Biomarkers Associated with Cardiometabolic Risk in Obesity

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Background: The US is facing an obesity epidemic. Recognizing the biomarkers associated with adipose tissue may impact physicians' management of cardiometabolic disease greatly. **Evidence of acquisition:** We searched PubMed for keywords 'obesity', 'leptin', and 'adiponectin', reviewed national surveys, and searched reference articles used in review articles retrieved via the PubMed search. We included articles with multiple relevant citations. Observational data acquired from two sources, not previously published, were also used to support our conclusion. **Results:** Literature review and analysis of observational data showed that the level of leptin increases with the increase in weight gain, while adiponectin decreases. The roles of these adipokines in the body have been defined. With the increase in leptin levels, the incidence and prevalence of the components of the metabolic syndrome were seen to be higher, resulting in higher cardiovascular disease, while adiponectin was seen to play a more protective role in the body against developing such disease. **Conclusions:** Measuring circulating levels of leptin and adiponectin as a screening tool may help recognize those individuals who do not only have obesity as a major risk factor toward developing cardiometabolic disease but also may have an unfavorable 'biomarker profile', putting them at highest risk. This may encourage the mobilization of resources to help these individuals lose weight rapidly with possibly aggressive measures such as bariatric surgery. **Keywords:** Obesity, biomarkers, cardiometabolic risk, adiponectin, leptin

Obesity is an epidemic in the US today. It is now recognized as America's greatest health risk—according to the Centers for Disease Control and Prevention (CDC), 34 % of the US population is obese (body mass index [BMI] >30). It is critically important to better understand obesity and how it affects cardiovascular health.

Figure 1 demonstrates the obesity trends among the US population from the Behavior Risk Factor Surveillance System (BRFSS) in 1990 and 2007.[1]

Fat cells (adipocytes) lie at the center of obesity. The traditional view has been that these adipocytes are merely fat storage depots. The new paradigm is that the adipose tissue acts as an endocrine organ with its own unique hormones. However, unlike other endocrine tissues, adipose tissue has the potential for limitless growth. The magnitude of its hormonal effects is similarly unlimited.

Adipose Tissue as an Endocrine Organ

Multiple studies have been undertaken to investigate the different fat hormones or 'adipokines' released from the adipocyte and the effects they may have on different components of the 'metabolic syndrome.'[2,3] The metabolic syndrome is defined in the US as:

- waist circumference >40 inches for men; >35 inches for women;
- fasting blood glucose >100 mg/dl (three measurements);
- high-density lipoprotein (HDL) <40 mg/dl for men; <50 mg/dl for women;
- triglycerides >150 mg/dl; and
- blood pressure >140/90 mmg (three measurements).

Insulin resistance, lipid metabolism (especially the well-recognized pattern of low HDL, high triglycerides, and small, dense low-density lipoprotein (LDL) particles), and blood pressure are affected by these hormones. Abdominal obesity appears to be the biggest driver of these important adipokines and thus abdominal girth becomes an important parameter in the metabolic syndrome. There is growing evidence that each of the components of the metabolic syndrome is independently atherogenic. Most patients with this syndrome exhibit resistance to

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the cellular actions of insulin. The presence of insulin resistance appears to be the result of a complex interplay of genetic factors with environmental factors, such as obesity and physical activity level, as explained by Grundy in the article titled "Hypertriglyceridemia, insulin resistance, and the metabolic syndrome."[4] From the public health standpoint, obesity and physical inactivity are the primary driving factors for the development of the metabolic syndrome in the US population.

As mentioned above, abdominal obesity appears to be one of the most important mediators of adipokines. Patients with abdominal obesity often manifest the multiple risk factors of the metabolic syndrome. Obese individuals may exhibit a state of insulin resistance due to the actions of adipocytes. Insulin resistance and the subsequently generated 'hyperinsulinemia' exerts a significant pathologic effect on several organs, most importantly the liver, adipose tissue, kidneys, blood vessels and the autonomic nervous system. These effects of hyperinsulinemia are summarized in *Table 1*.

Obesity and the generated state of hyperinsulinemia seem to tie together the different aspects of the metabolic syndrome. The adipose tissue provides the liver with excess free fatty acids, which leads to the overproduction of triglycerides and very-low-density lipoprotein (VLDL). Another mechanism contributing to the elevated serum triglycerides may be an enhanced synthesis of apolipoprotein C-III, which interferes with the action of lipoprotein lipase, thereby inhibiting the hydrolysis of VLDL triglyceride. Apolipoprotein C-III also interferes with the uptake of VLDL remnants by LDL receptors on liver cells, raising the serum levels of these remnants. Moreover, most patients with isolated low HDL cholesterol also exhibit insulin resistance.

Grundy, in the article referred to above, describes this triad of lipid abnormalities characterized by a low HDL, a predominance of small, dense LDL particles, and elevated triglycerides as being unique to obesity and insulin resistance and significantly promoting the development of atherosclerosis.

Hyperinsulinemia and Hypertension

Insulin resistance and the resulting hyperinsulinemia have been shown to predispose patients to developing high systemic blood pressures, as described by Theodore in the chapter "Insulin resistance and hypertension."[5] According to the Health and Nutrition Exam Survey II, persons with blood pressure >140/90 mmHg or taking medication for hypertension will also likely have cholesterol >240 mg/dl; thus emphasizing the inter-linkage between all these different components of metabolic syndrome.

Figure 1: Behavior Risk Factor Surveillance System Obesity Trends Among US Adults

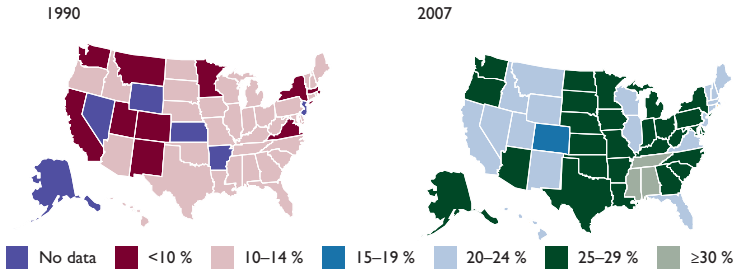

Table 1: Hyperinsulinemia

Organ Affected	Effect Generated
Adipose tissue	Increased secretion of non-esterified (free) fatty acids
Liver	Increased synthesis of apolipoprotein C III Increased synthesis of Factors VII, IX, X and prothrombin Increased synthesis of plasminogen activator inhibitor-1 (PAI-1)
Kidneys	Na^{+} retention, uric acid retention
Central nervous system	Increased sympathetic nervous system stimulation
Blood vessels	Interference with Ca^{++} transport in the smooth muscle of arterioles Increase in smooth muscle proliferation

Hyperinsulinemia stimulates the sympathetic nervous system, decreases Ca^{++} ion transport in arterioles (causing vasoconstriction), and causes inhibition of natriuresis in the kidney, all of which result in an increase in systemic blood pressure.

Another mechanism by which insulin resistance may yield hypertension may be linked to the resulting hypercholesterolemia associated with it. The cholesterol profile previously described as being generated in this state may cause endothelial injury, resulting in increased endothelial superoxide anion production, which results in increased degradation of nitric oxide, therefore impairing endothelium-dependant vasodilatation, yielding high blood pressures systemically.

Obesity and the Pro-thrombotic State[6]

Obesity may also result in a pro-thrombotic state. The clinical observation of obesity as a risk factor for myocardial infarction (MI), stroke, deep venous thrombosis, and even pulmonary embolus (as described by Goldhaber et al. in an article published in *JAMA*)[7] is well known. This state appears to be driven by insulin resistance and concomitant hyperinsulinemia. High level of insulin causes an increase in

Table 2: Effects of Adipokines

Adipokine	Effect of Weight Loss	Effect of Weight Gain	Insulin Resistance	Type 2 Diabetes Mellitus	Inflammation	Cardiovascular Risk
Leptin	Decreases	Increases	Increases	Increases	Increases	Increases
Adiponectin	Increases	Decreases	Decreases	Decreases	Decreases	Decreases

Table 3: Observed Effects of Lifestyle Modifications

		BMI	Adiponectin (µg/ml)	Leptin (ng/ml)	Glucose (mg/dl)	C-peptide (ng/ml)	Insulin (µIU/ml)	CRP (µg/ml)	IL-8 (pg/ml)
A	Before	54.1	2.1	4.5	102	4.66	14	3.9	28
	After	25.2	6.7	0.35	72	1.23	2.5	0.51	30
B	Before	50.8	0.93	38	95	3.38	10	8.1	19
	After	31.9	2.1	0.74	77	0.587	<0.86	1.6	23
C	Before	58.3	5.5	47	119	0.943	3.8	7.0	35
	After	32.3	5.2	1.6	107	0.9	<0.86	12	32
D	Before	41.5	2.2	41	90	3.07	4.9	6	35
	After	18.9	5.2	0.58	77	1.22	2.0	1.9	25
E	Before	43.4	1.0	64.0	86	2.2	6.1	3.5	48
	After	20.5	2.4	0.4	73	0.712	1.0	0.48	21
F	Before	40.1	2.2	58	89	4.06	8.8	2.1	9
	After	27.4	3.4	30	89	3.35	5.2	1.2	12

The timing of blood draw to obtain levels does not necessarily correlate with the timing of the change in shown BMI.
BMI = body mass index, CRP = C-reactive protein, IL-8 = interleukin 8.

clotting factors (see *Table 1*) as well as an increase in platelet activator inhibitor-1 (PAI-1). Platelet aggregation is also seen to be increased. Finally, due to hyperinsulinemia and the pathologic lipid triad, vascular endothelial dysfunction results and its anti-thrombotic mechanisms are impaired.

Adipokines

Leptin and adiponectin are the two core adipokines produced from the adipocytes and are involved in mediating multiple metabolic effects of the adipocyte.

Leptin

Leptin is one of the adipokines produced from the adipocyte whose normal function is to provide information to the satiety center of the brain that the body's fat storage is sufficient. Unfortunately, humans can fairly easily override leptin's signal such that weight gain continues and leptin levels continue to rise. Hyperleptinemia has been studied extensively and has been shown to be positively correlated with the adverse effects of obesity, as illustrated in *Table 2*. With the increase in body fat, the levels of leptin are seen to be higher.

Increased circulating leptin has been shown to be independently associated with insulin resistance and cardiovascular disease in humans. High leptin levels also stimulate macrophages resident in adipose tissue to release inflammatory cytokines (e.g. interleukin-6 [IL-6] and IL-8 and tumor necrosis factor alpha [TNF-alpha]) to create an overall environment of inflammation that subsequently injures numerous peripheral tissues, including liver, pancreas, platelets, vasculature, and myocardium,[8,9] as evidenced by multiple studies. Martin[10] concludes that plasma levels of leptin and inflammatory markers are correlated and also predict cardiovascular risk; it is conceivable that part of the risk mediated through leptin resistance is related insulin resistance, chronic inflammation, type 2 diabetes mellitus, hypertension, atherothrombosis, and myocardial injury.

In terms of coronary artery disease, higher levels of leptin have been shown not only to predispose patients to develop coronary artery disease, but also have been related to the severity, extent, and lesion complexity in coronary artery disease and major adverse clinical events (MACE) after a coronary event or intervention.[11]

Adiponectin

Adiponectin is another important adipokine released from the adipocyte, but its role is more protective. Higher levels of circulating adipokines have been shown to produce metabolic changes in the human body that yield a protective effect against insulin resistance and cardiometabolic risk.[12,13] This relationship is also depicted in *Table 2*. High adiponectin levels are also inversely related to the severity, extent, and lesion complexity in coronary artery disease and major adverse coronary events (MACE).[14] This adipokine may work by inhibiting macrophage-mediated inflammation and thus protecting various organ systems against the adverse effects of inflammation.[15,16]

Higher circulating levels of adiponectin are present with oxidative stress and coronary artery calcification (adjusting for weight and insulin resistance). This may indicate an enhanced adiponectin secretory response of adipose tissue to the metabolic environment present in the early development of macrovascular disease, thus suggesting that the elevated levels of adiponectin may comprise an attempt to alleviate risk for additional development and progression of macrovascular disease in an at-risk environment. *Table 2* summarizes the effects of these adipokines.

Presented in *Table 3* are observational data from the participants of a program that involved six months of exercise training and dietary changes to impact the BMI of the participants at the end.

As individuals lost weight via lifestyle modification, adiponectin levels were seen to increase and leptin levels decrease, thus also affecting the related cardiometabolic factors as described previously.

Tuomilehto et al. in 2001[17] provided evidence that type 2 diabetes mellitus can be prevented by changes in lifestyles of high-risk individuals. Some individuals have high baseline adiponectin levels that, as they lose weight, become higher and provide further protection against cardiometabolic risk. It is interesting to review the above presented data in the light of this knowledge.

The woman presented in *Table 4* has a BMI of 113.5, which relates well with her high blood pressure as the relationship between obesity and hypertension is well established, as described by Theodore. The relationship between diabetes mellitus and obesity has also been very well established. While 85 % of patients with type 2 diabetes mellitus are obese, only 15 % of obese individuals have type 2 diabetes mellitus.

A striking feature in this observation is that despite carrying such a large burden of adipocytes, the patient has not yet developed diabetes mellitus. This may be due to the fact that her adiponectin levels are relatively high, thus providing her with relative protection against diabetes mellitus. Not every individual is genetically endowed with the same capacity to produce adiponectin and thus not every individual has the same cardiovascular and metabolic risk associated with obesity.

Of further interest in regards to the role of these biomarkers of obesity, leptin, and adiponectin, are the effects that medications used in managing cardiovascular disease have on their circulating levels. Krysiak has shown that certain angiotensin-converting enzyme (ACE) inhibitors result in decreased levels of leptin and an increase in the level of adiponectin.[18]

Table 4: Data Obtained from a Woman who Weighs 700 lbs

BMI	113.5
Blood pressure	180/100 mmHg
IL-6 level	11 pg/ml (<12 pg/ml)
TGF-alpha	73 pg/ml (<30 pg/ml)
Total LDL	81 mg/dl (<130 mg/dl)
Total HDL	64 mg/dl (>40 mg/dl)
Total VLDL	14 mg/dl (<30 mg/dl)
Total cholesterol	160 mg/dl (<200 mg/dl)
Triglycerides	68 mg/dl (<150 mg/dl)
CRP	>15 µg/ml (<1 µg/ml)
Fasting glucose	104 mg/dl (65–100 mg/dl)
HbA_{1C}	5.9 (4.0–5.6 %)
Leptin	111 ng/ml (<20 ng/ml)
Adiponectin	5.2 µg/ml (>2.7 µg/ml)
Insulin	5.6 µIU/ml (<5.4 µIU/ml)
Glucose/insulin ratio	4.1 (>4.5)

BMI = body mass index, CRP = C-reactive protein, HDL = high-density lipoprotein, IL-6 = interleukin-6, LDL = low-density lipoprotein, TGF-alpha = transforming growth factor alpha, VLDL = very-low-density lipoprotein.

Ohashi[19] and Suglyama[20] have also independently demonstrated that lipid lowering therapy increases the concentrations of adiponectin in patients with coronary artery disease and impaired glucose tolerance. In addition, pioglitazone, an anti-diabetic medication, has been shown to increase adiponectin levels in diabetics as well as non-diabetic individuals.[21]

The measurement of these unique adipokines as biomarkers is key. The US is facing an epidemic of obesity with limited resources to care for these individuals. It is paramount that we use these powerful tools to determine who is at greatest risk for developing insulin resistance and type 2 diabetes mellitus and focus our greatest efforts on them. These biomarkers can also be used to guide our interventions as patients lose weight and decrease their risk.

Understanding the adipocyte and recognizing these adipokines as biomarkers has the potential to change the way physicians manage high-risk individuals. Management options for those individuals with an unfavorable biomarker profile in addition to being obese may prompt more aggressive measures such as bariatric surgery. Gastric bypass surgery has been shown to produce considerable improvement in the prevalence of metabolic syndrome, as demonstrated by Batsis et al. at the Mayo Clinic in 2008.[22] The risks of such interventions may seem minor compared with the overall detriments that adipose tissue poses to the body. ■

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