Metabolic complications of obesity:

Inflated or inflamed?

Manisha Chandalia, M.D.

UT Southwestern Medical Center
Internal Medicine Grand Rounds
February 3, 2005

This is to acknowledge that Manisha Chandalia, M.D. has disclosed no financial interests or other relationship with commercial concerns related directly or indirectly to this program. Dr. Chandalia will not be discussing 'off-label' uses in her presentation.

Manisha Chandalia, M.D.
Assistant Professor of Internal Medicine

The Center for Human Nutrition
Division of Endocrinology and Metabolism

Interests:
1. Management of Metabolic syndrome, dyslipidemia, diabetes and obesity.
2. Prevention of Diabetes and Cardiovascular disease.
3. Etiopathogenesis of insulin resistance and inflammation.

Introduction:

Major epidemic we all fear in this century is not influenza or plague, but Obesity. The "pleasantly plump" or so called "chubby" of earlier era are a far cry from current concern of obesity which is rooted in the metabolic complications and mortality related to it. Obesity is steadily increasing in prevalence in US and other developed and rapidly developing nations with an increase in childhood obesity as well. The US statistics shows that one in 5 American is obese. Various insurance company data suggests that obese individuals are more likely to use health care facility than non-obese individuals in the same age range. However, recently news media headlines were ablaze with statements like "CDC overstated obesity deaths" and made every one wonder and reach for that next piece of brownie!

In a press conference related to a publication from CDC group it was stated "overweight and obesity are literally killing us" (1). Using the risk associated with excess weight that had been calculated in a 1999 study, the report linked 400,000 deaths a year to obesity. In this article it was stated that obesity will overtake cigarette smoking as a risk factor very soon. Subsequently, several epidemiologists at CDC and NIH voiced concerns about statistical bias that inflated the deaths associated with obesity. After the uproar on the data, CDC recently retracted the number of deaths due to obesity and stated that statistical bias may have led to inflated number and a revised version is published in JAMA as a letter (2). **"Through an error in our computations we overestimated the number of deaths caused by poor diet and physical inactivity," the Centers for Disease Control and Prevention said**. "Our principal conclusions, however, remain unchanged: the number of deaths related to poor diet and physical inactivity is increasing," it added. Many other biases are obvious in this report. The data used goes back as far as 1948, and authors assumed that our ability to treat metabolic complications of obesity have not improved over past 50 years. Another issue is related to ethnic bias in the studies chosen to calculate the mortality due to obesity, and assumption that all excess mortality in obese people is due to obesity. It is no surprise that due to these type of conflicting reports, average Americans do not take the obesity risk seriously and obesity issue ends up being a reality and talk show topic only.

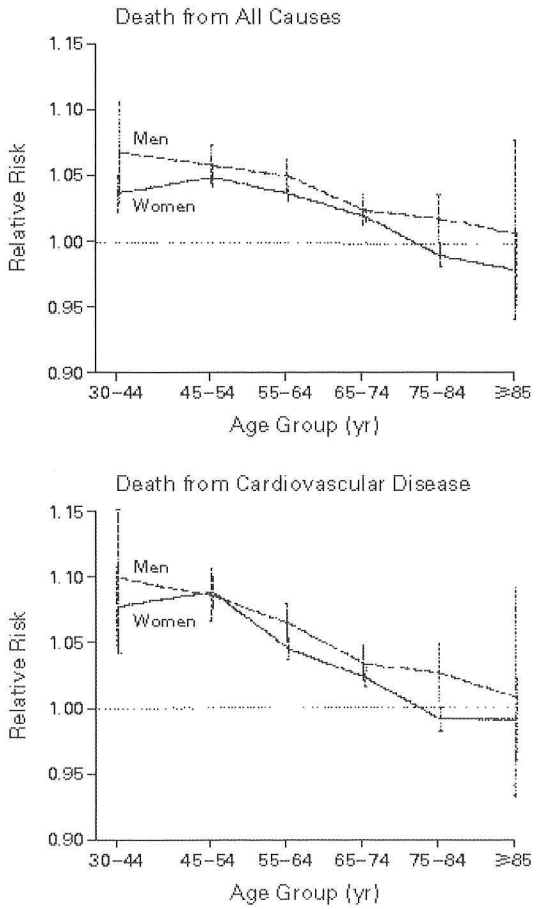
Metabolic changes mediating increased morbidity and mortality risk in obesity is determined by functional changes in adipose tissue of obese people. Increasing evidence demonstrates that adipose tissue functions as an endocrine organ and is involved in regulation of various metabolic pathways. In this grand round I will review some of the evidence to support the need for a conceptual shift from fat "quantity" to adipose tissue "function" (**adiposopathy**) in the evaluation of metabolic implications of obesity.

Is obesity risk over inflated?

A simple and visual definition of obesity is excessive body fat. However, in epidemiological literature, marker of obesity is body mass index (weight in kg/height in m^2). Over past decade large body of literature, both epidemiological and cross sectional, has accumulated underlying the correlation between obesity and increased mortality due to cardiovascular disease. Even a modest increase in body weight is thought to result in a four-fold increase in the risk of cardiovascular disease in both men and women. The surgeon general announced the cutoff of BMI>30 as obese and >25 and <30 as overweight. Many celebrities like Michael Jordan, Pierce Brosnan and Will Smith fell in overweight and Tom Cruise, Sylvester Stallone and Mel Gibson in obese category with these BMI definitions and has caused disbelief in public opinion regarding risk of obesity.

However, studies linking obesity and increased mortality as well as beneficial effects of weight loss are not conclusive and have many confounding variables like physical inactivity, low socioeconomic status and low education levels, to name a few. Furthermore, the association between BMI and mortality appears to be highly age-dependent in a study (figure 1) which showed a steady decline in mortality due to obesity with age until about 74 years after which there appears to be no correlation between BMI and mortality (3).

Figure 1:Relative risk of mortality associated with an increment of 1.0 in BMI

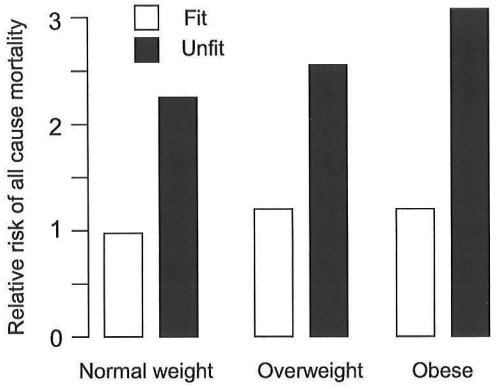


Adapted from Stevens j et al, N Engl J Med 338:1,1998

The distribution of adipose tissue is important when considering the risk of obesity. Cardiovascular and metabolic risk is more closely associated with truncal obesity. The literature is full of references to so called visceral fat, which in many instances means abdominal subcutaneous fat. Several investigators have demonstrated that truncal subcutaneous adipose tissue is a strong predictor of insulin resistance (4,5). One clinical method to assess for upper body or truncal obesity is measuring waist

circumference. Waist circumference is a predictor of both subcutaneous and visceral adipose tissue quantity. ATP III guidelines have defined that a waist circumference of >40 inches in men and >35 inches in women to be considered as truncal obesity (6). These cutoff are largely derived from data pertaining to Caucasians and do not seem to apply to Asians. Lower cutoff are suggested for other ethnic groups like Asians, and Europeans. However, it leads to more complicated algorithms in our multicultural society and appears to not have the necessary impact in identifying people at risk by medical community in the fields.

Figure 2. Relationship between Cardiorespiratory fitness and mortality



Wei et al. JAMA 282:1547-1553,1999

Are all obese people metabolically unhealthy?

When we focus on obesity as expression of fat mass, we are not taking into account a large body of literature which supports the notion that not all fat people are created equal. The first and foremost issue is lifestyle. It is very clear that physical inactivity plays a major role in accumulation of fat. Therefore, data reported on obesity do not routinely correct for physical activity. One recent epidemiological study has reported that fit obese individuals have decreased relative risk of mortality, but they do not reach the level of risk enjoyed by the lean fit individuals (7). In this study, weight and exercise patterns were self reported. Various well planned studies have clearly shown that active obese individuals have lower morbidity and mortality than normal weight individuals who are sedentary (8). One study conducted in Cooper clinic measured all parameters of obesity as well as fitness in detail and showed that lean unfit individual has higher risk of mortality than obese fit individual (figure

Table 1: Definition of Metabolic Syndrome:

NCEP Definition:

Three of the following in any combination;

Abdominal Obesity (waist circumference)	
Men	> 40 inches
Women	>35 inches
•Triglcerides (TG)	> 150 mg/dL
•HDL cholesterol (HDL)	
Men	<40 mg/dL
Women	<50 mg/dL
•Blood pressure	> 130/85 mm Hg
•Fasting Glucose	> 110 mg/dL

WHO Definition:

Hyperinsulinemia or fasting glucose ≥110 mg/dL

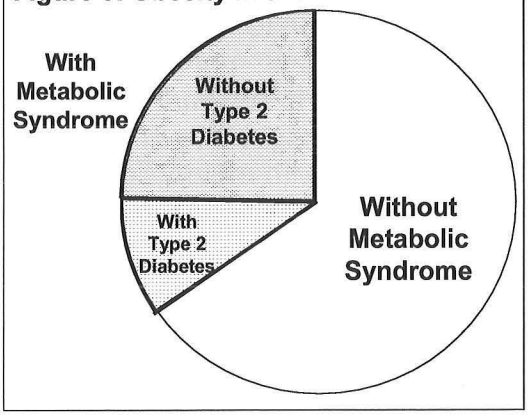
And two of the following:

√Abdominal obesity (wiast to hip ratio > 0.9 or waist >37 inches)

√Dyslipidemia (TG ≥ 150 mg/dL or HDL < 35 mg/dL

√Hypertension (BP ≥ 140/90)

Figure 3: Obesity in the United States



2). Similarly, adiposity does not lead to attenuated response to physical activity and fitness.

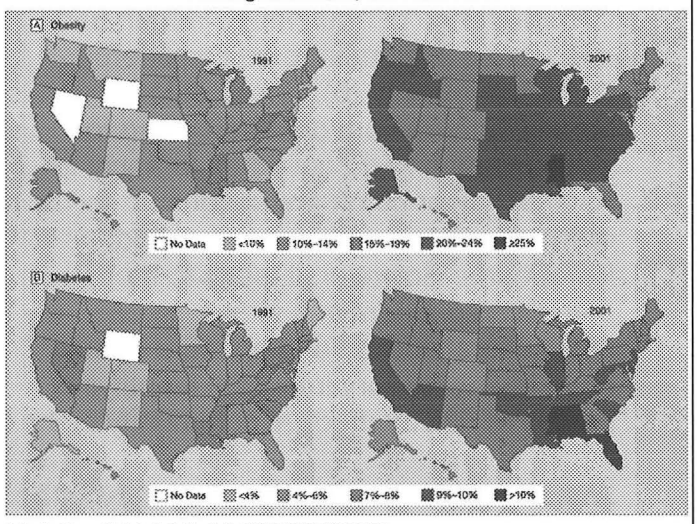


Figure 4:Prevalence of Obesity and Diagnosed Diabetes Among US Adults, 1991 and 2001

Adapted from Mokdad, A. H. et al. JAMA 2003;289:76-79.

Some recent studies have shown that cardiovascular risk among obese subjects varies substantially depending upon the level of other risk factors associated with obesity. These risk factors are abnormalities of glucose metabolism, dyslipidemia as well as hypertension. The constellation of features seen as complications of obesity is termed as metabolic syndrome (table 1). However, the prevalence of metabolic syndrome, benchmark of increased cardiovascular risk, is also not uniformly high in obese subjects (figure 3: estimate from multiple data sources). The CDC data shows that with increasing prevalence of obesity, there is an increase in the prevalence of type 2 diabetes (figure 4). However, only about 12% of US adult patients with BMI >=27 kg/m^2 have type 2 diabetes mellitus. Conversely, 67% of U.S. patients diagnosed with type 2 diabetes mellitus have a BMI > =27 kg/m^2, while 46 % have a BMI > =30 kg/m^2 (9) Thus, not all patients who are overweight have type 2 diabetes mellitus (Figure 5) and not all patients with type 2 diabetes mellitus are overweight. Therefore, while excessive body fat clearly increases the risk of type 2 diabetes mellitus, excess body fat alone is not sufficient towards development of type 2 diabetes mellitus.

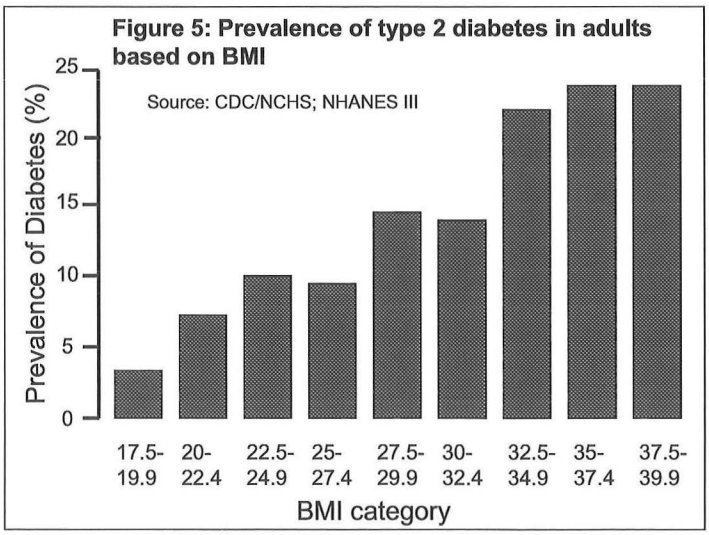


Figure 5: Prevalence of type 2 diabetes in adults based on BMI

Thus the concept emerges of **metabolically healthy-obese (MHO)** subjects, who probably do not require intense identification and intervention to reduce morbidity and mortality. Though it is known that modest weight loss in obese subjects with metabolic complications leads to reduction in morbidity and mortality, there is no

conclusive proof that weight loss, even if sustained, will be beneficial in patients who do not have metabolic complications. Some studies have suggested that weight fluctuations may increase mortality (10). Given the lack of evidence of benefit of weight loss in metabolically healthy subjects, and potential side effects of therapy for weight loss, be it fad diets, pharmacological agents or bariatric surgery, it becomes clear that another approach to identify people at risk is needed. One other approach to identify obese people at-risk is the identification of metabolic syndrome. However, we are still at the cross road of defining waist circumference cutoffs. Furthermore, there are problems with the definition of metabolic syndrome that need to be addressed. For example, it appears counterproductive to identify people at-risk after they have already developed diabetes. Since diabetes is one of the outcomes of metabolic syndrome we should aim to find markers to identify metabolic syndrome-prone people before they have reached this outcome.

Are there metabolically obese normal weight people?

Another major fallacy of identifying people at-risk by either BMI or waist circumference and focusing on obesity as we know it now is the problem of excluding a very large cohort of population from the equation (table 2). For example, it is well established that Asian Indians have several fold higher risk of both cardiovascular disease (CVD) and diabetes (11). We have demonstrated that Asian Indians living in Dallas have much higher insulin resistance than Caucasians living in Dallas when matched for total body fat (12).These volunteers had significantly lower waist circumference compared to Caucasian volunteers, contrary to popular myth that Asian Indians have higher "visceral fat" content. Our recent studies have determined that a point mutation (K121Q) of the gene coding for ENPP1 (PC-1), is much more common in migrant South Asians and associated with obesity-independent insulin resistance in this population (13). Ecto-nucleotide pyrophosphatase/ phosphodiesterase (ENPP1- also known as PC-1) is a type II trans-membrane glycoprotein which, when over-expressed in cells, impairs insulin receptor signal transduction from the α- to the β-subunit of the insulin receptor. "In vitro" studies suggest that this effect is amplified by an A/C substitution in exon 4 of the PC-1 gene, which determines replacement of glycine with glutamine in position 121 (K121Q) and stronger interaction with the insulin receptor (gain of function). The same mutation has been associated with increased risk for type 2 diabetes in other populations (14, 15). Recently we have also shown that PC-1 K121Q

Table 2: Two 'healthy' young volunteers participating in our study

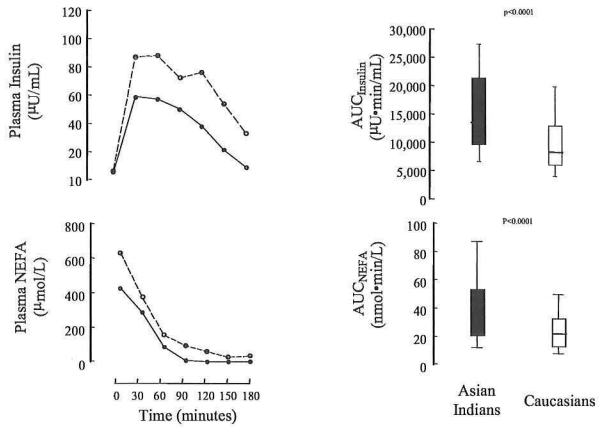
Metabolically Obese Normal weight		Metabolically Healthy Obese
24	BMI (kg/M^2)	38
82	Waist (cm)	113
125	SBP (mm Hg)	126
30	HDL (mg/dL)	50
85	TG (mg/dL)	67
95	FPG (mg/dL)	94
248	2 hr PP (mg/dL)	108
2.2	Glucose disposal rate (mg/kg/min)	5.1

predicts type 2 diabetes in three populations that differ in ethnic origin and in environmental exposure: South Asians living in Chennai (India), South Asians living in Dallas and European-descent persons living in Dallas (16).

It is well known in literature and by previous grand rounds that nonesterified free fatty acid (FFA), a marker of insulin resistance, is elevated in obesity and suppress incompletely in presence of insulin. Similarly, plasma leptin levels are higher and adiponectin levels are lower in obesity. We have demonstrated that non-obese South Asians have higher non esterified fatty acid (FFA) and insulin-mediated FFA suppression is impaired in South Asian men compared with Caucasians (figure 6). Also, leptin levels are higher and adiponectin levels are lower in Asian men compared with Caucasians (figure 7) (17).Taken together, these data support the notion of adipose tissue dysfunction, either due to increasing mass (as seen in many obese people) or due to other factors (genetic like PC-1 K121Q allele or environmental) leads to metabolic complications of dyslipidemia, insulin resistance, type 2 diabetes and CVD.

Figure 6: FFA are excessively released from adipose tissue in patients genetically predisposed to type 2 diabetes.

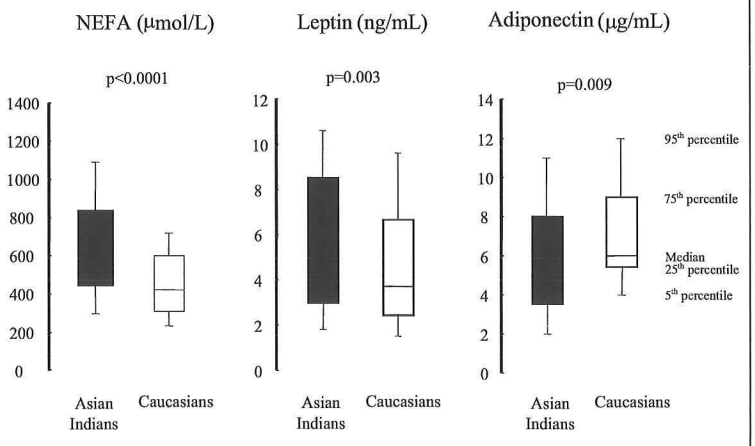
	Asian Indians	Caucasians	p-value
n	79	61	—
Age (years)	31 ± 12	30 ± 7	0.5
BMI (kg/m^2)	24 ± 3	26 ± 4	0.004



Adapted from N. Abate, M. Chandalia et al. JCEM 2004.

Thus the concept of **metabolically obese-normal weight (MONW)** individuals emerges. These individuals require early identification, intense management for prevention of complications and would not be picked up either by our current obesity definition or by news media and reality shows. Similar data regarding the uneven relationship between body fat and insulin resistance seems to be now emerging from other Asian populations including Chinese and Korean populations (18, 19). The minority populations in

Figure 7: Plasma concentrations ofadipokines in non-obese South Asians and Caucasians



Adapted from N. Abate, M. Chandalia et al. JCEM, 2004

United States is steadily rising and striving hard at this point to define obesity based solely on body size or waist size may exclude these ever increasing populations in United States and any measures to curb the outcomes of "obesity" by early identification may not bring desired results.

It has become clear that adipose tissue is no longer an inert storage site of energy but a very active multifunctional organ involved in insulin resistance, FFA, leptin, adiponectin, recently discovered visfatin and may be yet undiscovered substances. The focus from adipose tissue mass must be shifted to the root problem and that is adipose tissue dysfunction which may be called **adiposopathy** (20). Figure 8 illustrates our hypothesis regarding adiposopathy. The potential implications of this shift in thinking would be first and foremost to identify better markers for defining and targeting people at risk. I will now discuss a recent development in the area of adipose tissue and inflammation as one manifestation of adiposopathy.

Figure 8 : Concept of Adiposopathy

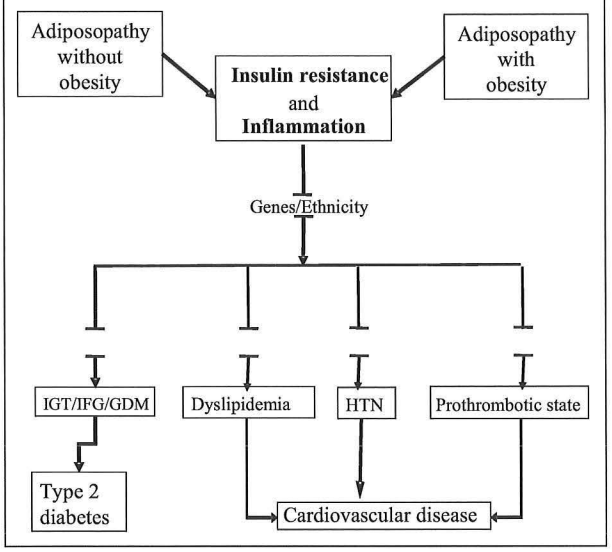
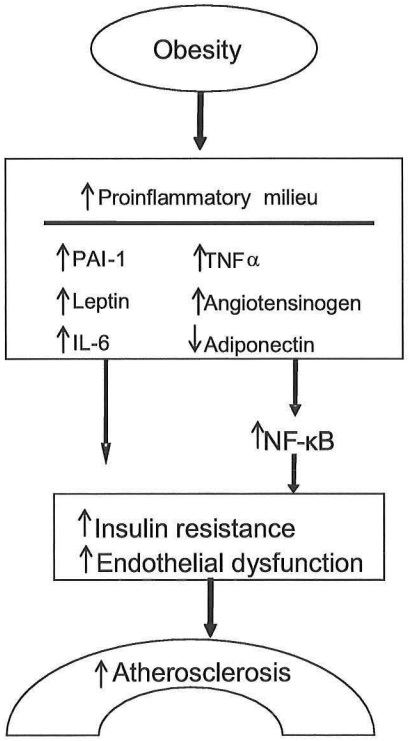


Figure 9: Current view of the mechanisms linking obesity to cardiovascular disease through low-grade inflammation.



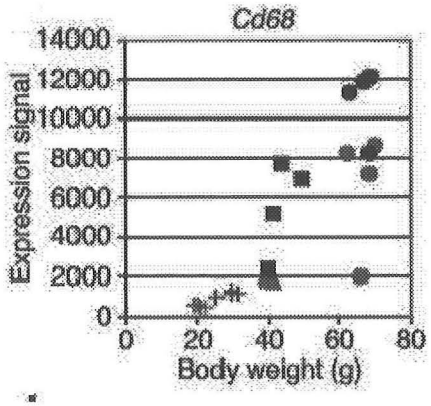
Adapted from Lyon et al. Endocrinology 144:2195,2003

Adipose tissue inflammation:

The origin of systemic inflammation in metabolic obesity is subject of debate in recent years and evidence is accumulating that adipose tissue plays a major role in production of cytokines like IL-6 and TNFα which in turn stimulates the production of CRP from the liver. Hotamisligil *et al.* (21), first demonstrated that adipocytes constitutively express the pro inflammatory cytokine TNF and that TNF expression in adipocytes of obese animals (ob/ob mouse, db/db mouse and fa/fa Zucker rat) is markedly increased. These observations provided the first link between an increase in the expression and the plasma concentration of a pro-

inflammatory cytokine and insulin resistance. A very interesting feature of the inflammatory response that seems to occur in the presence of obesity in animal models is that it appears to be triggered and initially maintained in adipose tissue. Subsequently, other metabolic sites may also be involved during the progression of complications (e.g. hepatic and skeletal muscle insulin resistance, atherosclerosis etc). Following meticulous examination, it has been shown that adipocyte precursors and diverse immune cells such as T lymphocytes and macrophages possess similar potentials in pathways such as inflammatory cytokine production (22). Adipocyte precursors have potent phagocytic capacity and can be transformed into macrophage-like cells in response to appropriate stimuli (23).Thus it appears that obesity is associated with a "local" low-grade inflammation characterized by increased macrophage infiltration of adipose tissue and production of inflammatory cytokines, such as IL-6 and TNFα which in turn may lead to endothelial dysfunction and insulin resistance and then eventually atherosclerosis and cardiovascular disease (figure 9).

Figure 10: Cd68 expression in Obese model of Mouse white adipose tissue



Adapted from Weisberg et al. J Clin Invest 112:1796,2003

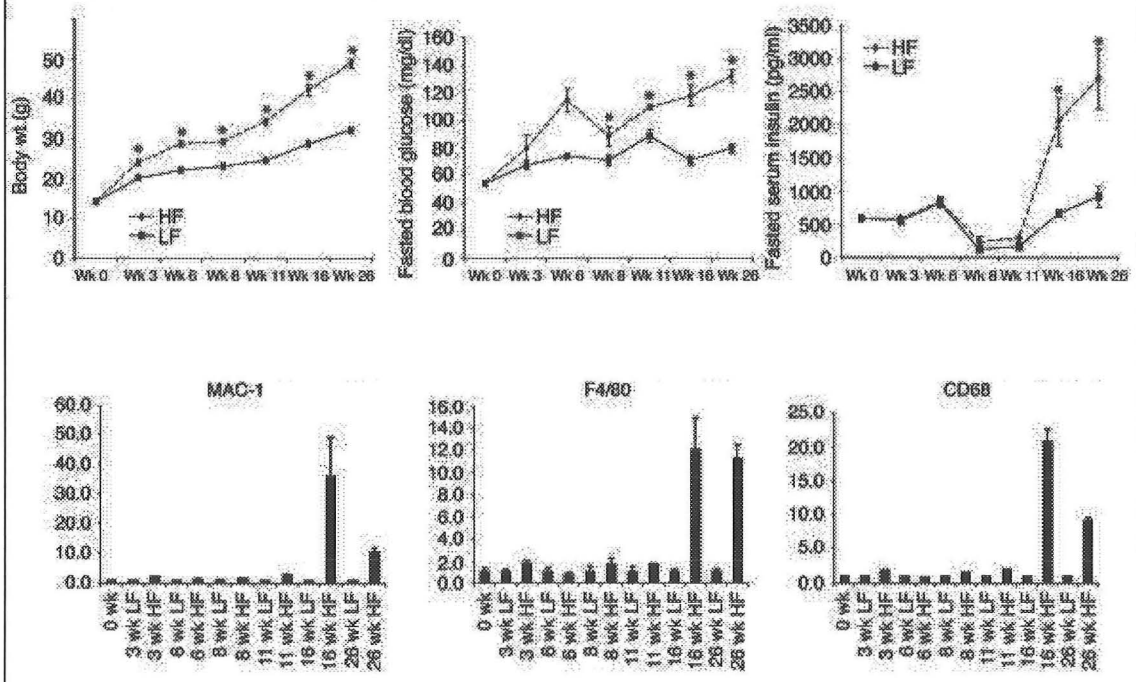
Two recent studies in mice models of obesity have shown that obese adipose tissue is characterized by macrophage infiltration and these macrophages are an important source of inflammation in this tissue (24, 25). Both of these studies have principally emerged from large scale gene-expression analysis of animal model of obesity. One group of investigators directly compared gene expression in multiple tissues between five obese mouse models and their lean controls (24). The other investigators chose to profile gene expression in the white adipose tissue of mice of varying degree of obesity in order to identify correlations between gene expression and degree of obesity (25). Both these approaches indicate that the largest classes of genes significantly regulated in obesity consist of macrophage and inflammatory genes in white adipose tissue. One other very interesting finding emerged from both these studies that significantly higher number of macrophages infiltrated in to the expanding adipose tissue and were responsible for the increased inflammation related gene expression (figure 10). However, upon stimulation with TNF-α, preadipocytes did express some inflammatory genes, suggesting that they also mount similar inflammatory response under specific conditions. TNF-α is one of the cytokines involved in obesity-related insulin resistance. This data may suggest that once inflammatory trigger is established in adipose tissue with increasing macrophage infiltration and increased cytokines, a self perpetuating mechanism develops. It also allows one to postulate that the trigger of macrophage infiltration may be related to

mechanisms other than fat mass expansion (obesity) and the need to study these factors in MONW subjects.

Xu et al, (24) focused on two genetic mouse models (ob/ob and db/db) and diet induced obesity model (DIO) to explore the inflammatory response in white adipose tissue (WAT). They selected six macrophage or inflammatory genes for these studies, including MAC1 (macrophage antigen 1), an antigen found predominantly on monocytes, macrophages, neutrophils and NK cells and CD68 (macrosialin), a heavily glycosylated transmembrane protein expressed specifically in macrophage and macrophage related cells. The mRNA of these genes were consistently and significantly upregulated in WAT of all three animal models that had been on a high-fat diet for 16 weeks.

They also conducted experiments to determine whether the upregulation of these genes occurs prior to the development of systemic insulin resistance characterized by hyperinsulinemia (24). They tracked the expression levels of these genes in WAT of mice with high-fat-diet-induced obesity at multiple time points for 26 weeks. The body weight and fasting blood glucose increased steadily over this period with a marked increase in diabetes range of blood glucose at week 16. They reported an increase in expression of some of the genes as early as week 3 in high fat diet group. A marked increase was noted on week 16 coinciding with increase in insulin levels as well as glucose levels (figure 11). Authors have concluded that adipose inflammatory response occurs with increasing adipose tissue mass (obesity) prior to insulin resistance, but

Figure 11:Transcription regulation of inflammation genes in obese mice

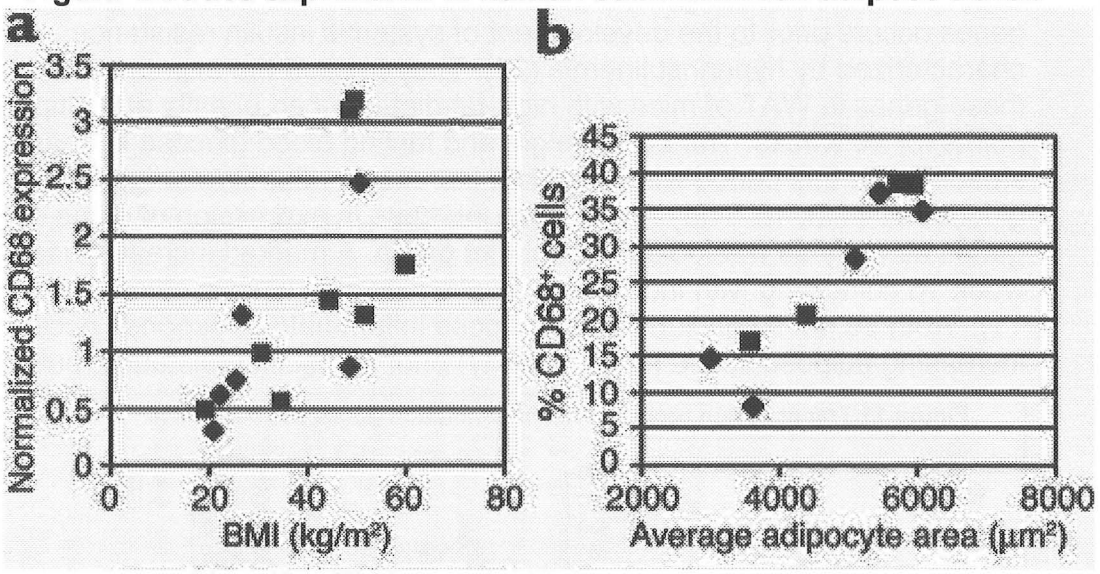


Adapted from Xu et al. J Clin Invest 112:1821,2003.

intensifies with insulin resistance. However, the increase before the week 16, in high-fat diet group is marginal at best and the real increase occurs at week 16. Since insulin resistance and obesity are very closely linked, it is not possible to reach the conclusion that obesity and not insulin resistance is the trigger for adipose tissue inflammation.

Weisberg et al also looked at the relationship between BMI and adipocyte size to macrophage (using relative levels of CD68 mRNA expression as the marker of macrophage presence) in abdominal subcutaneous tissue of humans (25).They reported that both BMI and adipocyte area were predictive of CD68 expression and obese (BMI >30) had significantly higher CD68 expression compared to lean (BMI<30) and concluded that adipose tissue macrophage accumulation is directly

Figure 12:Cd68 expression in human subcutaneous adipose tissue



Adapted from Weisberg et al. J Clin Invest 112:1796,2003

proportional to measures of adiposity (figure 12). However, no details of metabolic characterization including insulin sensitivity are available on these human subjects. Since insulin resistance and adiposity are so closely linked, any conclusions drawn about relative impact of obesity must take insulin resistance parameters in to account. It also is necessary to study models of MONW people, before concluding that macrophage infiltration secondary to expanding adipose tissue mass leads to insulin resistance. Our preliminary data in these MONW human subjects suggests that macrophage infiltration is present independent of obesity and strongly associated with parameter of systemic insulin resistance. Our data support the view of adiposopathy illustrated in figure 8.

Clinical implication:

Identification of Adiposopathy:

Pro-inflammatory markers:

Over past decade, steady stream of information and data has shown correlation between inflammation and obesity and its complications i.e. type 2 diabetes and cardiovascular disease. Infact, it is believed that inflammation may be the link between obesity/diabetes and atherosclerosis leading to CVD. An important recent development in our understanding of obesity is the emergence of the concept that obesity is characterized by a state of chronic low grade inflammation (26- 28). The evidence to support this view is based on several human studies demonstrating increased levels of pro and anti inflammatory markers in obese and their correlation with type 2 diabetes and cardiovascular events. A long list of these markers exist (table 3), however, C-reactive protein (CRP) and adiponectin appear to be the clear favorite at the moment.

Table 3: Partial list of potential biomarkers for inflammation:

TNFα	Adiponectin
IL-6	Resistin
IL-1β	Leptin
IL-10	Visfatin
CRP	Plasminogen activator 1
Fibrinogen	

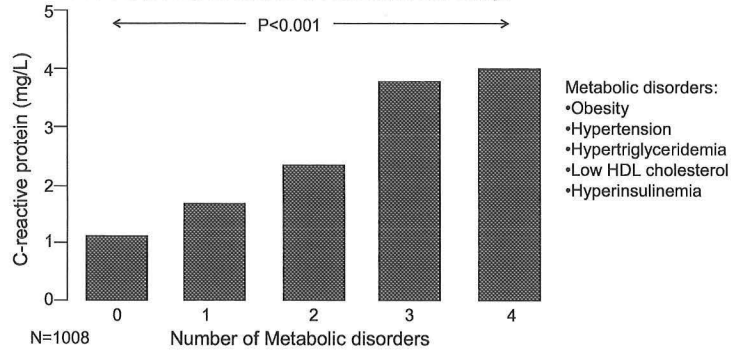
Plasma CRP levels are shown to be elevated in obese subjects and correlated with BMI, waist circumference, features of metabolic syndrome as well as insulin resistance and type 2 diabetes and cardiovascular disease. CRP is also being proposed as a marker for metabolic syndrome.

Numerous prospective studies from populations throughout the world have suggested that elevated levels of CRP confer a greater risk of CVD, including coronary artery disease, stroke, sudden death and peripheral vascular disease (29, 30). Some of these data are obtained from several large cross-sectional and prospective population studies conducted in United States, including the US Physicians Health Study, the MRFIT study and the Women's Health study. Individuals with diabetes or with impaired fasting glucose had increased levels of CRP compared to those with a normal fasting glucose. In other studies, in diabetics, level of CRP was significant predictor of cardiovascular mortality as well as all cause mortality and that this risk was independent of the known conventional risk factors (31-33).

Elevated plasma CRP concentrations have not only been reported in diabetes, but also appear to predict T2DM (34-40). Data collected from the Third National Health and Nutrition Examination Survey suggested a possible role of inflammation in insulin resistance and glucose intolerance (41). Further confirmation of this 'inflammatory' hypothesis has also come from the 'Insulin Resistance Atherosclerosis Study' (IRAS) where those individuals that converted to Type 2 diabetes had higher base-line levels of inflammatory proteins, including

plasma fibrinogen, CRP and plasminogen activator inhibitor-1 (PAI-1) than those that did not develop diabetes (42).

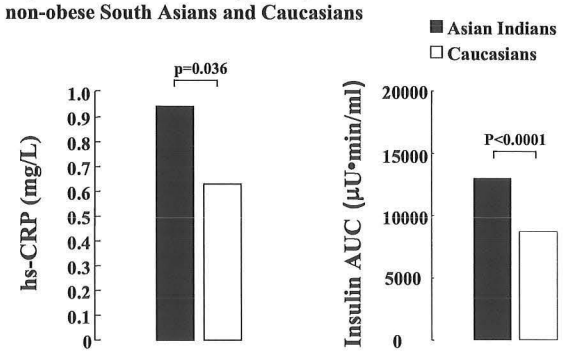
Figure 13: Relationship between C-reactive protein and number of metabolic disorders in the Insulin resistance Atherosclerosis Study:



Adapted from Festa et al. Circulation, 102:42,2000

Findings from IRIS have also demonstrated a strong correlation between inflammation and the metabolic syndrome in a larger, free-living population of non-diabetics without clinical CAD (n=1008, 33% with impaired glucose tolerance). In that study CRP was positively correlated with body mass index (BMI), waist circumference, blood pressure, triglycerides, cholesterol, LDL-cholesterol, plasma glucose and fasting insulin; and, inversely correlated with HDL-cholesterol and insulin sensitivity index (43). The correlations of CRP with measures of obesity, fasting insulin and insulin sensitivity were particularly strong ($r>0.3$). The findings were consistent across ethnic groups (Non-Hispanic Whites, Blacks and Hispanics). There was a linear increase in CRP levels with increase in the number of metabolic disorders (figure 13). Multivariate linear regression models reported the strongest correlation of CRP with BMI and insulin sensitivity index. The mechanistic relationship between these variables and CRP is not yet clear.

Figure 14: Marker of low grade systemic inflammation in non-obese South Asians and Caucasians



Adapted from M. Chandalia, N. Abate et al. JCEM, 2003

The ongoing discussion would seem to clinch the view that CRP is strongly associated with adiposity and further increase in plasma levels of CRP may be observed with onset of type 2 diabetes and its complications. Data from weight loss study either by low caloric diet or bariatric surgery supports this notion with reduction in plasma CRP level following weight loss (44, 45). However, recent data from abdominal liposuction did not show any significant alteration in plasma CRP levels or insulin resistance despite about 18% loss of total body fat (46). This study suggests that negative energy balance has specific effects on inflammation and insulin resistance, which are necessary for benefits to metabolic abnormalities and can not be obtained by simply removing fat. One other study in 197 children (age 10-15 yrs) showed that physically fit but obese children had levels of markers of inflammation as lean children (47). This again brings up important notion that not all obese individuals are metabolically abnormal. On the

same lines, we have recently reported increased plasma CRP in insulin resistant migrant South Asians in absence of obesity (figure 14) (48). Therefore, it appears that one metabolic criteria to identify persons with adiposopathy, independent of body fat quantity, could be plasma hs-CRP concentrations.

Anti-inflammatory markers:

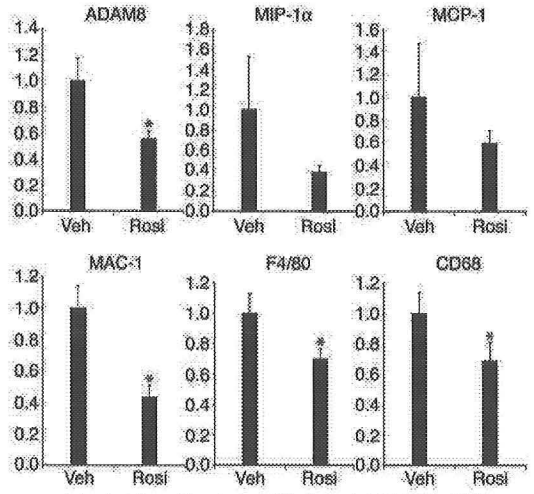
Adiponectin is recognized as anti-inflammatory cytokine and is exclusively produced from adipocytes (49). Plasma adiponectin levels are decreased in obesity, insulin resistance, type 2 diabetes and CVD (50-53). The adiponectin levels are shown to improve with weight loss by negative energy balance, and treatment with insulin sensitizer thiazolidinedione (54, 55). In vitro studies have shown that adiponectin suppresses macrophage function in endothelial cells (56). Thus, compared to other cytokines derived from adipose tissue, adiponectin seems to have protective metabolic and anti inflammatory properties. One recent study has shown that decreased plasma levels of adiponectin are associated with reduced adiponectin gene expression in subcutaneous abdominal adipose tissue (57). This study also demonstrated that low levels of adiponectin were associated with higher levels of plasma CRP and IL-6. One other interesting study looked at the relationship between plasma adiponectin levels,TNFα, insulin resistance and adiposity (58). The study found an inverse correlation between number of features of metabolic syndrome and plasma TNFα levels with plasma adiponectin levels. However, they did not find any change in adiponectin and TNFα levels with 4 to 6 weeks of weight loss. So it appears that short term weight loss may not improve inflammation in adipose tissue. Given these interesting data, it is possible to imagine that in a state of adiposopathy, decreased production of adiponectin may contribute to local and systemic inflammation. This then, may suggest that adiponectin may serve as a marker of increased metabolic and inflammatory risk. Further studies are needed to understand the regulation of adiponectin production by adipocyte and whether inflammatory mediators influence it. As mentioned earlier, we have also demonstrated low levels of plasma adiponectin in insulin resistant non-obese individuals (17).

This finding is important in establishing that inflammation may exist even in the absence of apparent obesity as we know, in people with primary insulin resistance. Therefore for any marker of obesity to have global validity, it must be tested in populations of metabolically obese-normal weight individuals as well. CRP and adiponectin may be the front runners as biomarkers of adiposopathy, but they have not yet reached the finish line. Infact, we may not find one single biomarker with adequate specificity and sensitivity and may have to resort to cluster of biomarkers as in metabolic syndrome.

Targets of therapy for adiposopathy:

The second important fall out of a focus shift from fat mass to adipose tissue dysfunction will be development of pharmacological agents that target the dysfunction of adipose tissue and may improve inflammatory markers. Weight loss may be the goal in obese individuals, but in metabolically obese-normal weight individuals, clearly alternate approach is desired. Physical activity and healthy lifestyle is very important in management of the problem of adiposopathy. However, as we understand more the role of inflammation in adiposopathy newer targets of therapy will not only be considered, but also tested. Thiazolidinedione are a class of drug, for example, approved for management of type 2 diabetes as insulin sensitizers. These are shown to attenuate macrophage activation in vitro and improve atherosclerosis in vivo, suggesting involvement of these agonists in anti-inflammatory activities, most likely mediated by PPARγ in macrophages. It is also reported to improve adiponectin levels, an anti inflammatory cytokine (59). Xu et al showed (figure 15) decreased mRNA expression in adipose tissue of mouse models of obesity when given glitazone suggesting a link between adipose tissue inflammation and insulin resistance (24). Further studies on their role in adipose tissue inflammation in human will be desirable. Another agent, Rimonabant (currently an investigational selective cannabinoid-1 (CB1) receptor anti obesity agent) has been shown to cause significant weight reduction after one year, and thus was effective in reducing adiposity (60). This weight loss benefit was subsequently found to be extended to two years (61). Rimonabant has also been shown to improve functional parameters associated with metabolic syndrome: increased HDL-C levels, reduced triglyceride levels, improved LDL particle size, improved insulin sensitivity (as determined by glucose tolerance testing and homeostasis model assessment), and reduced C reactive protein levels. From an adipocyte standpoint, Rimonabant increased adiponectin levels, and decreased leptin levels (60, 61). It has been suggested that the metabolic benefits of Rimonabant may not totally be explained through weight reduction, (61) with the implication that, in addition to its appetite suppressive effects upon the central nervous system, CB-1 receptor antagonism may also have direct adipocyte activity. Indeed, animal studies have found that CB-1 receptors are found in adipose tissue (62). This opens the possibility that Rimonabant's overall efficacy is the result of both (1) body weight reduction through CB-1 antagonism-induced

Figure 15: WAT of ob/ob mice treated with rosiglitazone



Adapted from Xu et al. J Clin Invest 112:1821;2003

reduction of appetite by its central nervous system effects, and (2) direct favorable anti-inflammatory and metabolic changes through CB-1 antagonism directly targeted at the adipocyte.

Conclusion:

Growing body of evidence is accumulating in favor of a need for a conceptual shift from adipose tissue mass to adipose tissue function. Adipose tissue dysfunction, here defined as adiposopathy, rather than excess adipose tissue mass (defined as obesity) is mechanistically related to development of metabolic diseases traditionally linked to obesity: the metabolic syndrome, type 2 diabetes and CVD. It appears that inflammation of adipose tissue is an important manifestation of adiposopathy and closely relates to insulin resistance, the putative mediator of obesity-related morbidity. The data reviewed lead to interesting questions about the initial trigger in adipose tissue. Who initiates what – does macrophage first infiltrates adipose tissue due to external stimuli and starts inflammatory response or is the adipose tissue dysfunctional to begin with and attracts macrophage to start inflammatory response. This dysfunction of adipose tissue may be brought on by increasing size and mass (obesity) as focused by majority of investigators or it could be some other factor- genetic or environmental, as observed by many investigators including us, in various ethnic groups including Asian Indians. Furthermore, it is not completely clear whether inflammation in adipose tissue leads to first local and then systemic insulin resistance or insulin resistance leads to adipose tissue inflammation, which in turn increases insulin resistance. These questions can only be answered by studying models of insulin resistance independent of obesity. However, current research is clearly biased towards the central role of adipose tissue mass and fat distribution on the metabolic consequences of "obesity". If we, clinicians and scientists, hope to control the epidemic of adipose tissue dysfunction then we must include metabolically obese-normal weight individuals and broaden our definition of obesity to adiposopathy. Our efforts in establishing markers to identify 'at risk' population and finding newer therapeutic agents must focus on adiposopathy and not on obesity alone.

References:

1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA. 2004 Mar 10;291(10):1238-45.

2. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Correction: actual causes of death in the United States, 2000. JAMA. 2005 Jan 19;293(3):293-4.

3. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. N Engl J Med. 1998 Jan 1;338(1):1-7.

4. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest. 1995 Jul;96(1):88-98.

5. Klein S. The case of visceral fat: argument for the defense. J Clin Invest. 2004 Jun;113(11):1530-2.

6. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143–3421.

7. Hu FB, Willett WC, Li T, Stampfer ML, Colditz GA, Manson JE. Adiposity as Compared with Physical Activity in Predicting Mortality among Women. N Engl J Med 2004; 351:2694-2703

8. Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS Jr, Blair SN. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA. 1999 Oct 27;282(16):1547-53.

9. National Institute of Diabetes & Digestive & Kidney Diseases. http://www.niddk.nih.gov/stastistics/index.htm. Prevalence statistics related to overweight and obesity. November 2004

10. Jeffery RW. Does weight cycling present a health risk? Am J Clin Nutr. 1996 Mar;63(3 Suppl):452S-455S

11. Chandalia M, Deedwania PC. Coronary heart disease and risk factors in Asian Indians. Adv Exp Med Biol. 2001;498:27-34.

12. Abate N, Chandalia M. Ethnicity and type 2 diabetes: focus on Asian Indians. J Diabetes Complications. 2001 Nov-Dec;15(6):320-7.

13. Chandalia M, Abate N, Garg A, Stray-Gundersen J, Grundy SM. Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. J Clin Endocrinol Metab. 1999 Jul;84(7):2329-35.

13. Abate N, Carulli L, Cabo-Chan A.V, Chandalia M, Snell PG, Grundy SM. Genetic polymorphism PC-1 K121Q and ethnic susceptibility to insulin resistance. J Clin Endocrinol Metab. 88(12):5927-34; 2003.

14. Hamaguchi K, Terao H, Kusuda Y, Yamashita T, Hazoury Bahles JA, Cruz LL M, Brugal V LI, Jongchong W B, Yoshimatsu H, Sakata T. The PC-1 Q121 allele is exceptionally prevalent in the Dominican Republic and is associated with type 2 diabetes. J Clin Endocrinol Metab. Mar;89(3):1359-64; 2004.

15. Kubaszek A, Markkanen A, Eriksson JG, Forsen T, Osmond C, Barker DJ, Laakso M. The association of the K121Q polymorphism of the plasma cell glycoprotein-1 gene with type 2 diabetes and hypertension depends on size at birth. J Clin Endocrinol Metab. May;89(5):2044-7; 2004.

16. N. Abate, M. Chandalia, P. Satjia, S.M. Grundy, S. Sandeep, V. Radha, R. Deepa and V. Mohan. E-NPP1/PC-1 K121Q Polymorphism and Genetic Susceptibility to Type 2 Diabetes. Diabetes 2005 (in press).

17. Abate N, Chandalia M, Snell PG, Grundy SM. Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men. J Clin Endocrinol Metab. 2004 Jun;89(6):2750-5.

18. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care. 2004 May;27(5):1182-6.

19. Lee WY, Park JS, Noh SY, Rhee EJ, Kim SW, Zimmet PZ. Prevalence of the metabolic syndrome among 40,698 Korean metropolitan subjects. Diabetes Res Clin Pract. 2004 Aug;65(2):143-9

20. Bays H, Abate N, Chandalia M. Adiposopathy-sick fat causes high blood sugars (diabetes), high blood pressure (hypertension) and dyslipidemia. Future Medicine 2005 (in press).

21. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993 Jan 1;259(5091):87-91.

22. Rosen BS, Cook KS, Yaglom J, Groves DL, Volanakis JE, Damm D, White T, Spiegelman BM. Adipsin and complement factor D activity: an immune-related defect in obesity. Science. 1989 Jun 23;244(4911):1483-7.

23. Charriere G, Cousin B, Arnaud E, Andre M, Bacou F, Penicaud L, Casteilla L. Preadipocyte conversion to macrophage. Evidence of plasticity. J Biol Chem. 2003 Mar 14;278(11):9850-5.

24. Xu H, Barnes GT, Yang Q, Tan G, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112(12):1821-30.

25. Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112(12): 1796-808.

26. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. Endocrinology. 2003 Jun;144(6):2195-200.

27. Rajala MW, Scherer PE. Minireview: The adipocyte--at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology. 2003 Sep;144(9):3765-73.

28. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol. 2004 Nov;15(11):2792-800.

29. Jialal I, Devaraj S. Inflammation and atherosclerosis: the value of the high-sensitivity C-reactive protein assay as a risk marker.Am J Clin Pathol. 2001;116 Suppl:S108-15.

30. Rifai N, Ridker OM. HsCRP-a novel and promising marker of CHD. Clin Chem. 2001;47: 403-411.

31. Pickup JC, Mattock MB, Chusney GD, et al. NIDDM as a disease of the innate immune system -association of acute-phase reactants and interleukin-6 with metabolic syndrome. Diabetologia. 1997;40:1286-1292.

32. Ford ES. The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey.Atherosclerosis. 2003;168(2):351-8.

33. Jager A, van Hinsbergh VW, Kostense PJ, et al. von Willebrand factor, C-reactive protein, and 5-year mortality in diabetic and nondiabetic subjects: the Hoorn Study. Arterioscler Thromb Vasc Biol. 1999;19(12):3071-8.

34. Folsom AR, Aleksic N, Catellier D, et al. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. Am Heart J. 2002;144(2):233-8.

35. Tracy RP, Lemaitre RN, Psaty BM, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol. 1997;17(6):1121-7.

36. Lindsay RS, Krakoff J, Hanson RL, et al. Gamma globulin levels predict type 2 diabetes in the Pima Indian population. Diabetes. 2001;50(7):1598-603.

37. Bermudez EA, Rifai N, Buring J, et al. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol. 2002;22(10):1668-73.

38. Freeman DJ, Norrie J, Caslake MJ, et al; West of Scotland Coronary Prevention Study. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes. 2002;51(5):1596-600.

39. Thorand B, Lowel H, Schneider A, et al. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. Arch Intern Med. 2003;163(1):93-9.

40. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001 ; 286(3):327-34.

41. Muntner P, He J, Chen J, et al. Prevalence of non-traditional cardiovascular disease risk factors among persons with impaired fasting glucose, impaired glucose tolerance, diabetes, and the metabolic syndrome: analysis of the Third National Health and Nutrition Examination Survey (NHANES III). Ann Epidemiol. 2004;14(9):686-95.

42. Hanley AJ, Festa A, D'Agostino RB Jr, et al. Metabolic and inflammation variable clusters and prediction of type 2 diabetes: factor analysis using directly measured insulin sensitivity. Diabetes. 2004;53(7):1773-81.

43. Festa A, D'Agostino R, Howard G, et al. Chronic subclinical inflammation as part of the insulin resistance syndrome - The Insulin Resistance Atherosclerosis Study (IRAS) Circulation. 2000; 102:42-47.

44. Clement K, Viguerie N, Poitou C, Carette C, Pelloux V, Curat CA, Sicard A, Rome S, Benis A, Zucker JD, Vidal H, Laville M, Barsh GS, Basdevant A, Stich V, Cancello R, Langin D. Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. FASEB J. 2004 Nov;18(14):1657-69.

45. Vazquez LA, Pazos F, Berrazueta JR, Fernandez-Escalante C, Garcia-Unzueta MT, Freijanes J, Amado JA. Effects of changes in body weight and

insulin resistance on inflammation and endothelial function in morbid obesity after bariatric surgery. J Clin Endocrinol Metab. 2005 Jan;90(1):316-22.

46. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, Mohammed BS. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med. 2004 Jun 17;350(25):2549-57.

47. Halle M, Korsten-Reck U, Wolfarth B, Berg A. Low-grade systemic inflammation in overweight children: impact of physical fitness. Exerc Immunol Rev. 2004;10:66-74.

48. Abate N, Chandalia M, Snell PG, Grundy SM. Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men. J Clin Endocrinol Metab. 2004 Jun;89(6):2750-5.

49. Ukkola O, Santaniemi M. Adiponectin: a link between excess adiposity and associated comorbidities? J Mol Med. 2002 Nov;80(11):696-702.

50. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. 1999;257(1): 79-83.

51. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol. 2000;20(6):1595-9.

52. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2000;86(5):1930-5.

53. Kumada M, Kihara S, Sumitsuji S, et al.; Osaka CAD Study Group. Coronary artery disease. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol. 2003;23(1):85-9.

54. Yang WS, Lee WJ, Funahashi T, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab. 2001;86(8):3815-9.

55. Xydakis AM, Case CC, Jones PH, et al. Adiponectin, inflammation, and the expression of the metabolic syndrome in obese individuals: the impact of rapid weight loss through caloric restriction. J Clin Endocrinol Metab. 2004;89(6): 2697-703.

56. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y. Adiponectin, a new

member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood. 2000 Sep 1;96(5):1723-32.

57. Engeli S, Feldpausch M, Gorzelniak K, Hartwig F, Heintze U, Janke J, Mohlig M, Pfeiffer AF, Luft FC, Sharma AM. Association between adiponectin and mediators of inflammation in obese women. Diabetes. 2003 Apr;52(4):942-7.

58. Xydakis AM, Case CC, Jones PH, Hoogeveen RC, Liu MY, Smith EO, Nelson KW, Ballantyne CM. Adiponectin, inflammation, and the expression of the metabolic syndrome in obese individuals: the impact of rapid weight loss through caloric restriction. J Clin Endocrinol Metab. 2004 Jun;89(6):2697-703.

59. Nesto R. C-reactive protein, its role in inflammation, Type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. Diabet Med. 2004 Aug;21(8):810-7.

60. Dale L, Anthenelli R, Despres J-P, Golay A, Sjostrom L. Effects of rimonabant in the reduction of major cardiovascular risk factors. Results from the STRATUS-US Trial (Smoking Cessation in Smokers Motivated to Quit) and the RIO-LIPIDS Trial (Weight Reducing and Metabolic Effects in Overweight/Obese Patients with Dyslipidemia). Late-Breaking Clinical Trials II. American College of Cardiology Scientific Session 2004, March 7-10, 2004, New Orleans, Louisiana.

61. Pi-Sunyer FX. Effect of rimonabant on weight reduction and weight maintenance: RIO-NORTH AMERICA (RIO-NA) trial. Late-Breaking Clinical Trials III, American Heart Association Scientific Sessions 2004, November 7-10, 2004, New Orleans, Louisiana.

62. Bensaid M, Gary-Bobo M, Esclangon A, et. al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol Pharmacol. 2003 Apr;63(4):908-14.