the nonfat cells rather than the fat cells isolated from human omental adipose tissue (Fain, 2010). Total lipocalin-2 release by explants of incubated human omental adipose tissue in vitro positively correlated with BMI of the humans from whom fat was obtained as was the case for release of pro-inflammatory adipokines such as IL-8, IL-10, CD14, and RANTES (Fain, 2010). However, the circulating levels of IL-8, IL-10, CD14, and RANTES did not correlate with BMI (Fain, 2011). Lipocalin-2 thus appears to be an inflammatory marker whose circulating levels are not invariably elevated in obesity.

5.20 Lipoprotein lipase [LPL]

This multi-functional enzyme is the rate-limiting enzyme for the hydrolysis of circulating lipids containing triglycerides (Wang and Eckel, 2009). LPL was shown by Rodbell (1964) to be preferentially released by fat cells rather than the non-fat cells of rat adipose tissue. Similar results are seen in human omental adipose tissue and the total release of LPL by adipose tissue correlated with BMI (Fain, 2010). The circulating levels of LPL have been reported to be unrelated to BMI (Kobayashi et al, 2007; Magkos et al., 2009). However, the elevated subcutaneous adipose tissue expression of LPL was reduced to control values in individuals 12 months after bariatric surgery (Pardina et al., 2009). Fain (2010) also found a positive correlation between BMI and the release of LPL by explants of human omental fat incubated in vitro. The available data indicate that LPL protein expression in adipose tissue, but not the circulating levels, correlate positively with obesity.

5.21 Macrophage migration inhibitory factor [MIF]

MIF is a pro-inflammatory cytokine that is involved in many inflammatory disorders (Donn and Ray, 2004; Kleemann and Bucala, 2010). Both MIF and MCP-1 seem to be especially important in macrophage recruitment into adipose tissue. Verschuren et al., (2009) found that in MIF knockout mice the development of obesity with age was not affected but the development of the inflammatory cascade and insulin resistance were markedly reduced. MIF release in vitro by incubated explants of human adipose tissue or adipocytes (Skurk et al., 2005) had a positive correlation coefficient of approximately 0.5 with BMI of the fat donors. Dandona et al., (2004) reported a similar correlation between circulating levels of MIF and BMI. Church et al., (2005) reported that a weight loss of approximately 14 kg over 8.5 months resulted in a 40% decrease in circulating levels of MIF. MIF appears to be an obesity-linked inflammatory factor whose circulating levels are elevated in obesity.

5.22 Monocyte chemoattractant protein 1 [MCP-1]

MCP-1 is also known as chemokine CCL2 and is a mononuclear cell chemoattractant protein that is a pro-inflammatory adipokine (Frangogiannis, 2004). Circulating levels of MCP-1 have been reported to be elevated in obese humans (Malavazos et al., 2005) and to have a positive correlation with BMI (Christiansen et al., 2005). However, neither Miller et al., (2002) or Fain (2011) found any effect of obesity on circulating levels of MCP-1. Madani et al., (2009) reported that MCP-1 and IL-6, but not RANTES, were released in vivo by human abdominal subcutaneous adipose tissue to a far greater extent in individuals with a BMI of 43 as compared to controls with a BMI of 25. Dahlman et al (2005) found that obesity increased the mRNA level of MCP-1 in human subcutaneous adipose tissue by 2.6-fold. The in vitro release of MCP-1 by adipose tissue explants was also increased by 6 to 10-fold without any change in the in vivo release. These data indicate that while obesity enhances MCP-1 release by adipose tissue there appears to be little contribution of adipose tissue to its circulating levels.

5.23 Nesfatin-1

This novel anorexigenic peptide is processed from nucleobindin-2 and released by adipose tissue (Ramanjaneya et al., 2010). While they reported a positive correlation of 0.63 between circulating levels of nesfatin-1 and BMI, the opposite was reported by Tsuchiya et al., (2010). However, Tan et al., (2011) found a positive correlation of 0.83 between the circulating nesfatin-1 and BMI, in 38 subjects [20 were women] with BMI values ranging from 16 to 38. It is unlikely that nesfatin-1 is derived from nucleobindin-2 gene expression solely in fat cells as is the case with leptin. I [unpublished studies] have found that the ratio of nucleobindin-2 gene expression in fat as compared to nonfat cells derived from human omental adipose tissue was 0.44 while that for leptin was 28. Furthermore, nucleobindin-2 is a ubiquitous Ca^{2+} binding protein that may participate in Ca^{2+} storage in the Golgi as well as in other biological processes involving DNA-binding and protein-protein interactions (de Alba and Tjandra, 2004). There is also evidence that it associates with cyclooxygenase-2 in human neutrophils (Leclerc et al., 2008). It is strange that nesfatin-1 is derived from a precursor protein with so many functions. However, it is possible that nesfatin-1 is formed in fat cells from nucleobindin-2. This hypothesis remains to be tested and at the moment the relationship of nesfatin-1 to fat cell metabolism is unclear and it also remains to be proven that nesfatin-1 is formed and released by fat cells much less that it functions physiologically as an anorexigenic peptide.

5.24 Omentin/intelectin

Omentin has been described as a novel adipokine secreted by omental adipose tissue (Schaffler et al., 2005; Yang et al., 2006b; Tan et al., 2008) but it is actually a lectin that binds to the galactofuranose moiety in the carbohydrate chains of bacterial cell walls (Tsuji et al., 2001). Omentin/intelectin is involved in mucosal defense mechanisms in the small intestinal brush border (Wrackmeyer et al., 2006). Fain et al., (2008b) found that omentin/intelectin gene expression was almost exclusively in the nonfat cells of omental fat and its expression in epicardial fat was 100-fold higher than that in subcutaneous fat. This is what is expected if omentin is made in endothelial cells of blood vessels derived from mesothelial cells of the sphlanchopleuric mesoderm of the gut. Thus it is hardly surprising that circulating levels of

omentin/intelectin are negatively correlated with the extent of carotid intima-media thickness (Shibata et al., 2011) since they are probably derived from the endothelial cells of the blood vessels. Female subjects have higher circulating levels of omentin than male subjects and those levels correlate with the circulating levels of adiponectin, both being negatively associated with insulin resistance (Yan et al., 2011). These findings confirm the original report by de Souza Batista et al., (2007) that circulating levels of omentin/intelectin are negatively correlated with BMI and insulin resistance. I conclude that omentin/intelectin is not really an adipokine but a circulating factor derived from the endothelial cells of all the blood vessels in the abdominal cavity. It appears to be a marker of endothelial cells rather than of fat cells.

5.25 Orsomucoid/α1 acid glycoprotein

Orsomucoid is also known as α1 acid glycoprotein and is one of the most abundant plasma proteins (Lee et al., 2010). It is an acute phase protein secreted by the liver in response to stress and inflammation. In mice, it is also induced in the adipose tissue in obesity and its formation is not further enhanced by inflammatory stimuli or reduced in the diabetic state (Lin et al., 2001; Lee et al., 2010). It is clearly not an inflammatory adipokine since in human omental adipose tissue incubated in primary culture, its gene expression is markedly enhanced by dexamethasone which inhibited expression of inflammatory adipokines (Fain et al., 2010b). In humans, circulating levels of orsomucoid are not lower in diabetic subjects and show a weak positive correlation with BMI as expected of an inflammatory response protein (Akbay et al., 2004; Maachi et al., 2004). Orsomucoid appears to be a unique inflammatory response protein whose circulating levels poorly respond to the degree of obesity or diabetes in humans.

5.26 Osteoprotegerin [OPG]

OPG is a secreted glycoprotein of the TNF receptor family that is released by many cells including those in atherosclerotic plaque lesions in response to inflammatory stimuli (Venuraju et al., 2010). There is evidence in humans for a positive relationship between circulating levels of OPG and the severity of atherosclerosis (Venuraju et al., 2010). However, circulating levels of OPG increase with age (Gannage-Yared et al., 2008; Sacks et al., 2011) and after correcting for age there was no effect of severe coronary artery disease on circulating levels of OPG (Sacks et al., 2011). Obesity effects on circulating OPG have been contradictory to say the least. Gannage-Yared et al., (2008) and Fain (2011) reported no change while Holecki et al., (2007) and Ashley et al., (2011) reported decreases in obesity. Venuraju et al., (2010) concluded that there is no consensus on the relationship between BMI or other cardiovascular risk factors and the circulating levels of OPG much less the function of this protein in humans.

5.27 Plasminogen activator inhibitor protein-1 [PAI-1]

PAI-1 is also known as serpin E1 and is a member of the serpin family of serine protease inhibitors. PAI-1 is the predominant inhibitor of the fibrinolytic system (Alessi et al., 2007). The release of PAI-1 by visceral adipose tissue is primarily by nonfat cells such as macrophages and greater than that by subcutaneous human fat (Bastelica et al., 2002; Fain et

al., 2004a). Total release by human fat in vitro correlates with BMI (Fain, 2010) and the gene expression of PAI-1 in visceral omental fat of obese women correlated to a greater extent with BMI than that of inflammatory adipokines such as TNFα, MCP-1, IL-1β, IL-6, IL-8 or MIF (Fain, 2011). Alessi et al., (2007) have reviewed the evidence that circulating PAI-1 levels are enhanced in obesity and are primarily produced by macrophages in adipose tissue. While Lindeman et al., (2004) confirmed the high correlation between visceral fat and circulating PAI-1, their in vivo measurements of release from visceral fat were negative. They concluded that the relationship between PAI-levels and visceral fat is as co-correlates rather than a causal relationship.

5.28 Secretory type II phospholipase A_2 [PLA_2]

PLA_2 is an acute phase protein that is able to degrade phospholipids present in lipoproteins and cell membranes thus releasing inflammatory molecules (Rosenson and Gelb, 2009). It is reported to be, like CRP, an independent risk factor for coronary heart disease (Kugiyama et al., 1999). Circulating levels of PLA_2 are higher in women than in men and reported to be positively correlated with waist circumference in obese women (Rana et al., 2011; Weyer et al., 2002; Fain, 2011). It has been claimed that PLA_2 is secreted by epicardial adipose tissue and over expressed in humans with coronary artery disease (Dutour et al., 2010) but Sacks et al., (2011) failed to see elevations in circulating PLA_2 in humans with severe coronary artery disease or any difference in its gene expression in epicardial, sternal or substernal fat of controls as compared to those with coronary artery disease. I conclude that PLA_2 is primarily an obesity marker.

5.29 Regulated on activation, normal T cell expressed and secreted [RANTES]

In obese mice, both the levels of mRNA in fat and protein secretion of RANTES are enhanced by obesity that is accompanied by increased accumulation in adipose tissue of T cells as well as macrophages (Wu et al., 2007). Maury et al., (2007) reported that RANTES was released in greater amounts by fat cells isolated from the omental adipose tissue of obese humans but Fain et al., (2010a) found no effects of obesity on the total release of RANTES by explants of human adipose tissue in primary culture. Furthermore, Madani et al., (2009) found no effect of obesity on in vivo release of RANTES by human subcutaneous adipose tissue under conditions where increases in IL-6 and MCP-1 could be readily detected. Madani et al., (2009) also observed that circulating levels of RANTES were far higher than could be accounted for release by adipose tissue. They concluded that it is more likely that RANTES acts on adipose tissue.

5.30 Renin receptor protein

This is an intracellular protein that is expressed in the nonfat cells of human adipose tissue. It may increase angiotensin I generation from angiotensinogen by enhancing the uptake of circulating renin thus enhancing the activity of the renin-angiotensin system in visceral adipose tissue (Engeli et al., 1999; Achard et al., 2007). In severely obese (BMI of 49) non-diabetic women taking anti-hypertensive agents the gene expression in omental adipose tissue of the renin receptor was increased by 60% while that of ACE and angiotensinogen was unaffected (Fain, 2011). Fowler et al., (2009) have shown in rodents that adipose tissue may control its own local renin concentration independent of plasma renin. These data

suggest that the renin receptor protein is important in local regulation of angiotensin II formation in adipose tissue. This is a promising area for future studies and suggests that the regulation of the renin-angiotensin system in adipose tissue is both more important and more complex than originally envisioned.

5.31 Resistin

Steppan et al., (2001) based on studies in rodents, postulated that resistin was secreted by fat cells and was the missing link between obesity and diabetes. However, studies in human adipose tissue have shown that resistin is neither released by fat cells (Fain et al., 2003) nor are detectable amounts of resistin mRNA expressed in human fat cells (Nagaev and Smith, 2001; Savage et al., 2001; Janke et al., 2002; Fain, 2010). It is now accepted that resistin is produced largely by macrophages (Lehrke et al., 2004) and not linked to markers for insulin resistance or adiposity (Hasegawa et al., 2005). The consensus is that circulating resistin is not derived from adipose tissue but is involved in inflammation under some conditions. Clearly in humans, resistin is not an important factor released by fat cells that links insulin resistance and obesity.

5.32 Retinol binding protein 4 [RBP-4]

This protein is a member of the lipocalin family of molecules that bind small hydrophobic molecules such as retinol and is expressed at high levels in liver as well as adipose tissue (Kotnik et al., 2011). Like leptin, but unlike most putative adipokines, it is expressed exclusively in the fat cells of human adipose tissue (Fain, 2010). The laboratory of Barbara Kahn suggested that RBP-4 is causally related to insulin resistance in obesity and type 2 diabetes (Yang et al., 2005; Graham et al., 2006). However, Kotnik et al., (2011) suggested that the evidence for an association between obesity and circulating as well as adipose tissue levels of RBP4 is not a consistent finding in clinical studies. Some of these differences could be due to confounding factors such as procedures for collection of blood and the antibodies used for the assays as well as sex differences, age, retinol status, iron status and kidney function which have all been shown to affect circulating levels of RBP4. Most probably, as suggested by Yao-Borengasser et al., (2007), RBP-4 gene expression in human fat correlates with inflammation rather than insulin resistance and the great hope that this would be a link between obesity and insulin resistance is still just a great hope.

5.33 Thrombospondin-1 [TSP1]

TSP1 is an inhibitor of angiogenesis that is able to activate the latent TGFβ1 complex and interact with CD36 on endothelial cells leading to apoptosis (Bornstein, 2009). Varma et al., (2008) postulated that TSP-1 is an adipokine associated with obesity, inflammation and insulin resistance. While they workers reported that its gene expression in fat cells was 4-fold that of nonfat cells, Fain (2010) found only a non-significant 1.8-fold increase in fat cells over that in nonfat cells of omental adipose tissue. Bornstein (2009) pointed out that TSP-1 is synthesized and secreted by a wide variety of cells in culture including endothelial cells, fibroblasts and smooth muscle cells. Clearly TSP-1 is not an adipokine in the sense of being a protein preferentially expressed in fat cells but is rather found in all cells examined to date. The major function of TSP-1 is to regulate angiogenesis and knockout mice have an increased density of capillaries in cardiac and skeletal muscle. Endothelial-derived TSP-1

has also been claimed to promote macrophage recruitment (Kirsch et al., 2010). Varma et al., (2008) reported a small but positive correlation between gene expression of TSP-1 in adipose tissue and BMI with no effect of prior metformin administration. However, Tan et al., (2009) found that 6-months treatment with metformin of women with PCOS elevated the low circulating levels of TSP-1. The available evidence does not support the claim that TSP-1 is an adipokine released by fat cells that has any causal relationship to obesity and insulin resistance.

5.34 TGF-β1

TGF-β1 is now accepted to be multifunctional regulator of the immune and inflammatory processes and works through regulating the activity of Smad proteins (Shi and Massague, 2003). Smad-3 deficient mice are protected from diet-induced obesity and diabetes and the adipocytes had marked increases in mitochondrial biogenesis and respiration accompanied by increased PGC-1α mRNA (Yadav et al., (2011). There is other evidence for perturbation of mitochondrial function, specifically reactive oxygen species formation, due to TGF-β1 since it enhanced mitochondrial reactive oxygen species formation in rodent hepatocytes (Albright et al., 2003) while preventing cell death due to caspase activation in synovial cells (Kawakami et al., 2004).

In obese hypertensive humans, circulating levels of TGF-β1 correlated with BMI (Scaglione et al., 2003) but not in a study where only 10% of the humans were hypertensive (Bastelica et al., 2002). In another study comparing circulating TGF-β1 in women with an average BMI of 32 against lean controls with a BMI of 21, the values were actually higher in the lean controls (Corica et al., 1997). However, both protein and gene expression (Alessi et al., 2000) of TGF-β1 in human adipose tissue positively correlates with BMI as does release of TGFβ1 by human adipose tissue in primary culture (Fain et al., 2005b). The formation and release of TGFβ1 by human adipose tissue is almost exclusively by the nonfat cells and is not inhibited by dexamethasone, as is the case for release of inflammatory adipokines such as the interleukins and IL-1Ra (Fain et al., 2005b; Fain et al., 2010b). While circulating levels of TGFβ1 do not appear to be elevated in obesity, one caveat is that what is measured is actually the latent form of TGFβ1. This accounts for most of the circulating TGFβ1 and obesity could affect conversion to the active form with a much shorter half-life (Flaumenhaft et al., 1993). I conclude that TGFβ1 is formed by the nonfat cells in human adipose tissue and acts as a local paracrine/autocrine factor that is required for the development of obesity and insulin resistance. However, this does not necessarily mean that it plays a causal role since it is a multifunctional regulator of cellular metabolism. The recent findings of Yadav et al., (2011) suggest that the inhibition of TGFβ1 release and/or action might have favorable effects on the development of insulin resistance in obesity by uncoupling respiration in white fat thus preventing fatty acid accumulation.

5.35 Tumor necrosis factor α [TNFα]

Hotamisligil et al., (1993) found elevated levels of TNFα and its gene expression in several rodent models of obesity and diabetes and neutralization of TNFα significantly reduced insulin resistance. In humans, Hotamisligil et al., (1995) found that obesity greatly enhanced TNFα release by adipose tissue explants and its gene expression in adipose tissue correlated

with both BMI and circulating levels of insulin, which is a marker for insulin resistance. Fain et al., (2004c) confirmed that the release of TNFα by both explants of human adipose tissue and adipocytes positively correlates with the BMI of the fat donors but the release of TNFα is primarily by the non-fat cells. In obesity there is increased accumulation of macrophages in adipose tissue and these cells release massive amounts of cytokines such as TNFα (Xu et al., 2003; Weisberg et al., 2003). However, Kern et al., (1995) and Fain et al., (2004c) found that TNFα is also released by nonfat cells other than macrophages in human adipose tissue. There is a reproducible correlation between BMI and TNFα release by human adipose tissue explants (Fain et al., 2004c; Arner et al., 2010) or adipocytes (Fain et al., 2004c). However, this has not been seen in all studies with respect to TNFα gene expression in adipose tissue and BMI (Kern et al., 1995; Koistinen et al., 2000).

It has been difficult to obtain evidence in humans by blocking TNFα action in vivo with etanercept that this improves insulin sensitivity (Lo et al., 2007). However, Fain et al., (2005a) found that blocking endogenous TNFα action on incubated human fat explants using etanercept had little effect on the release of IL-6 or IL-8. However, in combination with an antibody that blocked the action of endogenous IL-1β there was a 55 to 60% decrease in the release of IL-6 and IL-8. There is little evidence that TNFα circulates as an adipokine. Rather it acts as an autocrine/paracrine factor since circulating levels are generally below the sensitivity of available assays. There is no evidence for its release in vivo into the circulation under conditions where release of IL-6 could be detected (Mohamed-Ali et al., 1997). I conclude that TNFα is an important component of the inflammatory response acting as an autocrine/paracrine adipokine along with IL-1β to activate the inflammatory cascade in adipose tissue in all cells resulting in enhanced release of pro-inflammatory adipokines such as IL-6 and IL-8. It will be important to understand how human adipocytes even after isolation from the adipose tissue environment and washed several times still show rates of TNFα release that reflect the BMI of the person from whom the adipocytes were obtained. The simplest explanation is that this reflects the average fat cell size as shown by Arner et al., (2010) and that 'stretch receptors' are involved that stimulate TNFα and leptin release.

5.36 Tumor necrosis factor receptor 2 [TNFR2]

The actual receptor for TNFα is TNFR1 but there is also a second soluble form of the receptor known as TNFR2 that can be cleaved from the TNFR1 or expressed directly and its expression in adipose tissue is markedly enhanced in obesity (Hotamisligil et al., 1997). Similar increases in circulating TNFR2 but not TNFR1 have been seen in obese humans (Fernandez-Real et al., 1998). These data suggest that increased formation of the TNFR2 is part of a feedback system designed to reduce the effects of TNFα since the soluble TNFR2 protein binds to and thus reduces the level of active TNFα.

5.37 Vascular endothelial growth factor A [VEGF] and VEGFR1 & 2

There is evidence that VEGF is involved in angiogenesis in adipose tissue which is a highly vascularized tissue (Cao, 2010) and that adipose tissue mass can be regulated through the vasculature (Rupnick et al., 2002). In overweight/obese humans, there is an inverse correlation between obesity and pO_2, temperature, capillaries per 1000 μm^2 and VEGF gene expression suggesting that the reduced pO_2 did not result in VEGF release and

neovascularization (Pasarica et al., 2009). Kabon et al., (2004) had previously reported that obesity decreased adipose tissue oxygenation in humans. Thus the question is why in obesity the reduced pO_2 in the expanding fat mass does not result in release of VEGF and growth of more blood vessels to enhance pO_2. But obesity in humans does enhance the circulating levels of VEGF and the best correlation [Pearson r of 0.49] was seen with visceral fat mass (Miyazawa-Hoshimoto et al., 2003). Cao (2010) has suggested that adipose tissue angiogenesis is a good therapeutic target for the treatment of obesity. However, we know so little about what regulates the growth of adipocytes and the endothelial cells of the blood vessels that we are literally groping in the dark. One way to regulate the activity of VEGF is through the formation and release of the soluble form of the VEGFR-1 receptor, known as sFlt-1, which competes with the VEGFR1 and VEGFR2 receptors for binding of VEGF. Obesity in rodents and man is associated with reduced mRNA content as well as release of sFlt1 while in isolated human adipocytes hypoxia enhances the expression of VEGF but not of sFlt1 (Herse et al., 2011).

5.38 Vaspin

This protein was originally described as a serine protease inhibitor derived from visceral adipose tissue (Hida et al., 2005) but Kloting et al., (2006) reported that it was present to the same extent in visceral as in subcutaneous adipose tissue of humans. It is not found in fat cells of human visceral omental adipose tissue but is found in the nonfat cells (Fain, 2010). Circulating levels of vaspin are not elevated in massively obese women (Auguet et al., 2011). Similarly a 10-month lifestyle intervention program led to a favorable change in metabolic parameters and circulating adiponectin but not vaspin (Kim et al., 2011). I conclude that vaspin is probably not an adipokine but rather a member of the serpin protease family with unknown functions whose circulating levels are not appreciably altered in obesity.

5.39 Visfatin/PBEF/Nampt

This putative adipokine was originally described as a protein selectively expressed in visceral fat with insulin-mimetic properties whose circulating levels are elevated in obesity (Fukuhara et al., 2005). However, this protein turned out to be identical to PBEF [pre-B-colony-enhancing factor] and Nampt [nicotinamide phosphoribosyltransferase]. Furthermore, the claim that visfatin was an insulin-like peptide has been withdrawn (Sommer et al., 2008) and its gene expression in human visceral fat is no higher than in subcutaneous fat (Berndt et al., 2005; Fain, 2010). Circulating concentrations of visfatin as measured by an ELISA specific for full-length visfatin are not elevated in obesity (Retnakaran et al., 2008; Korner et al., 2007). Visfatin gene expression is primarily in the nonfat cells of human adipose tissue (Fain et al., 2010a) and it is unclear at this time whether it is more than an intracellular enzyme involved in NAD biosynthesis in all fat depots not just visceral adipose tissue.

5.40 Zinc α2 glycoprotein [ZAG]

This protein has been postulated to be an adipokine modulator of body fat mass (Bing et al., 2010). However, ZAG is a novel adhesive protein (Takagaki et al., 1994) secreted by epithelial cells, sweat glands and many tumors that is found in high concentrations in seminal plasma

(Bing et al., 2010). ZAG is identical to a lipid mobilizing factor isolated from the urine of humans with cancer cachexia that causes selective loss of fat in rodents but there is no evidence that ZAG either enhances lipid mobilization or lipid utilization in humans (Bing et al., 2010). ZAG has been postulated to be a candidate gene for obesity, but like adiponectin and unlike most adipokines, its gene expression in adipose tissue is lower in obese than in lean humans (Bing et al., 2010). There is also an inverse relationship between circulating levels of ZAG in humans and insulin resistance but no effect of BMI on circulating levels of ZAG (Ceperuelo-Mallafre et al., 2009). However, Selva et al., (2009) reported just the opposite results, with obesity lowering both circulating levels and gene expression of ZAG in adipose tissue but no correlation was observed between ZAG levels and insulin resistance. ZAG, like adiponectin, is preferentially expressed in the fat cells of human omental adipose tissue where it is expressed at higher levels than in subcutaneous adipose tissue (Fain, 2010). While the available data are conflicting with regard to circulating levels of ZAG, there is consensus that gene expression of ZAG in adipose tissue correlates with that of adiponectin (Mracek et al., 2010) and that weight loss reduces insulin resistance in humans while enhancing gene expression of ZAG in adipose tissue. However, what we have are correlations and there is no consistent relationship between circulating levels of ZAG and obesity.

6. Summary of adipokines most likely linked in a causal way to morbid obesity

Of the 40 adipokines mentioned in the previous sections, the circulating levels of only adiponectin and ZAG appear to be reduced under some conditions by obesity. The circulating levels of 14 of the remaining 38 putative adipokines are elevated in obesity, and of these only leptin appears to be released exclusively by the fat cells of human adipose tissue as shown in Table 2.

Circulating adipokines released only by fat cells	Circulating adipokines released by fat cells and non fat cells	Circulating adipokines released primarily by non fat cells	Circulating factors released primarily by liver
Leptin	Amyloid A	Adipsin	Cathepsin S
	FABP4	Apelin	CRP
	VEGF	IL-6 & IL-8	Haptoglobin
		MIF	
		PAI-1	
		IL-1Ra	
		$sPLA_2$	

Table 2. Circulating adipokines whose release is reproducibly elevated in obesity over BMI values from 25 to 70

While amyloid A, FABP4 and VEGF levels are elevated in obesity there is no proof that their circulating levels are derived primarily from adipose tissue release. Furthermore, there is ample evidence that both the fat cells and the nonfat cells of adipose tissue release all three and with amyloid A, the liver makes and releases large amount of this acute phase protein. I

refer to amyloid A as an adipokine because it is formed and released by adipose tissue in appreciable amounts in contrast to CRP where the release by adipose tissue is too small to contribute to circulating levels. Except for leptin, there is no evidence that the circulating levels of the other putative adipokines are derived exclusively from adipose tissue or even that release by adipose tissue regulates their circulating levels. Probably the circulating levels of adipsin, apelin and IL-6 are influenced primarily by release by lymphoid tissues but in any case it is unlikely that release by adipose tissue is derived from fat cells. Finally, we have acute phase proteins such as CRP and haptoglobin whose circulating levels are elevated in obesity along with that of cathepsin S and are released primarily by liver in response to circulating inflammatory factors such as IL-6.

Interestingly in female bariatric surgery patients, the mRNA levels in omental adipose tissue positively correlated with visceral obesity as measured by waist circumference for only four of the 12 adipokines whose circulating levels are consistently elevated in obesity as shown in Table 3. Furthermore, except for IL-1Ra, the increased mRNA expression in omental adipose tissue in obese women was abolished in those taking anti-hypertensive drugs (Fain, 2011). It is unclear why only IL-1Ra mRNA expression correlate with waist circumference but not that for MIF, IL-8 and IL-6. This suggests that hypertension in obese women has profound effects upon mRNA levels and abolishes the effect of obesity. The increase in leptin is expected and so far it is the only adipokine released solely by fat cells whose circulating levels are elevated in obesity. The elevated mRNA levels in visceral omental adipose tissue and circulating levels of both PAI-1 and Amyloid A suggest that these proteins may have a special role in visceral obesity.

Positive correlations for these adipokines with severe obesity in women and			
mRNA levels in Omental fat	**Circulating levels**		
Amyloid A	Amyloid A	Adipsin	IL-8
IL-1Ra	IL-1Ra	Apelin	MIF
Leptin	Leptin	FABP4	$sPLA_2$
PAI-1	PAI-1	IL-6	VEGF

Table 3. Comparison of effects of severe obesity in women based on gene expression in visceral omental adipose tissue as compared to effects on circulating levels. The data on mRNA levels are from Fain (2011) and on circulating levels the data reviewed in sections 5.1 to 5.40 of this chapter.

The division between primary signals, pro- and anti-inflammatory molecules, secondary response molecules and unlikely adipokines is outlined in Table 4. The levels of secondary response molecules are elevated in obesity but are probably not regulated by release from adipose tissue. In contrast unlikely adipokines are those proteins whose circulating levels are not appreciably altered in obesity and are derived from sources other than adipose tissue in humans. The primary response signal in obesity is probably related to the expansion of the fat cells, which results in enhanced release of both fatty acids and leptin. Either or both of these signals could act as autocrine/paracrine factors to enhance the release of inflammatory mediators by both the fat and nonfat cells of visceral omental adipose tissue. This is accompanied by decreased release of adiponectin and enhanced release of IL-1Ra, IL-10 and TNF-R2 that act as anti-inflammatory mediators to reduce inflammation. The

inflammatory response is associated with enhanced formation of the so-called secondary response molecules whose role in promoting insulin resistance is unclear while apelin is linked in some way to the renin-angiotensin system and hypertension.

Primary signals	Pro-inflammatory mediators	Anti-inflammatory mediators	Secondary response molecules	Unlikely adipokines in humans		
Fatty acids	IL-1β	Adiponectin	Adipsin	Cathepsin S	Nesfatin	RBP-4
Leptin	IL-6	IL-1Ra	Amyloid A	CD14	Omentin	TSP-1
	IL-8	IL-10	Apelin	CRP	Orsomucoid	Vaspin
	MCP-1	TNF-R2	FABP4	Endothelin-1	OPG	Visfatin
	MIF		PAI-1	Haptoglobin	RANTES	ZAG
	TNFα		$sPLA_2$	Lipocalin-2	Resistin	

Table 4. Separation of putative adipokines by their role in the inflammatory response seen in obesity

It should be noted that correlations of obesity with regards to mRNA levels in omental adipose tissue and elevations in the circulating levels of any protein do not prove a cause and effect relationship and most likely these are marker not maker molecules of obesity. Furthermore, it is likely that additional proteins other than those listed as unlikely adipokines will be found whose circulating levels are altered in obesity under some circumstances. Of the 12 listed in Table 3 as adipokines whose circulating levels are elevated in obesity, only leptin still remains as a primary response signal by fat cells in obesity.

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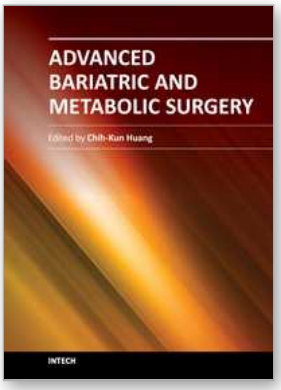

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Bariatric surgery has gained importance in the last 20 years because of the high prevalence of global obesity, and the vast understating of the physiological and pathological aspects of obesity and associated metabolic syndromes. This book has been written by a number of highly outstanding authors and pioneering bariatric surgeons from all over the world. The intended audience for this book includes all medical professionals involved in caring for bariatric patients. The chapters cover the choice of operation, preoperative preparation including psychological aspect, postoperative care and management of complication. It also extends to concept and result of metabolic surgery and scarless bariatric surgery.

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