Review Article

# The Clinical Biochemistry of Obesity

**Ken A Sikaris**
Melbourne Pathology, 103 Victoria Parade, Collingwood, VIC 3066, Australia
For correspondence: Dr KA Sikaris e-mail: ken.sikaris@mps.com.au

**Abstract**

Obesity is essentially an excessive accumulation of triacylglycerols in fatty tissue that is the net result of excessive energy intake compared to energy usage. Severe forms of the disease are most likely to have a predominantly genetic basis and this is probably polygenic. The 'thrifty gene' hypothesis also describes the disturbance that a modern environment, including higher energy intake and decreased physical activity, has on otherwise advantageous genetic variations. While the physical consequences of obesity, such as arthritis, are debilitating and costly, the metabolic consequences are the drivers behind the modern epidemics of insulin resistance, diabetes, fatty liver disease, coronary artery disease, hypertension and polycystic ovary syndrome. The pathophysiological mechanisms behind these diseases are probably a combination of the toxic metabolic effects of free fatty acids and adipokines - the numerous messengers that adipose tissue has been discovered to produce.

## Introduction

Obesity is a condition of increased adipose tissue mass.[1] Obesity can also be defined as an increase in body weight beyond the limits of physical requirement, as the result of an excessive accumulation of fat. Accumulation of fat, or triacylglycerol, is essentially the only way that body weight can become excessive, as other energy storage (e.g. carbohydrate glycogen or protein in liver and muscle) does not have the potential of adipose tissue to exceed the limits of requirement. Although anabolic steroids can increase lean body mass and therefore body mass, this has only been described in those already malnourished.[2]

Adipose tissue is a tissue entity that can, through hyperplasia and hypertrophy, vary enormously between individuals, more so than any other tissue. However it is misleading to think of it as a single entity, as there are subtypes of adipose tissue (e.g. visceral and subcutaneous) which appear to have different implications for health.[3]

Adipose tissue is not purely a storage tissue for triacylglycerols, it acts as an endocrine organ also,[4,5] releasing numerous chemical messengers (adipokines) that communicate and affect other tissues.

This review considers the changes in clinical biochemistry measurements that are associated with obesity, and the insights into the pathophysiology behind this most important health issue in western and developing countries.

## Definitions

The definition of obesity cannot be simply made in terms of body weight because we should expect short people to be lighter than tall people. Therefore we need to standardise body weight against body height. The simplest expression for this is the body mass index (BMI) calculated as weight (kg) divided by height squared ($m^2$). The critical importance of this weight for height adjustment is illustrated in its origins from life insurance tables.[6] A simple prediction of life risk was interpreted as a weight that was 20% above the average for frame size, which was equivalent to a BMI of 27.8 ($kg/m^2$).[7] The World Health Organisation (WHO) guidelines of 1985 defined obesity as a BMI >30.0 for men and >28.6 for women.[8] Although women have lower bone and muscle mass, they usually have slightly more subcutaneous fat but these subtleties are often ignored in standardised approaches. Similarly, both muscle mass and bone mass decrease with age and so like sex, age should be considered as a variable of interest in many obesity studies and standards. The definitions were further refined by the WHO with a BMI over 25 being defined as 'overweight' and over 30 as being 'obese'.[9] Finally,

there are racial differences in body composition that should also be taken into account.[10]

It should be also stated that the ratio of waist to hip circumference (normally below 0.95 in men and 0.85 in women) is generally a better prognostic indicator for disease than BMI[11-13] especially when the BMI is less than 35, and there may be advantages in applying both measurements.[14]

**Acquired Causes of Obesity**

The prevalence of overweight and obesity varies from country to country but in Western countries like Australia, it is becoming true that most of the population can be affected.[15] The prevalence is also increasing in children.[16] The variation from country to country and from time to time implies that environmental factors are the major determinant of disease prevalence. While obesity is thought to be the second most preventable cause of death behind smoking, a recent study suggests that the health care costs of obesity exceed those of smoking.[17]

Fundamentally, obesity is the result of excessive energy intake compared to energy expenditure. In children, increased energy intake as sugar[18] or fat[19] has been linked to obesity, as has decreased physical activity in children.[20] However even in children this is not a simple problem as other factors such as low weight in infancy can also predict later obesity.[21]

Cushing's syndrome may cause obesity. It is also associated with truncal or visceral obesity, which can be difficult to differentiate from simple obesity. This distinction is one of the main purposes of tests such as low dose dexamethasone suppression tests used to differentiate Cushing's syndrome from obesity.

Although slight decreases in energy expenditure in clinical or subclinical hypothyroidism may contribute to weight gain,[22] hypothyroidism is a rare cause of obesity and much of the weight gain is due to water retention which is reversible after thyroid hormone treatment. Insulinoma can cause massive weight gain due to the excessive energy intake consumed to avoid hypoglycaemia but is an extremely rare condition and therefore a very uncommon cause of obesity.

Normally signals from the gut and adipose tissue are integrated in the central nervous system to affect appetite and energy homeostasis and limit weight gain. Pathological obesity may result from the failure of these homeostatic mechanisms[23] although our understanding of these processes is still relatively rudimentary.

**Genetic Causes of Obesity**

The idea that some people are born with a tendency to obesity is not new and Hippocrates stated that "sudden death is more common in those who are naturally fat than in the lean". But why would nature allow such genes to exist? The basic premise of the 'thrifty gene' hypothesis[24,25] is that certain populations may have genes that determine increased fat storage, which in times of famine represent a survival advantage, but in a modern environment result in obesity and type 2 diabetes.[26] Identification of such thrifty gene candidates may help provide insight into the pathogenetic processes of the numerous physical inactivity-mediated disorders.[27]

Underweight newborns become overweight children who become overweight adults[28,29] although this natural progression is being questioned.[30] There is a suggestion that homeostatic set points for adipose tissue mass and insulin sensitivity may be set both by genetic factors and by energy metabolism in utero (Barker hypothesis). [31]

Twin studies have shown important (up to 75%) genetic explanation to BMI.[32,33] With the exception of the rare mutations that cause severe morbid obesity, it seems that numerous genes, each with modest effect, contribute to an individual's predisposition toward the more common forms of obesity.[34] Some genetic syndromes often have obesity as part of a larger syndrome of manifestations and these include Prader-Willi, Angelman and Wilson-Turner syndromes.

Genome-wide scans for obesity susceptibility genes have been performed in several populations of diverse ethnic backgrounds, and many have been replicated in corresponding studies.[35] Although there have been hundreds of loci with high log of the odds scores, some of the most promising include 1p36 (D1S468 a tumour necrosis factor alpha (TNFα) receptor gene), 2q14 (D2S410 a gene associated with high triglyceride levels) and 6q27 (a locus associated with transient neonatal diabetes mellitus).[36] In contrast, candidate gene approaches look for mutations in genes that are presumed to be relevant.

Leptin Associated Genes

Leptin is secreted from adipocytes into the circulation, traverses into the central nervous system and binds to leptin receptors in the hypothalamic arcuate nucleus. This stimulates the production of pro-opiomelanocortin (POMC). The two products of POMC are alpha-melanocyte stimulating hormone (alpha-MSH) and adrenocorticotropin (ACTH). Alpha-MSH binds to melanocortin-4 receptors in the hypothalamic paraventricular nucleus which cause a decrease in food intake.

It appears that a genetically lean individual will gain an extra 7 to 8 kg before leptin increases sufficiently to stop weight gain. Individuals who gain more must be unresponsive to the hormone either because it cannot enter the brain sufficiently or because there is a mutation in one of the many steps of leptin action.[37] Mutations of this system (leptin,[38] leptin receptor,[39] POMC,[40] alpha MSH receptor[41]) are generally uncommon or rare but can cause obesity. Although it was hoped that leptin deficiency caused obesity, we now know that obesity usually has high leptin levels and leptin resistance is likely.[42]

Beta-3 Adrenergic Receptor (ADRB3) Gene

This is expressed in adipose tissue and is involved in the regulation of lipid metabolism and thermogenesis. A missense mutation (Trp64Arg) has a high frequency in Pima Indians[43] and has been frequently associated with obesity in other populations.[44-46] The interaction of this receptor with other receptors may also affect its ability to couple with its mediators such as G-proteins.

Peroxisome Proliferator Activated Peptide Receptor Gamma (PPAR-γ) Gene

The importance of this receptor in obesity is supported by the efficacy of thiazolidinediones in the treatment of visceral obesity. These drugs, also known as glitazones, bind avidly to the PPAR-γ receptor[47] leading to improved insulin sensitivity with major changes in fat metabolism including a reduction in free fatty acids (FFA)[48] by improved peripheral and subcutaneous uptake.[49] They also decrease insulin levels presumably by reducing FFA, reducing the release of TNF-α and restoring adiponectin levels.[50] Note that this is not the same receptor as PPAR-α which also potentiates FFA catabolism in the liver but is the molecular target of the lipid-lowering fibrates (e.g. gemfibrozil).[51]

PPAR-γ is a nuclear receptor that is important for adipogenesis and insulin signalling. The Pro12Ala mutation is common and results in a decreased ability to bind to PPAR-γ responsive genes. The mutation has effects on BMI that are variable but it could be that its greatest effect is on individuals that are already predisposed to obesity.[52] Similarly individuals with the ADRB3 Trp64Arg mutation are far more likely to be obese if they also have the Pro12Ala PPAR-γ mutation.[53] Other genes associated with the PPAR-γ, including its coactivator-1 (PGC-1), have also been found to have many alleles associated with obesity.[54]

Adiponectin Gene

This adipocyte derived peptide has had many regulatory actions on energy homeostasis, glucose and lipid metabolism and anti-inflammatory pathways described. High levels of adiponectin generally lead to weight loss. Polymorphisms of the adiponectin gene have also been associated with obesity and insulin sensitivity.[55]

**Physical Pathology of Obesity**

Osteoarthritis is one of the major costs of obesity. Osteoarthritis in the knees and ankles may be directly related to the trauma associated with the degree of excess body weight.[56] Non-weight bearing joints may still be affected by altered cartilage and bone metabolism.

Obstructive sleep apnoea is a physically defined entity characterised by the absence of airflow in the presence of thoracoabdominal movements. 70% of patients with obstructive sleep apnoea are obese[57] and this may be due to neck fat and fat deposits in the pharyngeal area.[58] Decreases in residual lung volume are associated with increased abdominal pressure on the diaphragm.[59] There is variable lowering of nocturnal oxygen saturation, which is usually mild, and measurement of oxygen saturation has limited diagnostic use.[60] When underlying pulmonary disease is absent, only major degrees of obesity affect pulmonary function. While only 5% of all obese patients have obstructive sleep apnoea, almost half have loud snoring and a third have excess daytime sleepiness. Obstructive sleep apnoea has been associated with all of the diseases of obesity including hypertension and coronary artery disease (CAD). Pulmonary hypertension is also possible due to vasoconstriction of pulmonary arterial bed during apnoea that extends into the waking hours. But although obstructive sleep apnoea has been suggested as a cause of pulmonary hypertension, it is not recognised as a risk factor on its own.

Finally one of the consequences of obesity is community stigma where public disapproval may affect education, employment, income, marital status and health care. These are significant detrimental effects on the quality of life and are associated with higher incidence of depression.

**Obesity and Insulin Resistance**

The risk of diabetes increases by 9% for each kg gained in self reported weight[61] and generally starts to increase at a BMI of 22[62] and is 40 times higher at a BMI over 35.[63,64]

Insulin resistance is widely recognized as a fundamental defect seen in obesity and type 2 diabetes. The development of type 2 diabetes is strongly associated with overweight and obesity in both genders and all ethnic groups. Over 90% of diabetics are overweight or obese.[65] Weight gain and insulin resistance usually precede the onset of diabetes. Current theories indicate that type 2 diabetes develops when pancreatic beta cell output can no longer satisfy the demands imposed by increased insulin resistance.[66]

The FFA Paradigm Linking Obesity to Insulin Resistance

The predominant paradigm used to explain insulin resistance is the elevated FFA concentrations in visceral obesity. The importance of a portal source of FFA and its direct access to the function of the liver could explain the insulin resistance of the liver with central obesity.[67] Increased adipose tissue stores, a disturbed insulin-mediated regulation of lipolysis and subnormal skeletal muscle FFA uptake under conditions of high lipolytic rate may further increase circulating FFA concentrations.[68] In addition, a disturbance of FFA uptake by adipose tissue post-prandially is also a critical determinant of plasma FFA concentration.

Elevated cellular levels of FFA can produce insulin resistance in skeletal muscle and liver, as well as reduce beta-cell function, and this has been referred to as lipotoxicity.[69] Several lines of evidence indicate that hepatic FFA and triglyceride accumulation are a causative factor involved in hepatic insulin resistance.[70] Evidence is increasing that insulin-resistant muscle is characterised by a lowered ability to oxidise FFA. Perturbations in FFA metabolism occur during accumulation of skeletal muscle triglyceride and may also be implicated in the pathogenesis of insulin resistance.[71] An imbalance between FFA uptake and FFA oxidation may in turn be a factor promoting accumulation of lipid intermediates and triacylglycerols within skeletal muscle, which is strongly associated with skeletal muscle insulin resistance.[72] FFA can block insulin-signalling pathways and lead to insulin resistance.[73] Unsaturated FFA may serve as a nutrient sensor to determine whether FFA are to be stored or oxidized and thereby reduce the risk of developing fatty liver and insulin resistance.[74] Chronically elevated FFA contribute to beta cell dysfunction by significantly increasing the basal rate of insulin secretion.[75,76] However it is also believed that the beta-cell changes found in diabetes are better correlated with increased glucose levels than with FFA levels, thus supporting an importance of glucotoxicity.[77]

The Adipokine Paradigm Linking Obesity to Insulin Resistance

This paradigm focuses on adipose tissue as an endocrine organ.[78] Recent studies have suggested that adipokines (adipose tissue-derived hormones and inflammatory cytokines) play essential roles in overall insulin sensitivity and the dysfunctions of adipose tissue which can lead to systemic insulin resistance.[79] This concept is not independent of FFA theories as there still seems to be a relationship between FFA levels and adipokines particularly in individuals who are overweight or insulin resistant.[80]

*Cytokines*

Cytokines produced by visceral adipose tissue are thought to be of possible major importance with the most studied of these adipose cytokines being TNF-α.[81] TNF-α is produced by adipose tissue[82] and its expression is elevated in the adipose tissue in multiple experimental models of obesity. TNF-α inhibits the synthesis of several other adipocyte-specific proteins including adiponectin and enhances the release of FFA from adipose tissue.[83] Neutralisation of TNF-α in one of these models improves insulin sensitivity by increasing the activity of the insulin receptor tyrosine kinase, specifically in muscle and fat tissues. On a cellular level, TNF-α is a potent inhibitor of the insulin-stimulated tyrosine phosphorylation on the beta-chain of the insulin receptor and insulin receptor substrate-1, suggesting a defect at or near the tyrosine kinase activity of the insulin receptor. Given the clear link between obesity, insulin resistance, and diabetes, these results strongly suggest that TNF-α may play a crucial role in the systemic insulin resistance of NIDDM. TNF-α can stimulate IL-6, which, in turn, stimulates the acute phase reactant production of CRP, Plasminogen activator inhibitor 1 (PAI-1) and fibrinogen from the hepatocyte.[84] Fibronectin is also elevated and shows some correlation with insulin, but not C-peptide or measures of body weight.[85]

*Leptin*

Leptin was discovered in 1994. The 'ob/ob' mouse lacks the ability to produce or respond to leptin resulting in severe obesity.[86] Leptin decreases neuropeptide Y in the hypothalamus and should suppress appetite. Fat mass is the primary determinant of serum leptin in humans with energy intake and gender also having significant effects.[87] Gender influences leptin production and reactivity,[88] presumably through the reproductive hormones.[89] Catecholamines also influence leptin production and the leptin signal to the appetite centre.[90] Additional regulators of leptin production include glucocorticoids, cytokines and agonists of PPAR-γ.

Leptin is not only produced by adipose tissue but is also produced in several other places including placenta, bone marrow, stomach, muscle and perhaps brain, thus increasing the number of potential regulatory roles for this hormone.[91]

*Adiponectin*

Adiponectin is a novel adipose tissue-specific protein that has structural homology to collagen VIII and X and complement factor C1q, and circulates in human plasma at high levels.[92] Adiponectin expression and/or secretion is increased by insulin like growth factor-1 and decreased by glucocorticoids and beta-adrenergic agonists. Adiponectin expression and secretion is increased by activators of PPAR-γ.[93] Adiponectin exhibits potent anti-inflammatory and anti-atherosclerotic effects[94] including inhibiting the expression of TNF-α induced endothelial adhesion molecules, macrophage-to-foam cell transformation, TNF-α expression in macrophages and adipose tissues, and smooth muscle cell proliferation.[95] Production is reduced in insulin resistance indicating that the degree of hypo-adiponectinaemia is more closely related to the degree of insulin resistance and hyperinsulinaemia than to the degree of adiposity or glucose intolerance.[96] Adiponectin's effects seem to be peripherally mediated and the evidence of an association between adiponectin and the metabolic and cardiovascular complications of obesity is growing all the time.[97]

*PAI-1*

PAI-1 is the primary physiological inhibitor of plasminogen activation in blood and is known to contribute to thrombus formation and to the development and the clinical course of acute and chronic cardiovascular diseases. Plasma levels of PAI-1 are regulated on a genetic basis but, more importantly visceral fat accumulation is considered as a major regulator of PAI-1. Expression by adipose tissue could be responsible for the elevated plasma PAI-1 level observed in insulin resistance. While adiponectin has anti-atherogenic properties, it is also inversely related to PAI-1[98] which is closely involved in the development of atherosclerosis. Elevated PAI-1 level is a core feature of insulin-resistance[99] and pro-inflammatory cytokines may have an important role in PAI-1 over-expression.[100] It is suggested that PAI-1 may not merely increase in response to obesity and insulin resistance, but may have a direct causal role in obesity and insulin resistance.[101]

*Adipsin*

Adipsin is a serine protease that is secreted by adipocytes and belongs to the alternative complement pathway (complement D).[102] It is deficient in mouse models of obesity however this may be a secondary phenomenon.[103]

*Resistin*

Resistin is an adipokine with putative pro-diabetogenic properties.[104] Although there is evidence that circulating levels are proportional to the degree of adiposity, levels are not related to the degree of insulin resistance.[105,106]

**Metabolic Syndrome Criteria**

The metabolic syndrome (previously known as syndrome X) has insulin resistance as its hallmark as indicated in the WHO classification of metabolic syndrome[107] (Table 1). The third report of The National Cholesterol Education Program (NCEP) Expert Panel also developed criteria[108] (Table 2) which are similar, but can lead to differences in classification of various populations.[109,110]

Although hyperuricaemia is also related to insulin resistance and was included in the original syndrome, the relation between serum urate and the risk of coronary heart disease depends heavily upon the presence of pre-existing myocardial infarction and widespread underlying atherosclerosis as well as the clustering of risk factors.[111,112]

**Advanced Tests of Insulin Resistance**

The so-called 'gold-standard' test of insulin resistance is the euglycaemic clamp which requires the infusion of glucose and insulin, and is therefore only useful for intensive physiological studies on small numbers of subjects. Furthermore, caution should be exercised when making comparisons between studies due to variations in infusion protocols, sampling procedures and hormone assays used. The minimal model approach is a frequently sampled IV glucose tolerance test but is also best suited to a research setting as it still requires up to 30 blood samples.

**Simple Tests of Insulin Resistance**

The simplest test is a fasting or random glucose level, however this is insensitive particularly as we do not know how much insulin is being secreted to maintain that glucose level.

The next simplest test is an insulin level. The main problem here is that insulin levels are highly variable from minute to minute, let alone after meals. This is no longer due to insulin assay imprecision but due to the pulsatile release of insulin coupled with its short half-life. A single fasting level is still

**Table 1.** WHO Criteria for Metabolic Syndrome:
Insulin resistance (Hyperinsulinaemia and/or Fasting Glucose >=6.1) + 2 of the following factors:

| | MEN | WOMEN |
|---|---|---|
| Body Mass Index | >= 30 kg/m$^2$ | >= 30 kg/m$^2$ |
| Or Waist Hip Ratio | >0.9 | >0.85 |
| Triglycerides | >1.7 mmol/L | >1.7mmol/L |
| HDL Cholesterol | <0.9 mmol/L | <1.0 mmol/L |
| Microalbuminuria | >2.5mg/mmol creatinine | >2.5mg/mmol creatinine |
| Blood Pressure | >=140/90 mmHg | >=140/90 mmHg |

**Table 2.** NCEP Criteria for Metabolic Syndrome:
3 of the following factors:

| | MEN | WOMEN |
|---|---|---|
| Waist Circumference | >= 102cm | >=88cm |
| Triglycerides | >=1.7 mmol/L | >=1.7mmol/L |
| HDL Cholesterol | <=1.0 mmol/L | <=1.3 mmol/L |
| Fasting Glucose | >=6.1 mmol/L | >=6.1 mmol/L |
| Blood Pressure | >=130/85 mmHg | >=130/85 mmHg |

so variable that it may easily be misleading and many suggest that at least three fasting levels should be taken and averaged to obtain a better estimate of the usual fasting insulin level.

Simple estimates of insulin sensitivity and pancreatic beta-cell function using fasting insulin and glucose levels serve as surrogate measures of insulin sensitivity and secretion.[113] A very simple tool is the fasting insulin to glucose ratio. A level greater than 4.5 (using SI units) has been described as being useful in the diagnosis of insulin resistance polycystic ovary syndrome[114] and greater than 7.0 in girls with premature adrenarche.[115]

An alternative calculation based on fasting insulin and glucose is the 'Homeostatic Model Assessment' (HOMA), as it is assumed that the fasting state is homeostatic. This calculation is essentially the product of fasting insulin and glucose concentrations and is more useful than either measure on its own. Note that it will also be influenced by the variability of single fasting insulin estimates as well as the insulin assay chosen. The HOMA calculation can be configured to be a measure of resistance (HOMA-R) or sensitivity (HOMA-S). It is more appropriate for large epidemiological studies however it is important to be aware that advanced tests of insulin resistance measure stimulated insulin resistance whereas HOMA gives an estimate of basal insulin resistance. Normal HOMA-R levels are awkward to define across age groups.[116]

The quantitative insulin sensitivity check index (QUICKI),[117] was designed to give a more linear relationship with clamp estimates than the HOMA (which is inversely and reciprocally related to clamp values). Both QUICKI and inverse of HOMA-R are useful measures[118] and suitable for diagnosis of insulin resistance in clinical and epidemiological practice[119] and only fail in unusual clinical scenarios.[120] However, a normal QUICKI reference interval needs to be established for each laboratory with an appropriate control group because of significant inter-laboratory variations in insulin values as well as differences in various populations.[121]

My own view is that most of the variation of both the HOMA and QUICKI correlates to fasting insulin variation and therefore up to 90% of the information can be obtained from the fasting insulin level alone. Insulin levels can also be measured during an oral glucose tolerance test and I have found them practically useful in assessing normoglycaemic individuals at high risk of insulin resistance. No single test of insulin resistance will be appropriate under all circumstances[122] and the tests should not be assumed to give equivalent assessments.[123,124]

**Clinical Associations of Obesity**

Liver Disease

Fat accumulation in the liver is independent of body mass index, intra-abdominal and overall obesity but characterized by several features of insulin resistance in normal weight and

moderately overweight subjects.[125] Increased hepatic VLDL production is associated with insulin resistance and the high rate of triglyceride turnover is often greater than the ability to secrete. Insulin resistance may also result in an inability to suppress apo B degradation.[126] Hepatic steatosis (fatty liver) consists of small or large intracytoplasmic lipid droplets especially around terminal hepatic veins (zone 3).[127]

Impaired triglyceride export and an insufficient increase in free FFA mitochondrial beta oxidation could aggravate the situation leading to the presence of oxidisable lipids in hepatocytes and could also trigger lipid peroxidation, mitochondrial dysfunction and cytokine production.[128] Non-alcoholic steatohepatitis (NASH) is a combination of steatosis with necro-inflammatory changes including enlarged hepatocytes, apoptotic bodies, Mallory bodies and giant mitochondria with loss of cristae. Peripheral insulin resistance, increased FFA beta-oxidation, and hepatic oxidative stress are present in both fatty liver and NASH, but NASH alone is associated with mitochondrial structural defects.[129] Inflammation appears with lymphocytic and neutrophilic infiltrates usually around altered hepatocytes or in the portal areas.

Fibrosis and cirrhosis may occur around the terminal hepatic veins and then form bridges between terminal hepatic veins or between adjacent portal tracts. Fatty liver and NASH is increasingly being recognised as an important cause of liver related morbidity and mortality[130] and is believed by many to be one of the most common causes of cryptogenic cirrhosis.[131] The morbidly obese can be expected to have fatty liver changes including portal inflammation and fibrosis in 30% and cirrhosis in 3%.[132]

Although ferritin levels have also been found to be predictive of fatty liver[133] it is important to recognise that ferritin levels will be increased when ALT levels are elevated and may be secondary to fatty liver rather than related to cause.

Laboratory abnormalities in fatty liver include a 2 to 4-fold elevation of serum transaminase levels with other liver function test results usually normal.[134] NASH is becoming the most common reason for referral for investigation of abnormal liver function tests. Central adiposity, hyperleptinaemia, and hyperinsulinaemia were the major determinants of the association of overweight with elevated serum ALT activity.[135] Performing oral glucose tolerance testing in cases with fatty liver disease may be useful for early screening of diabetes mellitus.[136]

Body weight, rather than alcohol consumption, may be the major factor in determining the serum level of liver enzymes. Even when body weight is not generally considered to be overweight, slight to moderate gains in weight are associated with increases in serum liver enzymes.[137] Laboratories should determine age-adjusted reference intervals for enzymes in children, and gender-adjusted reference intervals for transaminases, gamma-glutamyltransferase, and total bilirubin in adults.[138] These reference intervals for ALT may include variations due to BMI[139] with body weight explaining 12% of the normal variation of ALT.[140]

The clinical adage “fat, female, fertile and forty” indicates that gallstone incidence is higher in the overweight and in fact very high in obesity.[141] Cholesterol production increases as body fat increases[142] (10 kg body weight gain is equivalent to an extra egg a day) and high concentrations of cholesterol relative to bile acids will increase the likelihood of gallstone precipitation.

Coronary Artery Disease

BMI increases the risk of CAD, and weight gain from any initial BMI further increases the risk (especially weight gain of 20 kg or more).

Dyslipidaemia may be the most important relationship of BMI to CAD.[143] Obesity increases VLDL (triglycerides) through increased production and decreased clearance of triglyceride rich lipoproteins due to lack of stimulation of lipoprotein lipase.[144] Obesity also lowers HDL in men and women of all ages[145-147] and ethnicities.[148] While LDL levels are not consistently elevated in obesity, LDL is smaller and denser[149] and more atherogenic.

Cholesterol ester transport protein (CETP) exchanges triglycerides from VLDL to LDL in exchange for cholesterol esters. This results in triglyceride rich LDL particles that are rapidly lipolysed by hepatic lipase leaving smaller denser LDL particles. Small dense LDL can more easily be oxidised or glycated possibly leading to less identification by the LDL receptor and decreased clearance. Possibly small dense LDL is also more likely to get through endothelial fenestrations.

CETP also exchanges triglycerides from VLDL to HDL in exchange for cholesterol esters. This similarly results in triglyceride rich HDL particles that are rapidly lipolysed by hepatic lipase allowing HDL to be cleared from the circulation.

High fasting triglyceride levels (i.e. VLDL) predict the presence of small dense LDL in diabetes,[150-152] non-diabetics[153] and hypopituitarism.[154] Remarkably the value of triglyceride

that predicts the small dense LDL phenotype is about 1.5 mmol/L, the same level used in the definitions of metabolic syndrome. More specifically the logarithm of the triglyceride concentration is inversely related to particle size.[155] The total cholesterol to HDLC ratio is more predictive than the LDLC to HDLC ratio because it mathematically includes also the component Trig/HDL which is crucially abnormal in insulin resistance and predicts the presence of small dense LDL.

Hypertension

Hypertension is present in about half of all overweight individuals[156] and obesity alone accounts for about 70% of essential hypertension.[157] Cardiac weight increases with increasing body weight, but heart weight as a percentage of total body weight is lower than in normal weight controls. In obesity, the increase in cardiac output is not explained by the presence of the new adipose tissue, but may be due to increased sympathetic activity. Adrenaline (from the adrenal medulla) tends to be normal to low in obesity and there is a decreased response of adrenaline to hypoglycaemia and exercise.[158] However, noradrenaline levels (from sympathetic nerve endings) tend to be higher.[159] Hypertension in the overweight is associated with increased sympathetic activity[160,161] and sympathetic blockers have greater effect in obesity.[162] The causes of sympathetic overactivity include hyperinsulinaemia, increased intrarenal pressures, hepatic FFA, angiotensin II, leptin, central chemoreceptor sensitivity and impaired baroreceptor reflex.[163]

Sodium reabsorption is increased with high fat diets[164] and the renin/angiotensin/aldosterone system (RAAS) is activated in obesity despite volume expansion and sodium retention.[165] Aldosterone tends to be higher in obese individuals while renin is often relatively normal and there is a positive correlation between BMI and the aldosterone to renin ratio.[166] Adipose has long been expected to produce a factor that directly affects RAAS and recently all the components of the renin-angiotensin system have been found to be fully represented in the adipose tissue. Furthermore, they appear to be up-regulated in obesity and circulating angiotensinogen levels are enhanced[167] due to elevated adipose angiotensinogen gene expression in obesity.[168-170]

Other findings of interest include the decreased levels of atrial and ventricular natriuretic peptides (natural antagonists of the RAAS) which may also help to explain the susceptibility of the obese to hypertensive disorders.[171]

Renal hyper-filtration together with glucose intolerance, hyperlipidaemia and hypertension can lead to obesity related focal segmental glomerulosclerosis.

Polycystic Ovary Syndrome (PCOS)

PCOS has been described as 'the thief of womanhood' as it is commonly associated with oligomenorrhoea and hirsutism.[172] Multiple ovarian cysts are actually a common ultrasound finding (up to 20% in 18-25 y/o) however this finding is usually not associated with infertility, although it may be associated with hirsutism.[173] It is generally the association of obesity with multiple ovarian cysts that leads to infertility.[174]

A universally accepted definition of PCOS does not exist, however most modern definitions acknowledge the association of insulin resistance together with hyperandrogenism and infertility. Up to 30% of all PCOS women have impaired glucose tolerance and an additional 7.5% have diabetes while even 10.3% of non-obese women with PCOS have impaired glucose tolerance and 1.5% have diabetes.[175] 16% of PCOS women develop diabetes by the age of menopause.[176] Conversely, up to 27% of pre-menopausal women with type 2 diabetes will also have PCOS.[177]

Sex hormone binding globulin (SHBG) is usually low in PCOS. The most important hormone that SHBG binds is testosterone. The presence of increased total testosterone in PCOS is uncommon compared to the prevalence of increased free testosterone estimates.[178] Free testosterone is believed to be the biologically active form but is difficult to measure, however it is clear that if there is little binding protein, more testosterone must be free and active. SHBG levels can be increased by oestrogen or thyroxine,[179] however low levels are usually due to androgens or insulin.[180] Levels of SHBG do not correlate with androgen levels but rather with body mass index[181,182] and insulin resistance.[183,184] SHBG is predictive of NIDDM in women[185,186] and similarly predictive of overall mortality in post-menopausal women.[187] Abnormal lipid levels are seen in 70% of women with PCOS particularly if they are obese.[188]

Increased LH pulse frequency and amplitude occurs in PCOS. This may be in part due to the effects of elevated free testosterone.[189] The normal LH/FSH ratio is below 2.0, whereas in PCOS it usually rises to over 2.5. Marked elevations of both LH and FSH are seen normally in mid-cycle when this ratio is less discriminatory.

Other Endocrine Effects of Obesity

Obesity has no effect on TSH, FT4, TRH, thyroglobulin or total T4. Reverse T3 (rT3) has been negatively correlated to BMI but it is already known that overfeeding can lead to increased levels of T3 (where rT3 is decreased) and this is the most likely relationship.[190]

Growth hormone (GH) levels are lower in obesity.[191] The circadian rhythm is maintained but GH responsiveness is also diminished and there are fewer GH pulses with lower amplitude.[192] Chronic hyperinsulinaemia in obesity may stimulate IGF-1 production but simultaneously suppress hepatic IGFBP-1 and IGFBP-2 production, which may result in inhibition of IGF-1 bioactivity.[193] Changes in IGF-1 levels may also be responsible for the lower GH levels, through negative feedback.[194]

Cortisol production is increased, but as there is also increased metabolism, basal levels of cortisol (and ACTH) are normal in obesity. Abnormalities in the pituitary adrenal axis have been described. However we need to distinguish between simple obesity and the obesity associated with Cushing's syndrome, otherwise it is difficult to assess the importance of differing responses in cortisol and ACTH stimulatory tests in obesity.[195]

Fat distribution develops in adolescence and androgens and oestrogens produced by the gonads and adrenals as well as the peripheral conversion of androstenedione to estrone in fat cells are pivotal in body fat distribution. Oestradiol and oestrone levels are increased in obese men probably due to the increased peripheral conversion of testosterone and androstenedione to estradiol and estrone. Despite the high levels there is generally no evidence of feminisation.

Total testosterone levels are lower in obese men, largely due to decreases in SHBG.[196] However, free testosterone levels seem to be normal and libido, testicular size, potency and spermatogenesis are also usually normal. Obesity has been proven to affect other aspects of sexual function as it is independently associated with erectile dysfunction and may improve with weight loss.[197] LH levels are usually normal[198] however gross obesity may cause low LH levels.[199] Low free testosterone levels may occur[200] as evidenced in sleep apnoea syndrome,[201] and this may be mediated by the significantly increased oestrogens in obese men.

Finally vitamin D levels are also lower in obesity[202,203] leading to higher PTH levels.[204] Social isolation and an indoor existence may be significant factors.

## Conclusion

The rate of obesity is increasing throughout the world. Environmental changes continue to occur in developed and developing countries creating a global pandemic with enormous implication of morbidity and mortality in the coming decades. It seems that each of us will have a polygenetic risk to developing obesity and can only hope that the improving understanding of the causes and complex relationships of obesity will lead to better prevention and treatments. The clinical biochemistry laboratory often provides useful evidence for clinicians and patients when the overt signs of the condition are either hidden or denied. Until then we only need to look around us for motivation in our personal battles with this disease!

## References


1. Gray DS. Diagnosis and prevalence of obesity. Med Clin North Am 1989;73:1-13.
2. Ferreira IM, Verreschi IT, Nery LE et al. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. Chest 1998;114:19-28.
3. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care 1991;14:1132-43.
4. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89:2548-56.
5. Prins JB. Adipose tissue as an endocrine organ. Best Pract Res Clin Endocrinol Metab 2002;16:639-51.
6. Metropolitan Life Insurance Company. New weight standards for men and women. Stat Bull Metrop Insur Co 1959;40:1
7. Burton BT, Foster WR. Health implications of obesity: an NIH Consensus Development Conference. J Am Diet Assoc 1985;85:1117-21.
8. World Health Organisation. Energy and protein requirements. Report of a joint FAO/WHO/UNU expert consultation. Geneva, Switzerland: World Health Organisation; 1985. WHO Technical Report Series 724.
9. World Health Organisation. The global epidemic of obesity. Geneva, Switzerland: World Health Organisation 1997.
10. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
11. Visscher TL, Seidell JC, Molarius A, van der Kuip D, Hofman A, Witteman JC. A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. Int J Obes Relat Metab Disord 2001;25:1730-5.
12. Wei M, Gaskill SP, Haffner SM, Stern MP. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other

anthropometric measurements in Mexican Americans--a 7-year prospective study. Obes Res 1997;5:16-23.
13. Dalton M, Cameron AJ, Zimmet PZ et al. AusDiab Steering Committee. Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. J Intern Med 2003;254:555-63.
14. Bigaard J, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL, Sorensen TI. Waist circumference, BMI, smoking, and mortality in middle-aged men and women. Obes Res 2003;11:895-903.
15. Cameron AJ, Welborn TA, Zimmet PZ et al. Overweight and obesity in Australia: the 1999-2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Med J Aust 2003;178:427-32.
16. Booth ML, Chey T, Wake M et al. Change in the prevalence of overweight and obesity among young Australians, 1969-1997. Am J Clin Nutr 2003;77:29-36.
17. Sturm R. The effects of obesity, smoking, and drinking on medical problems and costs. Obesity outranks both smoking and drinking in its deleterious effects on health and health costs. Health Aff (Millwood) 2002;21:245-53.
18. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. Lancet 2001;357:505-8.
19. Butte NF. Fat intake of children in relation to energy requirements. Am J Clin Nutr 2000;72(Suppl):1246S-1252S.
20. Robinson TN. Television viewing and childhood obesity. Pediatr Clin North Am 2001;48:1017-25.
21. Bhargava SK, Sachdev HS, Fall CH et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004;350:865-75.
22. al-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. J Clin Endocrinol Metab 1997;82:1118-25.
23. Wynne K, Stanley S, Bloom S. The gut and regulation of body weight. J Clin Endocrinol Metab 2004;89:2576-82.
24. Neel JV, Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 1962;14:353-62.
25. Bjorntorp P. Thrifty genes and human obesity. Are we chasing ghosts? Lancet 2001;358:1006-8.
26. Joffe B, Zimmet P. The thrifty genotype in type 2 diabetes: an unfinished symphony moving to its finale? Endocrine 1998;9:139-41.
27. Chakravarthy MV, Booth FW. Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. J Appl Physiol 2004;96:3-10.
28. Ong KK, Dunger DB. Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults. Best Pract Res Clin Endocrinol Metab 2002;16:191-207.
29. National Institutes of Health. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults – the evidence report. Obes Res 1998;6(Suppl):51S-209S.
30. Vanhala M. Childhood weight and metabolic syndrome in adults. Ann Med 1999;31:236-9.
31. Law CM, Barker DJ, Osmond C, Fall CH, Simmonds SJ. Early growth and abdominal fatness in adult life. J Epidemiol Community Health 1992;46:184-6.
32. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. The body-mass index of twins who have been reared apart. N Engl J Med 1990;322:1483-7.
33. Moll PP, Burns TL, Lauer RM. The genetic and environmental sources of body mass index variability: the Muscatine Ponderosity Family Study. Am J Hum Genet 1991;49:1243-55.
34. Damcott CM, Sack P, Shuldiner AR. The genetics of obesity. Endocrinol Metab Clin North Am 2003;32:761-86.
35. Snyder EE, Walts B, Perusse L et al. The human obesity gene map: the 2003 update. Obes Res 2004;12:369-439.
36. Liu YJ, Xu FH, Shen H et al. A follow-up linkage study for quantitative trait loci contributing to obesity-related phenotypes. J Clin Endocrinol Metab 2004;89:875-82.
37. Proietto J, Baur LA. 10: Management of obesity. Med J Aust 2004;180:474-80.
38. Montague CT, Farooqi IS, Whitehead JP et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903-8.
39. Clement K, Vaisse C, Lahlou N et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998;392:398-401.
40. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Gruters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet 1998;19:155-7.
41. Branson R, Potoczna N, Kral JG, Lentes KU, Hoehe MR, Horber FF. Binge eating as a major phenotype of melanocortin 4 receptor gene mutations. N Engl J

Med 2003 ;348:1096-103.
42. Considine RV, Sinha MK, Heiman ML et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292-5.
43. Walston J, Silver K, Bogardus C et al. Time of onset of non-insulin-dependent diabetes mellitus and genetic variation in the beta 3-adrenergic-receptor gene. N Engl J Med 1995;333:343-7.
44. Widen E, Lehto M, Kanninen T, Walston J, Shuldiner AR, Groop LC. Association of a polymorphism in the beta 3-adrenergic-receptor gene with features of the insulin resistance syndrome in Finns. N Engl J Med 1995;333:348-51.
45. Clement K, Vaisse C, Manning BS et al. Genetic variation in the beta 3-adrenergic receptor and an increased capacity to gain weight in patients with morbid obesity. N Engl J Med 1995;333:352-4.
46. Kurokawa N, Nakai K, Kameo S, Liu ZM, Satoh H. Association of BMI with the beta3-adrenergic receptor gene polymorphism in Japanese: meta-analysis. Obes Res 2001;9:741-5.
47. Gurnell M, Savage DB, Chatterjee VK, O'Rahilly S. The metabolic syndrome: peroxisome proliferator-activated receptor gamma and its therapeutic modulation. J Clin Endocrinol Metab 2003;88:2412-21.
48. Oakes ND, Kennedy CJ, Jenkins AB, Laybutt DR, Chisholm DJ, Kraegen EW. A new antidiabetic agent, BRL 49653, reduces lipid availability and improves insulin action and glucoregulation in the rat. Diabetes 1994;43:1203-10.
49. Furnsinn C, Waldhausl W. Thiazolidinediones: metabolic actions in vitro. Diabetologia 2002;45:1211-23.
50. Mudaliar S, Henry RR. New oral therapies for type 2 diabetes mellitus: The glitazones or insulin sensitizers. Annu Rev Med 2001;52:239-57.
51. Lee CH, Olson P, Evans RM. Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. Endocrinology 2003;144:2201-7.
52. Ek J, Urhammer SA, Sorensen TI, Andersen T, Auwerx J, Pedersen O. Homozygosity of the Pro12Ala variant of the peroxisome proliferation-activated receptor-gamma2 (PPAR-gamma2): divergent modulating effects on body mass index in obese and lean Caucasian men. Diabetologia 1999;42:892-5.
53. Hsueh WC, Cole SA, Shuldiner AR et al. Interactions between variants in the beta3-adrenergic receptor and peroxisome proliferator-activated receptor-gamma2 genes and obesity. Diabetes Care 2001;24:672-7.
54. Muller YL, Bogardus C, Pedersen O, Baier L. A Gly482Ser missense mutation in the peroxisome proliferator-activated receptor gamma coactivator-1 is associated with altered lipid oxidation and early insulin secretion in Pima Indians. Diabetes 2003;52:895-8.
55. Stumvoll M, Tschritter O, Fritsche A et al. Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes 2002;51:37-41.
56. Felson DT, Anderson JJ, Naimark A et al. Obesity and knee osteoarthritis. The Framingham study. Ann Int Med 1988;109:18-24.
57. Malhotra A, White DP. Obstructive sleep apnoea. Lancet 2002;360:237-45.
58. Fleetham JA. Upper airway imaging in relation to obstructive sleep apnea. Clin Chest Med 1992;13:399-416.
59. Strohl KP, Strobel RJ, Parisi RA. Obesity and pulmonary function. In: Bray GA, Bouchard C, James WP, editors. Handbook of Obesity. New York: Marcel Dekker; 1997. pp. 725-39.
60. Series F, Marc I, Cormier Y, La Forge J. Utility of nocturnal home oximetry for case finding in patients with suspected sleep apnea hypopnea syndrome. Ann Intern Med 1993;119:449-53.
61. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of U.S. adults. Am J Epidemiol 1997;146:214-22.
62. Colditz GA, Colditz GA, Willett WC et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990;132:501-13.
63. Hu FB, Manson JE, Stampfer MJ et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001;345:790-7.
64. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523-9.
65. Albu J, Pi-Sunyer FX. Obesity and diabetes. In: Bray GA, Bouchard C, James WPT, editors. Handbook of Obesity. New York: Marcel Dekker; 1998. pp. 697-707.
66. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988;37:667-87.
67. Bergman RN. Non-esterified FFA and the liver: why is insulin secreted into the portal vein? Diabetologia 2000;43:946-52.
68. Shepherd PR, Kahn BB. Glucose transporters and

insulin action--implications for insulin resistance and diabetes mellitus. N Engl J Med 1999;341:248-57.
69. Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol 2003;14:281-7.
70. den Boer M, Voshol PJ, Kuipers F, Havekes LM, Romijn JA. Hepatic steatosis: a mediator of the metabolic syndrome. Lessons from animal models. Arterioscler Thromb Vasc Biol 2004;24:644-9.
71. Kelley DE, Goodpaster BH. Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance. Diabetes Care 2001;24:933-41.
72. Blaak EE. FFA metabolism in obesity and type 2 diabetes mellitus. Proc Nutr Soc 2003;62:753-60.
73. Goldstein BJ. Insulin resistance as the core defect in type 2 diabetes mellitus. Am J Cardiol 2002;90:3G-10G.
74. Clarke SD. The multi-dimensional regulation of gene expression by FFA: polyunsaturated fats as nutrient sensors. Curr Opin Lipidol 2004;15:13-18.
75. Bollheimer LC, Skelly RH, Chester MW, McGarry JD, Rhodes CJ. Chronic exposure to free FFA reduces pancreatic beta cell insulin content by increasing basal insulin secretion that is not compensated for by a corresponding increase in proinsulin biosynthesis translation. J Clin Invest 1998;101:1094-101.
76. Zhou YP, Grill VE. Long-term exposure of rat pancreatic islets to FFA inhibits glucose-induced insulin secretion and biosynthesis through a glucose FFA cycle. J Clin Invest 1994;93:870-6.
77. Weir GC, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A. Beta-cell adaptation and decompensation during the progression of diabetes. Diabetes 2001;50(Suppl):S154-9.
78. Scheen AJ. Pathophysiology of type 2 diabetes. Acta Clin Belg. 2003;58:335-41.
79. Ruan H, Lodish HF. Regulation of insulin sensitivity by adipose tissue-derived hormones and inflammatory cytokines. Curr Opin Lipidol 2004;15:297-302.
80. Fernandez-Real JM, Broch M, Vendrell J, Ricart W. Insulin resistance, inflammation, and serum FFA composition. Diabetes Care 2003;26:1362-8.
81. Borst SE. The Role of TNF-alpha in Insulin Resistance. Endocrine 2004;23:177-82.
82. Hotamisligil GS, Spiegelman BM. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. Diabetes 1994;43:1271-8.
83. Ruan H, Lodish HF. Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alpha. Cytokine Growth Factor Rev 2003;14:447-55.
84. Castro JP, El-Atat FA, McFarlane SI, Aneja A, Sowers JR. Cardiometabolic syndrome: pathophysiology and treatment. Curr Hypertens Rep 2003;5:393-401.
85. Dejgard A, Andersen T, Gluud C. The influence of insulin on the raised plasma fibronectin concentration in human obesity. Acta Med Scand 1986;220:269-72.
86. Halaas JL, Gajiwala KS, Maffei M et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543-6.
87. Considine RV. Regulation of leptin production. Rev Endocr Metab Disord 2001;2:357-63.
88. Woods SC, Gotoh K, Clegg DJ. Gender differences in the control of energy homeostasis. Exp Biol Med (Maywood) 2003;228:1175-80.
89. Wauters M, Van Gaal L. Gender differences in leptin levels and physiology: a role for leptin in human reproduction. J Gend Specif Med 1999;2:46-51.
90. Brunetti L, Orlando G, Recinella L, Michelotto B, Ferrante C, Vacca M. Resistin, but not adiponectin, inhibits dopamine and norepinephrine release in the hypothalamus. Eur J Pharmacol 2004;493:41-4.
91. El-Atat F, Aneja A, Mcfarlane S, Sowers J. Obesity and hypertension. Endocrinol Metab Clin North Am 2003;32:823-54.
92. Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 2003;148:293-300.
93. Stefan N, Stumvoll M. Adiponectin--its role in metabolism and beyond. Horm Metab Res 2002;34:469-74.
94. Goldstein BJ, Scalia R. Adiponectin: a novel adipokine linking adipocytes and vascular function. J Clin Endocrinol Metab 2004;89:2563-8.
95. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol 2003;14:561-6.
96. 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 2001;86:1930-5.
97. Ukkola O, Santaniemi M. Adiponectin: a link between excess adiposity and associated comorbidities? J Mol Med 2002;80:696-702.
98. Maruyoshi H, Kojima S, Funahashi T et al. Adiponectin is inversely related to plasminogen activator inhibitor type 1 in patients with stable exertional angina. Thromb Haemost 2004;91:1026-30.
99. Juhan-Vague I, Alessi MC, Mavri A, Morange PE. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. J

Thromb Haemost 2003;1:1575-9.
100. Mavri A, Alessi MC, Juhan-Vague I. Hypofibrinolysis in the insulin resistance syndrome: implication in cardiovascular diseases. J Intern Med 2004;255:448-56.
101. Ma LJ, Mao SL, Taylor KL et al. Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. Diabetes 2004;53:336-46.
102. White RT, Damm D, Hancock N et al. Human adipsin is identical to complement factor D and is expressed at high levels in adipose tissue. J Biol Chem 1992;267:9210-3.
103. Dugail I, Quignard-Boulange A, Le Liepvre X, Lavau M. Impairment of adipsin expression is secondary to the onset of obesity in db/db mice. J Biol Chem 1990;265:1831-3.
104. Steppan CM, Lazar MA. The current biology of resistin. J Intern Med 2004;255:439-47.
105. Volarova de Courten B, Degawa-Yamauchi M, Considine RV, Tataranni PA. High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima Indians. Diabetes 2004;53:1279-84.
106. Heilbronn LK, Rood J, Janderova L et al. Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. J Clin Endocrinol Metab 2004;89:1844-8.
107. Alberti FGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;5:539-53.
108. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The 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). JAMA 2001;285: 2486-97.
109. Hanley AJ, Wagenknecht LE, D'Agostino RB Jr, Zinman B, Haffner SM. Identification of subjects with insulin resistance and beta-cell dysfunction using alternative definitions of the metabolic syndrome. Diabetes 2003;52:2740-7.
110. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 2002;156:1070-7.
111. Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. Heart 1997;78:147-53.
112. Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol 2000;10:136-43.
113. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. J Pediatr 2004;144:47-55.
114. Legro RS, Finegood D, Dunaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1998;83:2694-8.
115. Silfen ME, Manibo AM, McMahon DJ, Levine LS, Murphy AR, Oberfield SE. Comparison of simple measures of insulin sensitivity in young girls with premature adrenarche: the fasting glucose to insulin ratio may be a simple and useful measure. J Clin Endocrinol Metab 2001;86:2863-8.
116. Yeckel CW, Weiss R, Dziura J et al. Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. J Clin Endocrinol Metab 2004;89:1096-101.
117. Katz A, Nambi SS, Mather K et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402-10.
118. Yokoyama H, Emoto M, Fujiwara S et al. Quantitative insulin sensitivity check index and the reciprocal index of homeostasis model assessment are useful indexes of insulin resistance in type 2 diabetic patients with wide range of fasting plasma glucose. J Clin Endocrinol Metab 2004;89:1481-4.
119. Chen H, Sullivan G, Yue LQ, Katz A, Quon MJ. QUICKI is a Useful Index of Insulin Sensitivity in Subjects with Hypertension. Am J Physiol Endocrinol Metab 2003;284:E804-12.
120. Skrha J, Haas T, Sindelka G et al. Comparison of the insulin action parameters from hyperinsulinemic clamps with homeostasis model assessment and QUICKI indexes in subjects with different endocrine disorders. J Clin Endocrinol Metab 2004;89:135-41.
121. Hrebicek J, Janout V, Malincikova J, Horakova D, Cizek L. Detection of insulin resistance by simple quantitative insulin sensitivity check index QUICKI for epidemiological assessment and prevention. J Clin Endocrinol Metab 2002;87:144-7.
122. Wallace TM, Matthews DR. The assessment of insulin resistance in man. Diabet Med 2002l;19:527-34.
123. Diamanti-Kandarakis E, Kouli C, Alexandraki K,

Spina G. Failure of mathematical indices to accurately assess insulin resistance in lean, overweight, or obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004;89:1273-6.
124. Wallace TM, Levy JC, Matthews DR. Use and Abuse of HOMA Modeling. Diabetes Care 2004;27:1487-95.
125. Seppala-Lindroos A, Vehkavaara S, Hakkinen AM et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum FFA independent of obesity in normal men. J Clin Endocrinol Metab 2002;87:3023-8.
126. Kendrick JS, Wilkinson J, Cartwright IJ, Lawrence S, Higgins JA. Regulation of the assembly and secretion of very low density lipoproteins by the liver. Biol Chem 1998;379:1033-40.
127. Zafrani ES. Non-alcoholic fatty liver disease: an emerging pathological spectrum. Virchows Arch 2004;444:3-12.
128. Pessayre D, Berson A, Fromenty B, Mansouri A. Mitochondria in steatohepatitis. Semin Liver Dis 2001;21:57-69.
129. Sanyal AJ, Campbell-Sargent C, Mirshahi F et al. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 2001;120:1183-92.
130. Sanyal AJ; American Gastroenterological Association. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002;123:1705-25.
131. Clark JM, Diehl AM. Nonalcoholic fatty liver disease: an underrecognized cause of cryptogenic cirrhosis. JAMA 2003;289:3000-4.
132. Del Gaudio A, Boschi L, Del Gaudio GA, Mastrangelo L, Munari D. Liver damage in obese patients. Obes Surg 2002;12:802-4.
133. Hsiao TJ, Chen JC, Wang JD. Insulin resistance and ferritin as major determinants of nonalcoholic fatty liver disease in apparently healthy obese patients. Int J Obes Relat Metab Disord 2004;28:167-72.
134. Reid AE. Nonalcoholic steatohepatitis. Gastroenterology 2001;121:710-23.
135. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2003;124:71-9.
136. Sargin M, Uygur-Bayramicli O, Sargin H, Orbay E, Yayla A. Association of nonalcoholic fatty liver disease with insulin resistance: is OGTT indicated in nonalcoholic fatty liver disease? J Clin Gastroenterol 2003;37:399-402.
137. Lee DH, Ha MH, Christiani DC. Body weight, alcohol consumption and liver enzyme activity--a 4-year follow-up study. Int J Epidemiol 2001;30:766-70.
138. Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. Clin Chem 2000;46:2027-49.
139. Leino A, Impivaara O, Irjala K, Maki J, Peltola O, Jarvisalo J. Health-based reference intervals for ALAT, ASAT and GT in serum, measured according to the recommendations of the European Committee for Clinical Laboratory Standards (ECCLS). Scand J Clin Lab Invest 1995;55:243-50.
140. Thulstrup AM, Norgard B, Steffensen FH, Vilstrup H, Sorensen HT, Lauritzen T. Waist circumference and body mass index as predictors of elevated alanine transaminase in Danes aged 30 to 50 years. Dan Med Bull 1999;46:429-31.
141. Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. Am J Clin Nutr 1992;55:652-8.
142. Ko CW, Lee SP. Obesity and gall bladder disease. In: Bray GA, Bouchard C, editors. Handbook of Obesity. New York: Marcel Dekker; 2003.
143. Despres JP, Krauss RM. Obesity and lipoprotein metabolism. In: Bray GA, Bouchard C, editors. Handbook of Obesity. New York: Marcel Dekker; 2003.
144. Taskinen MR. Lipoprotein lipase in diabetes. Diabetes Metab Rev 1987;3:551-70.
145. Denke MA, Sempos CT, Grundy SM. Excess body weight. An underrecognized contributor to high blood cholesterol levels in white American men. Arch Intern Med 1993;153:1093-103.
146. Denke MA, Sempos CT, Grundy SM. Excess body weight. An under-recognized contributor to dyslipidemia in white American women. Arch Intern Med 1994;154:401-10.
147. Sternfeld B, Sidney S, Jacobs DR Jr, Sadler MC, Haskell WL, Schreiner PJ. Seven-year changes in physical fitness, physical activity, and lipid profile in the CARDIA study. Coronary Artery Risk Development in Young Adults. Ann Epidemiol 1999;9:25-33.
148. Howard BV, Bogardus C, Ravussin E et al. Studies of the etiology of obesity in Pima Indians. Am J Clin Nutr 1991;53(Suppl):1577S-1585S.
149. Williams PT, Krauss RM. Associations of age, adiposity, menopause, and alcohol intake with low-density lipoprotein subclasses. Arterioscler Thromb

Vasc Biol 1997;17:1082-90.
150. Reaven GM, Chen YD, Jeppesen J, Maheux P, Krauss RM. Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. J Clin Invest 1993;92:141-6.
151. Lahdenpera S, Syvanne M, Kahri J, Taskinen MR. Regulation of low-density lipoprotein particle size distribution in NIDDM and coronary disease: importance of serum triglycerides. Diabetologia 1996;39:453-61.
152. Stewart JM, Kilpatrick ES, Cathcart S, Small M, Dominiczak MH. Low-density lipoprotein particle size in type 2 diabetic patients and age matched controls. Ann Clin Biochem 1994;31:153-9.
153. Halle M, Berg A, Baumstark MW, Konig D, Huonker M, Keul J. Influence of mild to moderately elevated triglycerides on low density lipoprotein subfraction concentration and composition in healthy men with low high density lipoprotein cholesterol levels. Atherosclerosis 1999;143:185-92.
154. O'Neal D, Hew FL, Sikaris K, Ward G, Alford F, Best JD. Low density lipoprotein particle size in hypopituitary adults receiving conventional hormone replacement therapy. J Clin Endocrinol Metab 1996;81:2448-54.
155 O'Neal D, Grieve G, Rae D, Dragicevic G, Best JD. Factors influencing Lp[a]- particle size as determined by gradient gel electrophoresis. J Lipid Res 1996;37:1655-63.
156. Rocchini AP. Obesity and blood pressure regulation. In: Bray GA, Bouchard C, editors. Handbook of Obesity. New York: Marcel Dekker; 2003.
157. Mark AL, Correia M, Morgan DA, Shaffer RA, Haynes WG. State-of-the-art-lecture: Obesity-induced hypertension: new concepts from the emerging biology of obesity. Hypertension 1999;33:537-41.
158. Del Rio G. Adrenomedullary function and its regulation in obesity. Int J Obes Relat Metab Disord 2000;24(Suppl):S89-91.
159. Young JB, Macdonald IA. Sympathoadrenal activity in human obesity: heterogeneity of findings since 1980. Int J Obes Relat Metab Disord 1992;16:959-67.
160. Hall JE. Mechanisms of abnormal renal sodium handling in obesity hypertension. Am J Hypertens 1997;10:49S-55S.
161. Landsberg L, Krieger DR. Obesity, metabolism, and the sympathetic nervous system. Am J Hypertens 1989;2:125S-132S.
162. Rocchini AP, Mao HZ, Babu K, Marker P, Rocchini AJ. Clonidine prevents insulin resistance and hypertension in obese dogs. Hypertension 1999;33:548-53.
163. Grassi G, Seravalle G, Colombo M et al. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. Circulation 1998;97:2037-42.
164. Hall JE, Brands MW, Dixon WN, Smith MJ Jr. Obesity-induced hypertension. Renal function and systemic hemodynamics. Hypertension 1993;22:292-9.
165. Egan BM, Stepniakowski K, Goodfriend TL. Renin and aldosterone are higher and the hyperinsulinemic effect of salt restriction greater in subjects with risk factors clustering. Am J Hypertens 1994;7:886-93.
166. Hiramatsu K, Yamada T, Ichikawa K, Izumiyama T, Nagata H. Changes in endocrine activities relative to obesity in patients with essential hypertension. J Am Geriatr Soc 1981;29:25-30.
167. Strazzullo P, Galletti F. Impact of the renin-angiotensin system on lipid and carbohydrate metabolism. Curr Opin Nephrol Hypertens 2004;13:325-32.
168. Van Harmelen V, Ariapart P, Hoffstedt J, Lundkvist I, Bringman S, Arner P. Increased adipose Obes Res 2000;8:337-41.
169. Giacchetti G, Faloia E, Sardu C et al. Gene expression of angiotensinogen in adipose tissue of obese patients. Int J Obes Relat Metab Disord 2000;24(Suppl):S142-3.
170. Karlsson C, Lindell K, Ottosson M, Sjostrom L, Carlsson B, Carlsson LM. Human adipose tissue expresses angiotensinogen and enzymes required for its conversion to angiotensin II. J Clin Endocrinol Metab 1998;83:3925-9.
171. Wang TJ, Larson MG, Levy D et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004;109:594-600.
172. Kitzinger C, Willmott J. 'The thief of womanhood': women's experience of polycystic ovarian syndrome. Soc Sci Med 2002;54:349-361.
173. Clayton RN, Ogden V, Hodgkinson J et al. How common are polycystic ovaries in normal women and what is their significance for the fertility of the population? Clin Endocrinol (Oxf) 1992;37:127-34.
174. Hassan MA, Killick SR. Ultrasound diagnosis of polycystic ovaries in women who have no symptoms of polycystic ovary syndrome is not associated with subfecundity or subfertility. Fertil Steril 2003;80:966-75.
175. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes

mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165-9.

176. Dahlgren E, Johansson S, Lindstedt G, et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertil Steril 1992;57:505-13.
177. Peppard HR, Marfori J, Iuorno MJ, Nestler JE. Prevalence of polycystic ovary syndrome among premenopausal women with type 2 diabetes. Diabetes Care 2001;24:1050-2.
178 Dechaud H, Lejeune H, Garoscio-Cholet M, Mallein R, Pugeat M. Radioimmunoassay of testosterone not bound to sex-steroid-binding protein in plasma. Clin Chem 1989;35:1609-14.
179. Crepy O, Dray F, Sebaoun J. Role of thyroid hormones in the interactions between testosterone and serum proteins. C R Acad Sci Hebd Seances Acad Sci D 1967;264:2651-3.
180. Plymate SR, Matej LA, Jones RE, Friedl KE. Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. J Clin Endocrinol Metab 1988;67:460-4.
181. Mathur RS, Moody LO, Landgrebe SC, Peress MR, Rust PF, Williamson HO. Sex-hormone-binding globulin in clinically hyperandrogenic women: association of plasma concentrations with body weight. Fertil Steril 1982;38:207-11.
182. Ducluzeau PH, Cousin P, Malvoisin E et al. Glucose-to-insulin ratio rather than sex hormone-binding globulin and adiponectin levels is the best predictor of insulin resistance in nonobese women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:3626-31.
183. Peiris AN, Sothmann MS, Aiman EJ, Kissebah AH. The relationship of insulin to sex hormone-binding globulin: role of adiposity. Fertil Steril 1989;52:69-72.
184. Jayagopal V, Kilpatrick ES, Jennings PE, Hepburn DA, Atkin SL. The biological variation of testosterone and sex hormone-binding globulin (SHBG) in polycystic ovarian syndrome: implications for SHBG as a surrogate marker of insulin resistance. J Clin Endocrinol Metab 2003;88:1528-33.
185. Haffner SM, Valdez RA, Morales PA, Hazuda HP, Stern MP. Decreased sex hormone-binding globulin predicts noninsulin-dependent diabetes mellitus in women but not in men. J Clin Endocrinol Metab 1993l;77:56-60.
186. Lindstedt G, Lundberg PA, Lapidus L, Lundgren H, Bengtsson C, Bjorntorp P. Low sex-hormone-binding globulin concentration as independent risk factor for development of NIDDM. 12-yr follow-up of population study of women in Gothenburg, Sweden. Diabetes 1991;40:123-8.
187. Lapidus L, Lindstedt G, Lundberg PA, Bengtsson C, Gredmark T. Concentrations of sex-hormone binding globulin and corticosteroid binding globulin in serum in relation to cardiovascular risk factors and to 12-year incidence of cardiovascular disease and overall mortality in postmenopausal women. Clin Chem 1986;32:146-52.
188. Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 2001;111:607-13.
189. Patel K, Coffler MS, Dahan MH, Malcom PJ, Deutsch R, Chang RJ. Relationship of GnRH-stimulated LH release to episodic LH secretion and baseline endocrine-metabolic measures in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2004;60:67-74.
190. Danforth E Jr, Horton ES, O'Connell M et al. Dietary-induced alterations in thyroid hormone metabolism during overnutrition. J Clin Invest 1979;64:1336-47.
191. Weltman A, Weltman JY, Hartman ML et al. Relationship between age, percentage body fat, fitness, and 24-hour growth hormone release in healthy young adults: effects of gender. J Clin Endocrinol Metab 1994;78:543-8.
192. Veldhuis JD, Iranmanesh A, Ho KK, Waters MJ, Johnson ML, Lizarralde G. Dual defects in pulsatile growth hormone secretion and clearance subserve the hyposomatotropism of obesity in man. J Clin Endocrinol Metab 1991;72:51-9.
193. Nam SY, Lee EJ, Kim KR et al. Effect of obesity on total and free insulin-like growth factor (IGF)-1, and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. Int J Obes Relat Metab Disord 1997;21:355-9.
194. Scacchi M, Pincelli AI, Cavagnini F. Growth hormone in obesity. Int J Obes Relat Metab Disord 1999;23:260-71.
195. Kokkoris P, Pi-Sunyer FX. Obesity and endocrine disease. Endocrinol Metab Clin North Am 2003;32:895-914.
196. Glass AR, Swerdloff RS, Bray GA, Dahms WT, Atkinson RL. Low serum testosterone and sex-hormone-binding-globulin in massively obese men.

J Clin Endocrinol Metab 1977;45:1211-9.
197. Esposito K, Giugliano F, Di Palo C et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA 2004;291:2978-84.
198. Schneider G, Kirschner MA, Berkowitz R, Ertel NH. Increased estrogen production in obese men. J Clin Endocrinol Metab.1979;48:633-8.
199. Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. J Clin Endocrinol Metab 1993;76:1140-6.
200. Haffner SM, Valdez RA, Stern MP, Katz MS. Obesity, body fat distribution and sex hormones in men. Int J Obes Relat Metab Disord 1993;17:643-9.
201. Gambineri A, Pelusi C, Pasquali R. Testosterone levels in obese male patients with obstructive sleep apnea syndrome: relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. J Endocrinol Invest 2003;26:493-8.
202. Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest 1985;76:370-3.
203. Parikh SJ, Edelman M, Uwaifo GI et al. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab 2004;89:1196-9.
204. Andersen T, McNair P, Fogh-Andersen N, Nielsen TT, Hyldstrup L, Transbol I. Increased parathyroid hormone as a consequence of changed complex binding of plasma calcium in morbid obesity. Metabolism 1986;35:147-51.