

Obesity as a Source of Endogenous Compounds Associated with Chronic Disease: A review.

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Abstract

In 2014, it was estimated that more than 1.9 billion adults were overweight with over 600 million classifiable as obese. Approximately two-thirds of US adults over 20 years of age are currently overweight with about 35% classified as obese, a figure thought likely to reach 42% by 2030 in those over 18 years of age.

Adipose cells from stored body fat secrete estrogen and a very large number (> 500) of biologically active substances termed adipokines, in addition to inducing, by other cell-driven effects, pathological alterations in insulin pathways. The U. S. National Cancer Institute reports that exposure to the hormone disrupting and pro-inflammatory effects of excess adipose tissue are associated with an increased risk for 11 different cancers. Obesity is also associated with a number of serious non-neoplastic conditions including metabolic syndrome and type II diabetes; menstrual cycle irregularities and lowered fertility (men and women); and abnormal bone morphology in a subset of female patients. In men hypogonadism, low testosterone levels, benign prostatic hyperplasia, and lowered sperm counts have been reported.

In developed countries, the endogenous adverse health burden associated with obesity is only matched, quantitatively and qualitatively, by the exogenous toxicity of cigarette smoking. The investigation of possible hormonal and/or pro-inflammatory effects of chemicals should include an assessment of the profound endocrine alterations associated with obesity.

Dimensions of the Obesity Epidemic

The United States Centers for Disease Control and Prevention (CDC) provides a standard definition of body mass index, and based upon body mass index, definitions of underweight, normal weight, overweight, and obese are assigned (Deurenberg *et al.*, 1991). Body mass index (BMI) is defined as weight in kilograms divided by (height) (Deurenberg *et al.*, 1991). Although body types vary, with some stocky or muscular individuals incorrectly classified as obese, a high BMI is used as an indicator or screening tool indicative of a high body fat percentage. Obesity has risen rapidly both worldwide and in the United States (US) over the last several decades. In 2014, it was estimated that more than 1.9 billion adults were overweight with over 600 million classifiable as obese (Picon -Ruiz *et al.*, 2017). Approximately two-thirds of US adults over 20 years of age are currently classified as overweight with about 35% classified as obese (Ogden *et al.*, 2014). The obesity rate in the US is predicted to reach 42% by 2030 in people over 18 years of age (Finkelstein *et al.*, 2012).

Biologically Active Substances Secreted by Adipose Tissue and Fat Cells

Adipose tissue is composed of a number of different types of cells that produce secretions including adipocytes, endothelial cells, macrophages, foam cells, neutrophils, lymphocytes and fibroblasts, and also contains various cell precursors (Fasshauer and Bluher, 2015). The range of biological activities, structural diversity, and sheer number of different molecules secreted by adipose tissue is enormous as illustrated in Table 1.

Molecules secreted by adipose tissue include:

- Cytokines and cytokine-like proteins
- Proteins of the fibrinolytic system

- Complement and complement-related proteins
- Enzymes
- Lipid transport molecules
- Endocannabinoids and other lipids, and
- Proteins of the Renin Angiotensin System (RAS) (Fasshauer and Bluher, 2015).

The class of molecules secreted by fat cells, termed adipokines, is sufficiently complex and important that it merits separate discussion. Approximately 500 adipokines have been discovered to date with the following examples demonstrating the extremely wide range of biochemical and physiological reactions reported in the literature: leptin regulates appetite; adiponectin enhances insulin sensitivity and lessens inflammation; ADAMTS1 affects fat stem cell differentiation, blood vessel formation and ovulation; chemerin increases inflammation and blood pressure; resistin mediates insulin resistance; retinol-binding protein 4 affects insulin resistance; lipocalin-2 increases insulin resistance and inflammation; isthmin-1 improves fat metabolism in the liver, mediates immune function, and influences embryonic developmental patterning; asprosin modulates glucose release from the liver; Slit2-C stimulates glucose metabolism; and lipocalin-5 improves skeletal muscle respiration (Fasshauer and Bluher, 2015; Madhusoodan, 2018).

Adipose tissue is hormonally active, possessing a large number of different receptors for classical endocrine hormones (Kershaew and Flier, 2004). Insulin and glucagon receptors are present as are receptors for growth hormone (GH), thyroid stimulating hormone (TSH), gastrin/CCK-B, glucagon like peptide-1 and angiotensin II receptors type 1 and 2. Adipose tissue also possesses enzymes capable of activating, interconverting, and inactivating steroid hormones (Belenger *et al.*, 2002; Meseguer *et al.*, 2002).

A large mass of adipose tissue leads to significant hormonal release. Adipose tissue contributes up to 100% of circulating estrogen in postmenopausal women and 50% of circulating testosterone in premenopausal women (Belenger *et al.*, 2002; Meseguer *et al.*, 2002). Stromal cells and pre-adipocytes in adipose tissue express cytochrome P450-dependent aromatase and 17 β -Hydroxysteroid dehydrogenases (17HSD), important in the conversion of androgens to estrogens. This aromatase regulates the conversion of the weakly androgenic androstenedione to the more powerful androgen testosterone and concomitantly the conversion of the weakly estrogenic estrone to the strong estrogen estradiol. In subcutaneous adipose tissue, the expression of 17HSD is decreased relative to the cytochrome P450-dependent aromatase. In contrast, in visceral adipose tissue the expression of 17HSD is increased relative to the cytochrome P450-dependent aromatase (Belenger *et al.*, 2002; Meseguer *et al.*, 2002). Deposition of body fat to the abdominal region in the pattern typically observed in males and post-menopausal females is associated with this increase in 17HSD expression relative to aromatase expression (Belenger *et al.*, 2002; Meseguer *et al.*, 2002).

Estradiol is of particular importance due to its role in increasing risk for development of breast, endometrial, and ovarian cancers (NIH, 2017). It is clear that locally produced, rather than circulating estrogens play an important role in breast cancer development, bone mineral maintenance, and preservation of cognition (Simpson, 2003).

Post-Obesity-Related Changes in Thyroid Hormones

The relationship between thyroid hormones and body weight is complex (Simpson, 2003). Basal metabolic rate (BMR) is decreased in patients suffering from hypothyroidism and an underactive thyroid is usually associated with an average weight gain of 5-10 pounds due to

accumulation of salt and water. Greater increases in body weight are usually not due to hypothyroidism.

Several studies have demonstrated that obesity can conversely alter thyroid hormone levels. Karavani *et al.* (2014) examined a large pediatric and adolescent database in Israel. The study subjects had either normal or slightly higher than normal thyroid stimulating hormone (TSH) levels (Karavani *et al.*, 2014). The reaction of thyroid follicular cells to TSH is altered and Karavani *et al.* (2014) demonstrated that across normal weight, overweight, and obese groups T3 but not T4 increased in proportion to the TSH increase, supporting the hypothesis that TSH preferentially stimulates T3 rather than T4. When compared with the normal weight group, TSH and T3 levels were slightly higher in the overweight and obese groups (Karavani *et al.*, 2014).

Al-Musa correlated levels of serum thyroid hormones with BMI in 278 Saudi Arabian adults (Al-Musa, 2017). Slightly more than three-fourths (75.9%) of the study subjects were either overweight (31.3%) or obese (44.6%). Mean TSH serum levels showed a significant increase with increasing BMI, although T3 and T4 were not significantly related to BMI.

Obesity, Insulin Resistance, and the Metabolic Syndrome

The relationships among obesity, the metabolic syndrome, and type 2 diabetes mellitus are complex and have been reviewed by Hardy *et al.* (2012). While abdominal (visceral) adipose tissue increases the risk for developing insulin resistance and type 2 diabetes, increased subcutaneous adipose tissue decreases the risk for these conditions. Hardy *et al.* (2012) hypothesized that excess fatty acids released by visceral adipose tissue drain into the portal vein, impair insulin signaling, and induce inflammation and cytokine production by macrophages.

Ye (2013) has reviewed inflammatory mechanisms influencing insulin resistance via inhibition of insulin signaling in adipocytes and hepatocytes. First, insulin receptor substrate 1 and insulin receptor are inhibited by inflammation (White, 2002; Ye and Gimble, 2011). Second, inflammation impairs PPAR γ function. (Ye, 2008; Ye and Gimble, 2011). Third, inflammation increases plasma free fatty acids via stimulation of lipolysis and inhibition of triglyceride synthesis (Ye, 2007). This third mechanism proposed by Ye (2013) is consistent with the mechanism proposed by Hardy *et al.* (2012).

Magnitude of Adverse Hormonal Changes Related to Obesity in Women

Several studies have measured hormone levels in groups of normal and obese women. In 1980, Kopelman *et al.* published a study comparing hormone levels in lean young women to levels in 23 extremely obese young women (mean age 29 years, range 20-38) with a mean weight of 230% over ideal body weight (range 200-280%). Sex hormone binding globulin (SHBG), plasma testosterone, androstenedione, estrone, and estradiol were measured. For the obese as compared with the lean young women, there were reported increases in plasma testosterone (3.2 ± 0.5 nmol/l vs. 1.7 ± 0.5 nmol; $p < 0.3$) and in androstenedione (9.7 ± 1.2 nmol/l vs. 4.4 ± 0.6 nmol/l; $p < 0.01$). SHBG was decreased from 60 ± 4 nmol/l in controls to 30 ± 4 nmol/l in the obese women ($p < 0.001$). The ratio of estrone to estradiol increased from 1.0 ± 0.1 in controls to 2.4 ± 0.4 in the obese women ($p < 0.1$). In 2010, Janssen *et al.* examined the relationship between visceral (abdominal) body fat and testosterone in 193 white and 166 black women (age 50.6 ± 3.9) undergoing the menopausal transition (13.4% pre-, 49.3% peri-, and 37.3% postmenopausal). The average BMI was classifiable as within the overweight range (29.3 kg/m²) with 40.7% being obese. Using multivariate statistical modeling, bioavailable

testosterone was positively associated with visceral (abdominal) fat independently of age, race, or percent total body fat (Janssen *et al.*, 2010). Freeman *et al.* (2010) enrolled 436 premenopausal women (ages 35-47) and followed them for 12 years. In premenopausal women wherein ovarian hormone production exceeded adipose tissue hormonal secretion, obese and overweight women showed significantly lower estradiol levels compared to non-obese women, independent of age, race, and smoking (obese: 32.8 picograms/ml; 95% confidence interval 30.6 to 35.2 versus non-obese: 39.8 picograms/ml; 95% confidence interval 37.0 to 42.8, $p < 0.001$). In contrast, in postmenopausal women where the major source of hormonal secretion was adipose tissue, obese women had higher estradiol levels (obese: 20.6 picograms/ml; 95% confidence interval 17.2 to 24.7 versus non-obese: 12.2 picograms/ml; 95% confidence interval 10.1 to 14.8, $p < 0.001$). Similar results reporting associations between high BMI and postmenopausal hormone secretion by adipose tissue have been reported by several other groups (see next paragraph).

Under carefully controlled dietary conditions, Mahabir *et al.* (2006) studied 51 postmenopausal women. After adjusting for age, race, parity, and menarche, overweight or obese women displayed higher serum concentrations of estradiol, bioavailable estradiol, estrone and estrone sulfate, and lower sex hormone-binding globulin as compared with normal weight women ($p < 0.05$). These authors examined the relationship between sex hormone concentrations and a one-unit change in four measures of adiposity including BMI (1 kg/m²), percentage body fat (1%), and central or peripheral fat (1 kg). A one-unit increase in BMI was associated with 14.7% (95% CI, 8.0-21.8%) more bioavailable estradiol. A 1% increase in total body fat was associated with 7.9% (95% CI, 3.4-12.5%) more bioavailable estradiol. Similarly, a 1 kg increase

in peripheral fat was associated with 12.7% (95% CI, 6.1-19.6%) higher bioavailable estradiol (Mahabir *et al.*, 2006).

Several other studies have measured hormone levels in overweight or obese women before and after weight loss. Stolzenberg-Solomon *et al.* (2012) measured sex hormone changes before and after weight loss in 278 overweight and obese postmenopausal women not taking hormone therapy. After a six-month dieting phase, each participant lost at least 4 kg. During the six-month diet phase, subjects lost an average of 7.7 kg. Following weight loss, changes in the following hormones were observed: concentrations of estrone (-5.7%, $p = 0.006$); estradiol (-9.9%, $p < 0.001$); free estradiol (-13.4%, $p < 0.0001$); free testosterone (-9.9%, $p < 0.0001$); SHBG concentration (+16.2%, $p < 0.001$); however, total testosterone did not significantly change (Stolzenberg-Solomon *et al.*, 2012). Kaaks *et al.* (2003) examined the effects of dietary intervention on insulin-like growth factor 1 (IGF-1), insulin-like growth factor-binding proteins, and sex steroid metabolism in 99 postmenopausal women. The 99 postmenopausal research subjects had elevated baseline plasma testosterone levels. The subjects were randomly assigned to a dietary intervention arm (49 women) and a control arm (50 women). The dietary intervention continued for five months. Women in the dietary intervention group showed significant reductions in body weight and waist circumference with concomitant reductions in fasting serum levels of testosterone (0.39 ng/ml controls versus 0.33 ng/ml dietary intervention), and increases in serum levels of SHBG (37.61 nmol/l control versus 45.10 nmol/l dietary intervention). Estradiol did not show a significant change (Kaaks *et al.*, 2003; Berrino *et al.* 2001).

In 2018, de Roon *et al.* published a meta-analysis examining the effect of reducing caloric intake and increasing exercising level on hormones secreted primarily by adipose tissue and

associated with an increased risk of breast cancer (de Roon *et al.*, 2018). From a starting point of 2599 articles, these authors found seven articles published on six randomized controlled trials; only these six were included in the meta-analysis. The six clinical trials enrolled 1588 healthy postmenopausal women ranging from 58-61 years of age. Intervention consisted of a combination of diet and exercise for durations ranging from 16 to 52 weeks.

The authors expressed their results in terms of a treatment effect ratio (TER) (de Roon *et al.*, 2018). A TER of 1.0 would represent no difference between the treatment and control groups. TER values less than 1.0 represent a protective effect of the treatment. The results of the meta-analysis of the six clinical trials were as follows: estrone, 0.90 (95% confidence interval (CI) = 0.83-0.97); total estradiol, 0.82 (0.75-0.90); free estradiol, 0.73 (0.66-0.81); free testosterone, 0.86 (0.79-0.93); and SHBG, 1.23 (1.15-1.31). The meta-analytic results for a reduced caloric intake without an exercise intervention were as follows: estradiol, 0.86 (0.77-0.95); free estradiol, 0.77 (0.69-0.84); free testosterone, 0.91 (0.84-0.98), and SHBG 1.20 (1.06-1.36). The results of this meta-analysis are consistent with the results from observational studies on postmenopausal women in reporting that reductions in body fat are associated with decreased estrogenic activity, decreased testosterone, and increased steroid hormone binding globulin (SHBG) (de Roon *et al.*, 2018).

Magnitude of Adverse Hormonal Changes Related to Obesity in Men

Several studies have reported lowered testosterone levels in association with male obesity (Derby *et al.*, 2006; Kelly and Jones, 2015). It has been estimated that a four-inch increase in male waist size increases the risk for low testosterone by approximately 75% while 10 years of aging increases the risk by 36% (Harvard Men's Watch 2011). In addition, waist circumference was a stronger predictor of low testosterone than BMI (Harvard Men's Watch, 2011). In

addition to lower testosterone levels in association with obesity, increased estrogen levels have also been observed (Schneider *et al.*, 1979).

In addition to obesity-related changes in male hormones, several studies have been conducted examining the relationship between obesity and sperm count and morphology. Several studies report decreases in sperm count in obese men (Sermondade *et al.*, 2013), others do not (Macdonald *et al.* 2013). Mixed results, usually with an adverse effect on sperm count but not on morphology have been reported (Eisenberg *et al.*, 2014; Bandel *et al.*, 2015).

Obesity is also associated with benign prostatic hyperplasia (BPH) (Chughtai *et al.*, 2016). Matsuda *et al.* (2004) reported that estrogen might play a pathophysiologic role in BPH (Lee *et al.*, 2009). Lee *et al.* found waist circumference to be positively correlated with prostate volume ($p = 0.034$) (Lee *et al.*, 2006; Lee *et al.*, 2009). Fu *et al.* (2017) demonstrated that low serum levels of the adipokine adiponectin were independently associated with larger prostate volumes and an increased risk for BPH. Differences in adipokine receptors were also found - BPH tissues showed decreased expression of AdipoR1 and increased expression of p-p90RSK compared with normal prostate (Fu *et al.*, 2017). Jung *et al.* (2016) reported that Korean men in the highest quartile for serum leptin levels were at 3.5-fold times the risk for BPH as those falling in the lowest quartile. In contrast, the highest adiponectin levels were associated with a decreased risk for high-volume BPH of 68.5%. In addition, the clinical efficacy of 5 α -reductase inhibitors is reduced in obese men treated for BPH (Raheem and Parsons, 2014).

Obesity-Related Alterations in Bone Density, Composition, and Resilience to Fracture

The relationship between obesity and bone health is extremely complicated with current understanding differing from previously held views (Migliaccio *et al.*, 2011). Studies conducted

in the early 1990s reported that total body fat was positively associated with bone mineral density in both healthy pre- and postmenopausal women and the view was generally held that high bone mineral density was protective against fracture (Cummings *et al.*, 1993; Melton *et al.*, 1993). High overall body weight and high BMI correlated with high bone mineral density, and concomitantly, low body weight was associated with bone loss (Felson *et al.*, 1993). Fat mass, the *sine quo non* of obesity, was reportedly associated with increased bone mass in white women but not in white men (Reid *et al.*, 1992).

In contrast with an apparent presence of an obesity-associated protective effect on bone density, more recent studies have reported that excess body fat is linked to adverse effects on bone. The majority of the older literature relied upon cross-sectional and longitudinal study designs wherein bone mass was correlated with either body weight or body mass index without measurements determining the composition of the excess body weight (Migliaccio *et al.*, 2011). If obesity is defined by percent body fat and anatomical distribution (i.e. visceral), obesity is a risk factor for osteoporosis (Migliaccio *et al.*, 2011).

Several different mechanisms have been proposed to explain the deleterious effects of excess body fat on bone health. Wang *et al.* (2017) have proposed a number of inflammation-related mechanisms to explain the adverse effects of excess adipose tissue on bone health. TNF- α and IL-6 are pro-inflammatory cytokines produced by adipose tissue-derived macrophages. Via autocrine or paracrine mechanisms, TNF- α and IL-6 stimulate both proliferation and apoptosis of adipocytes, promote lipolysis, and inhibit lipid synthesis thereby decreasing blood lipids (Wang *et al.*, 2017). TNF- α and IL-6 regulate bone metabolism when released into the systemic circulation; TNF- α can downregulate osteoblast differentiation while upregulating osteoclast proliferation and differentiation (Wang *et al.*, 2017). Additional obesity-related adverse impacts

on bone health have been ascribed to oxidative stress and the endocannabinoid system (Shapses *et al.*, 2017).

Obesity-Related Increases in Inflammation in Obese Men and Women

C-reactive protein (CRP) increases in response to inflammation (Thompson *et al.*, 1999) and is stimulated by IL-6 (Del Giudice and Gangestad, 2018). A large number of studies have reported elevations in CRP (Asztalos *et al.*, 2014), IL-6 (Braune *et al.*, 2017), or in both biomarkers of inflammation in association with obesity (Pang *et al.*, 2016). Obesity displays a stronger direct relationship with CRP levels than does cigarette smoking. Gallus *et al.* (2018) analyzed data from two large screening studies conducted in Italy from 2000-2010 on 3,050 heavy smokers, including 777 ex-smokers. In a subgroup of the smokers in Gallus *et al.* (2018), BMI in subjects in the obesity range versus normal weight subjects showed an odds ratio for CRP ≥ 2 mg/L of 5.26 (95% CI: 3.94-7.03). In this large Italian cohort, mean CRP values at baseline were 2.84 mg/L among current smokers and 2.53 mg/L among ex-smokers. Median values were somewhat lower than the mean values at 1.61 mg/L (interquartile range (IQR): 0.82–3.18) and 1.35 mg/L (IQR: 0.73–2.75), respectively (p on medians < 0.001). Therefore, even in heavy smokers the median CRP levels were in the low range (< 2 mg/L) while the mean values fell at the low end of the high range (> 2 mg/L).

Tumor necrosis factor alpha (TNF- α) is frequently elevated in association with obesity (Tzanavari *et al.*, 2010) where macrophages secrete TNF- α when invading adipose tissue (Tzanavari *et al.*, 2010; Duque and Descoteaux, 2014). Adiposity and insulin resistance correlate with the TNF- α level (Tzanavari *et al.*, 2010).

Obesity-Related Inflammation in the Brain

In addition to systemic inflammation, obesity is associated with inflammatory changes in the brain (Uranga and Keller, 2019). Obesity-associated inflammation was first reported in the hypothalamus (Williams, 2012). Miller and Spencer (2014) have reported that circulating cytokines, free fatty acids, and immune cells cross the blood brain barrier into the hypothalamus. Once there, these systemic factors induce local inflammation, including the proliferation of microglia. These authors (Miller and Spencer, 2014) hypothesize that the localized inflammation remodels synapses and causes neurodegeneration thereby disrupting the hippocampus and amygdala. Obesity-related inflammation may also affect the hippocampus, brainstem, amygdala, and cortical structures (Guillemot-Legrís and Muccioli, 2017).

Cancers Associated with Obesity

The National Cancer Institute (NCI) has identified 11 different human cancers that show a positive association with obesity as reported in epidemiology studies (NIH, 2017). These are endometrial, esophageal, gastric, liver, kidney, pancreatic, colorectal, gallbladder, breast, ovarian and thyroid cancers. Multiple myeloma and meningioma are also increased in incidence in the obese.

A variety of mechanisms are thought to be involved. Estrogen secreted by adipose tissue contributes to the genesis of breast, endometrial, and ovarian cancers (NIH, 2017). Obesity is associated with a chronic low-grade inflammatory state and inflammation can contribute to cancer risk in at least two ways – by exposing cells to potential mutation by activated oxygen and nitrogen species (Smith *et al.*, 2019) and by inducing cell proliferation rate as part of a repair response (Király *et al.*, 2015). Acid reflux from gastroesophageal reflux can lead to Barrett's

esophagus, strongly associated with esophageal adenocarcinoma. Gallbladder inflammation from stones is a risk factor for gallbladder cancer (NIH, 2017) and chronic ulcerative colitis is a risk factor for colon cancer. Hepatitis increases a number of forms of liver cancer (NIH, 2017). Hyperinsulinemia or insulin resistance may promote the growth of colon, kidney, prostate, and endometrial cancers (NIH, 2017).

Additional suggested mechanisms include direct and indirect effects on cell growth regulators, alterations in the mechanical properties of connective tissue matrix scaffolding that supports breast cells, altered immune responses, and effects on the nuclear factor kappa beta system (NIH, 2017).

Conclusions

The adverse health effects of obesity are likely to be extensive and include many factors apart from the widely understood type II diabetes risk. A significant body of literature reports that exposure to endocrine disrupting chemicals can adversely affect the endocrine glands, with an increased tendency toward developing obesity among the notable effects (Lauretta et al., 2019). Any study on the potential adverse effects of exposures to relatively low concentrations of chemicals that might alter the endocrine system must take into account the very high percentages of societal obesity and the clear biological activity of the many molecules released by adipose tissue.

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Table 1. Examples of Molecules Secreted by Adipose Tissue, Their Biological Responses and Effects (Fasshauer and Bluher, 2015)
mac

Classes of Molecules Secreted by Adipose Tissue	Examples of Individual Molecules	Examples of Biological Responses	Effects*
A) Cytokine and cytokine-like proteins			
	TNF α (Tumor necrosis factor alpha)	Pro-inflammatory inflammation, antagonism of insulin signaling.	↑
	IL-6 (Interleukin 6)	Pro-inflammatory, regulates energy homeostasis and inflammation.	↑
	MCP-1 (Monocyte chemotactic factor 1)		
	Resistin	Regulation of inflammation.	↑
	Progranulin		
B) Proteins of the fibrinolytic system			
	PAI-1 (Plasminogen activator inhibitor)	Inhibit endothelial plasminogen activator, elevated in inflammatory and obese states.	↑
	VEGF (Vascular endothelial growth factor)	Stimulates vasculogenesis, angiogenesis, and T-cell cytokine production.	↑
	TGF- β (Transforming growth factor)	Regulate of cell growth, cell proliferation, cell differentiation and apoptosis.	↑
	Tissue factor		
C) Complement and complement-related proteins			
	Adipsin	Enhance fat storage.	↑
	Complement Factor B		
	ASP (Acylating simulation protein)		
	CTRPs (C1q/TNF-related proteins)		
	CRP (C-reactive protein)	Family of acute-phase proteins, increased during inflammatory condition.	↑

	Leptin	Regulates food intake and energy expenditure.	↑
	Visfatin	Insulin-mimetic effects.	↑
D) Enzymes			
	DPP-4 (Dipeptidyl peptidase-4)		
E) Lipid transport molecules			
	Apolipoprotein E		
	Cholesterol ester transfer protein		
	Lipoprotein lipase		
	SAA (Serum amyloid A)	Family of acute-phase proteins, elevated with inflammation.	↑
F) Endocannabinoids and other lipids			
	Anandamide		
	2-AG (2-arachidonoylglycerol)		
	Free fatty acids		
	Adiponectin	Regulates glucose and lipid metabolism, insulin sensitivity, food intake.	↓
G) Proteins of the Renin Angiotensin System (RAS)			
	AGT-p (Angiotensinogen)	Plasma angiotensinogen levels are increased by plasma corticosteroid, estrogen, thyroid hormone, and angiotensin II levels. There is a possible involvement of increased p-AGT in hypertension in obese patients.	↑

*↑ = increase; ↓ = decrease