Endocrine Reviews

# Adiposity and insulin resistance in humans: the role of the different tissue and cellular lipid depots

--Manuscript Draft--

| | |
|---|---|
| **Manuscript Number:** | |
| **Full Title:** | Adiposity and insulin resistance in humans: the role of the different tissue and cellular lipid depots |
| **Short Title:** | Regional Adiposity and Insulin Resistance |
| **Article Type:** | Review |
| **Corresponding Author:** | Donald Chisholm, MB BS, FRACP<br>Garvan Institute of Medical Research<br>Sydney, NSW AUSTRALIA |
| **Corresponding Author Secondary Information:** | |
| **Corresponding Author's Institution:** | Garvan Institute of Medical Research |
| **Corresponding Author's Secondary Institution:** | |
| **First Author:** | Samantha L Hocking, MB BS M. Med (Clin. Epi) FRACP PhD |
| **First Author Secondary Information:** | |
| **Order of Authors:** | Samantha L Hocking, MB BS M. Med (Clin. Epi) FRACP PhD |
| | Kerry-Lee Milner, MB BS FRACP |
| | Dorit Samocha-Bonet, PhD |
| | Jerry R Greenfield, MB BS PhD |
| | Donald Chisholm, MB BS, FRACP |
| **Order of Authors Secondary Information:** | |
| **Abstract:** | Human adiposity has long been associated with insulin resistance and increased cardiovascular risk, and abdominal adiposity is considered particularly adverse. Intraabdominal fat is particularly associated with insulin resistance, possibly mediated by greater lipolytic flux, lower adiponectin levels, resistance to leptin and increased inflammatory cytokines, although the latter contribution is less clear. Liver fat is also closely associated with insulin resistance which may, in part, result from the lipogenic pathway of insulin action being "non-resistant". Again intramyocellular lipid (IMTG) is associated with muscle insulin resistance but anomalies include higher IMTG in insulin-sensitive athletes and women (versus men). Such issues could be explained if the "culprits" were active lipid moieties such as diacylglycerol and ceramide species, dependent more on lipid flux than triglyceride amount.<br>Subcutaneous fat, especially gluteo-femoral, appears metabolically protective, illustrated by insulin resistance and dyslipidemia in patients with lipodystrophy. However, in some studies, deep subcutaneous abdominal fat may have adverse properties.<br>Pericardial and perivascular fat relate to atheromatous disease but not clearly to insulin resistance.<br>There has been recent interest in recognizable brown adipose tissue (BAT) in adult humans, which may be augmented by a hormone, irisin, from exercising muscle. BAT is metabolically active, oxidizes fatty acids and generates heat but, because of its small and variable quantities, its metabolic importance in humans under usual living conditions is still unclear.<br>Further understanding of specific roles of different adipose depots may help new approaches to control obesity and its metabolic sequelae. |
| **Suggested Reviewers:** | Gerald Watts<br>University of Western Australia |

| | |
|---|---|
| | gerald.watts@uwa.edu.au |
| | Steve O'Rahilly<br>University of Cambridge<br>so104@medschl.cam.ac.uk |
| | Robert  Rizza<br>Mayo Clinic<br>rizza.robert@mayo.edu |
| **Opposed Reviewers:** | |

**Professor Donald J. Chisholm MB BS FRACP AO**
384 Victoria Street t 61 2 9295 8205
Darlinghurst Sydney f 61 2 9295 8201
NSW 2010 Australia www.garvan.org.au
email: d.chisholm@garvan.org.au

GARVAN INSTITUTE
*Breakthrough Medical Research*

22nd June 2012

Editor-in-Chief
Endocrine Reviews

Dear Sir,

We are now submitting the following review manuscript for consideration by Endocrine Reviews. We have had a long-standing interest in this area and, as indicated later, have made a number of seminal contributions. Although Endocrine Reviews has published several papers overlapping this area I do not believe there has been a review directly on this topic in the last decade - yet because of advances in understanding of measurement techniques, genetic and environmental influences and molecular mechanisms, as well as the "epidemic" of obesity it is one that is very topical and advancing rapidly.

**Title: Adiposity and Insulin Resistance in Humans: the role of the different tissue and cellular lipid depots.**

**OUR CREDENTIALS**

I believe our credentials for producing this review are strong and include the following contributions:

- Multiple studies of the relationship of insulin resistance to abdominal, visceral or intramyocellular lipid
- Original descriptions of the HIV Lipodystrophy Syndrome, 2 papers - *combined cites >2300.*
- Relationship of insulin sensitivity to muscle phospholipids incl. N. Engl. J. Med. 1993, *cites 543*.
- Studies of twins examining genetic v environmental influences on adiposity and fat distribution.
- Characterization of the human Melanocortin 4 Receptor obesity phenotype; the commonest single gene cause of obesity, N Engl J Med. 2009, *cites 71*.
- Studies of the effect of energy restriction, energy excess, increased physical activity and lipodystrophy on abdominal and intramyocellular lipid.
- Numerous animal studies of high fat feeding and other manipulations with pioneering use of clamp plus glucose and analogue tracers to measure individual tissue insulin sensitivity in relation to adipose tissue and lipids.
- Original study [Gastroenterology 2010] in Hepatitis C showing insulin resistance of Hep C is predominantly in muscle rather than liver and related to subcutaneous fat and viral load but not liver fat.
- Studies of the relationship of visceral fat and adipokines to NAFLD/NASH.
- Studies of the presence and function of brown fat in humans.
- Original studies showing enhanced glucose tolerance on transplantation of SC fat to the visceral compartment and major differences in the secretome of visceral and SC fat.
- Recognition of the transcription factor Islet 1 uniquely in visceral and not SC fat in humans and rodents and its inverse correlation with adiposity.

Our suggested reviewers are:

- Prof Robert Rizza, Mayo Clinic
- Prof Steve O'Rahilly, Cambridge University, UK.
- Prof Gerald Watts, Royal Perth Hospital and University of Western Australia

Yours sincerely,

Professor Donald Chisholm
Professor of Endocrinology, Garvan Institute of Medical Research, St Vincent's Hospital and University of New South Wales

**Title:** Adiposity and insulin resistance in humans: the role of the different tissue and cellular lipid depots

**Authors:** Dr Samantha Hocking MB BS M. Med (Clin. Epi) FRACP PhD
Dr Kerry-Lee Milner MB BS FRACP
Dr Dorit Samocha-Bonet PhD
Associate Professor Jerry R. Greenfield MB BS PhD FRACP
Professor Don J. Chisholm MB BS FRACP AO

**Abbreviated Title:** Regional Adiposity and Insulin Resistance

**Corresponding Author and person to whom reprint requests should be addressed:**

Professor Don Chisholm
Garvan Institute of Medical Research
384 Victoria Street
Darlinghurst NSW 2010
Sydney Australia
Phone: (612) 9295 8205
Fax: (612) 9295 8201
Email: d.chisholm@garvan.org.au

**Grants and Fellowships supporting the paper are:**

National Health and Medical Research Council. Program Grant #535921 "Pathways to Diabetes Prevention-Alleviating the type 2 diabetes burden in Australia".

**No Conflicts of interest.**

Human adiposity has long been associated with insulin resistance and increased cardiovascular risk, and abdominal adiposity is considered particularly adverse. Intraabdominal fat is particularly associated with insulin resistance, possibly mediated by greater lipolytic flux, lower adiponectin levels, resistance to leptin and increased inflammatory cytokines, although the latter contribution is less clear. Liver fat is also closely associated with insulin resistance which may, in part, result from the lipogenic pathway of insulin action being "non-resistant". Again intramyocellular lipid (IMTG) is associated with muscle insulin resistance but anomalies include higher IMTG in insulin-sensitive athletes and women (versus men). Such issues could be explained if the "culprits" were active lipid moieties such as diacylglycerol and ceramide species, dependent more on lipid flux than triglyceride amount.

Subcutaneous fat, especially gluteo-femoral, appears metabolically protective, illustrated by insulin resistance and dyslipidemia in patients with lipodystrophy. However, in some studies, deep subcutaneous abdominal fat may have adverse properties.

Pericardial and perivascular fat relate to atheromatous disease but not clearly to insulin resistance.

There has been recent interest in recognizable brown adipose tissue (BAT) in adult humans, which may be augmented by a hormone, irisin, from exercising muscle. BAT is metabolically active, oxidizes fatty acids and generates heat but, because of its small and variable quantities, its metabolic importance in humans under usual living conditions is still unclear.

Further understanding of specific roles of different adipose depots may help new approaches to control obesity and its metabolic sequelae.

I. Introduction

II. Measurements of lipid depots
- A. Anthropometric
- B. Bioimpedance
- C. Dual-energy X-ray absorptiometry (DXA)
- D. Computed tomography (CT)
- E. Magnetic resonance imaging (MRI) and Magnetic resonance spectroscopy (MRS)
- F. Ultrasound
- G. Positron emission spectroscopy (PET), for brown fat

III. Different lipid depots and their relationship to insulin sensitivity and related metabolic dysfunction
- A. Visceral fat
- B. Liver fat - Non-alcoholic fatty liver disease, hepatitis C, hypobetalipoproteinemia and choline deficiency.
- C. Muscle lipid; intra- and extra-myocellular
- D. Subcutaneous fat (including differences of different regions)
- E. Perivascular and pericardial lipid
- F. Pancreatic fat
- G. Brown fat and "beiging" of subcutaneous fat

IV. Determinants of total adiposity and individual lipid depots
- A. Genetic and ethnic influences
  1. Genetic
  2. Ethnic
- B. Nutrition, including overfeeding and underfeeding.
- C. Physical activity (including role of irisin)
- D. Effects of gut microbiota
- E. Gender
- F. Hormones
  1. Estrogen
  2. Testosterone
  3. Growth hormone
  4. Cortisol
  5. Thyroid hormone
- G. Pharmacological agents
- H. Bariatric surgery

V. Other Conditions of fat depletion or excess
- A. Lipodystrophies
- B. Lipomatosis

VI. Mediation of effects on Insulin Sensitivity
- A. Fat cell size and number
- B. Inflammation
- C. Adipokines
  1. Leptin
  2. Adiponectin
  3. Interleukin 6
  4. Adipocyte fatty acid binding protein
  5. Retinol binding protein 4
  6. Resistin
  7. Visfatin

## I. Introduction

In the general population, a powerful correlation between insulin resistance and adiposity has been long recognized (1); this relationship applies, at least in univariate analysis, to all fat depots with, not surprisingly, strong correlations between the various fat depots themselves (2). Therefore, these data alone are relatively unhelpful in determining insulin resistance causation. For a long time there has been great interest in the question of whether body fat distribution was an important determinant of metabolic characteristics, including insulin resistance, and consequential deleterious health outcomes including diabetes and cardiovascular disease (3); this was indicated by early work of Vague and others (4) suggesting an adverse effect of upper body, or "android", compared with lower body, or "gynoid", adiposity. Progressing our understanding of this issue and dissecting potentially causative relationships is dependent on careful analyses of human studies of the general population, assessment of unusual human disorders and extrapolation from relevant animal studies.

Until recently it was assumed that different white adipose tissue depots were similar in developmental lineage but functionally altered by anatomical and local environmental differences. However it is now clear (5) that subcutaneous and visceral fat are quite different in developmental and patterning genes, have significant differences in peptide/protein secretion (6) and respond differently to PPAR-γ agonists (7), indicating they should be regarded as distinct and separate tissues.

Theoretically fat depots could contribute to insulin resistance by altering supply (either in absolute terms or in particular anatomical locations, e.g. portal vein to liver) or type of fatty acids; by increasing or decreasing secretion of humoral factors from adipocytes (adipokines) or other cells residing in adipose tissue (cytokines) which enhance (e.g. adiponectin, (8)) or inhibit (e.g. TNFα, (9)) insulin signalling; by conversion of a circulating factor to a form with more metabolic activity (e.g. conversion of cortisone to cortisol by 11β-hydroxysteroid

dehydrogenase (10)); or adipose tissue volume could simply be a marker of a process which adversely affects insulin action.

This review will examine the likely contribution of the main adipose depots, subcutaneous, visceral, hepatic, perivascular/perimyocardial, intramyocellular and brown adipose tissue (BAT) to insulin resistance and possible mechanisms involved, concentrating particularly on human data; these terms have been used in Pubmed and Medline to augment our review of the relevant literature.

## II. Measurement of lipid depots

Recognition of the contribution of abdominal and ectopic fat masses, rather than an individual's excess weight (as measured by body mass index, BMI), to insulin resistance and cardiometabolic risk has led to the evolution of technologies to accurately and non-invasively define these fat depots.

### A. Anthropometry

Anthropometric measurements (using weight, height, skinfold thickness, waist and hip circumference) are quick, easy to perform and cost-efficient, but have many limitations particularly in regard to assessing abdominal fat depots (11). Waist circumference (most commonly circumferential measurement midway between the lower rib margin and iliac crest or at the umbilicus) is a good surrogate marker of visceral adiposity predicting cardiovascular risk (12-14) and has independent predictive value in many diabetes risk assessment systems (15, 16); there has been controversy as to whether waist/hip (WHR) or waist/height (WhtR) ratios give additional discriminatory value with some evidence that WHtR is superior across different ethnic groups, but the benefit compared to waist measurement alone appears small (17, 18).

### B. Bio-impedance

Bioelectrical impedance analysis (BIA) has been widely used to assess body composition (19). It is based on the differences in resistance when an electrical current is conducted through fat and lean components of body fat with prediction equations used to determine fat-free mass. Although it is cost-efficient, safe, avoids radiation and is easily accessible, it lacks specificity and accuracy. BIA may be useful in epidemiological studies and for defining abdominal obesity in individuals but cannot accurately measure visceral fat mass.

**C. Dual energy X-ray absorptiometry (DXA)**

DXA measures the attenuation of two energies passing through all or part of the body to distinguish and quantitate fat, lean and bone mineral content. It can accurately detect whole body fat mass (within 2% cv) and modified setting of the software allows analysis of particular regions of the body; a measure of central abdominal adiposity (a rectangle from upper L2 to lower L4 and lateral margin at inner edge of rib cage) which includes predominantly subcutaneous, but also some hepatic and intraabdominal fat, correlates very strongly with insulin resistance (20). However DXA is not able to define different abdominal fat compartments and its accuracy in quantifying intra-abdominal fat in obese individuals may be limited (21). DXA still remains superior to anthropometric techniques and BIA in assessing whole body fat composition and compared to indirect measures of adiposity is a very strong predictor of insulin resistance as measured by euglycemic-hyperinsulinemic clamp in lean men (22). It is more cost efficient and delivers little radiation compared to CT.

**D. Computed tomography (CT)**

Currently the gold standard for quantitative measurement of abdominal adipose tissue compartments is CT or MRI (23). While moderately expensive, these are the only direct measures of abdominal fat depots and can differentiate visceral and subcutaneous abdominal fat as well as superficial and deep subcutaneous fat (separated by a fascia) which appear to have differing metabolic contributions) (24). Cross-sectional areas can be measured at single

or multiple slices at predetermined landmarks (25). CT uses Hounsfield units as a measure to decipher between different tissues and then volume of fat can be measured in voxels and translated into cubic centimeters. CT is easily accessible, but subjects individuals to small but significant amounts of radiation.

### E. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS)

MRI involves no ionizing radiation and its accuracy and precision in measuring abdominal fat depots has been validated with weighing of adipose tissue in human cadavers and differences were less than 5% (26). MRI scanners can also be used to quantify ectopic fat using MRS. MRS techniques using $^{1}$H MRS allow non-invasive studies of the molecular composition of tissues in vivo and can accurately measure hepatic, intramyocellular (27), myocardial (28) and pancreatic fat (29). MRI and CT are also able to quantify liver fat, although CT is not accurate for mild liver fat infiltration (30) and MRI techniques (other than using MRS) of liver fat measurement are still experimental and require further evaluation. Epicardial fat can also be quantified using CT (31) and MRI, which can additionally measure pericardial fat (32).

### F. Ultrasound

Liver ultrasound is frequently used to evaluate liver fat clinically but not in research studies; although it is cheap and involves no radiation, it is operator dependent and is unable to provide reproducible quantitative information. Ultrasound can also be used to measure subcutaneous fat thickness. Echocardiography is used to assess the thickness (echo-free space between the outer wall of the myocardium and the visceral layer of pericardium) and volume of epicardial fat (33).

### G. Positron emission tomography (PET)

Combined PET and CT (PET-CT) used for tumor surveillance, has identified areas of adipose tissue with a high rate of uptake of 18 F-fluorodeoxyglucose (18F-FDG) as putative

brown adipose tissue (BAT) in adults (34, 35); this has been confirmed by increased uncoupling protein 1 (UCP-1) expression on biopsy (see section III. G).

## III Different lipid depots and their relationship to insulin sensitivity and related metabolic dysfunction

### A. Visceral fat

In the general population, subcutaneous, intraabdominal, and intramyocellular fat depots all correlate strongly with insulin resistance up to a BMI of around 30 $kg/m^2$, but above this level, only the correlation with visceral fat is maintained (2). Moreover, in a recent study examining the relative correlations of subcutaneous, intraabdominal and liver fat with fasting insulin, hepatic insulin sensitivity and dyslipidemia (36) intraabdominal and liver, but not subcutaneous, fat were strongly and independently linked to each of these variables. In an Asian Indian population visceral but not subcutaneous fat was also associated with insulin resistance and glucose intolerance as well as increasing levels of C-reactive protein (CRP) and TNF$\alpha$ (37), while in established type 2 diabetes visceral fat has been associated with both insulin resistance and poor glycemic control (38). In addition, the incidence of type 2 diabetes is much more strongly predicted by waist/hip ratio than by BMI (39, 40).

If one compares premenopausal women with men of similar age and BMI, women have substantially more total body fat, but much less intraabdominal fat (41) and substantially greater whole body and muscle insulin sensitivity (42-45), also suggesting an important negative influence of intraabdominal fat on insulin sensitivity. Surgical removal of visceral fat (46) improves insulin sensitivity and delays onset of diabetes in insulin-resistant rats. In humans, the response to omentectomy has been examined, but only in conjunction with bariatric surgery; the results have been conflicting (47-49) and may have been confounded by the weight loss and metabolic benefits of the concurrent bariatric surgery (50) – further study is required. In addition, humans who remain insulin-sensitive despite being obese have lower

amounts of intraabdominal fat compared to insulin-resistant obese humans, further highlighting the importance of this fat depot as an important correlate, and perhaps contributor to, impaired insulin action (51).

Suggestions as to the means by which intraabdominal fat creates it's adverse effects include (Table 1) lability of lipolysis with direct drainage of fatty acids to the liver via the portal vein; this mechanism would be supported by two reports of a stronger correlation of insulin resistance measured by hyperinsulinemic-euglycemic clamp (52) or the homeostasis model assessment of insulin resistance (HOMA-IR) (53) with intraperitoneal rather than retroperitoneal fat and by the finding in mice of a more adverse effect on hepatic insulin sensitivity of epididymal fat transplanted to the mesenteric rather than parietal abdominal compartment (54). Another proposed mechanism is excessive production of inflammatory molecules from immune cells whose numbers may be higher in visceral fat than other fat depots in lean and obese humans (55, 56) and be associated with reduced AMP-activated protein kinase (AMPK) activity, at least in the morbidly obese (57). There is some difficulty rationalizing these proposed mechanisms with the fact that the contribution of visceral fat to the total circulating load of fatty acids and inflammatory molecules is relatively small (58). Nevertheless visceral fat is a strong predictor of hepatic inflammation and fibrosis in fatty liver disease independent of hepatic steatosis (59) and with microalbuminuria in men (60), which may reflect renal inflammation. It is possible that visceral fat is the source of an as-yet-undiscovered adipokine(s) with adverse systemic effects, including inhibition of adiponectin secretion, which is strongly linked to visceral fat volume (61).

Visfatin and omentin are two other adipokines produced particularly by intraabdominal fat which were originally thought to be possible contributors to insulin resistance, however there is no strong evidence at this stage that either plays an important role in modulating insulin action in humans (62) ( see section VI. C).

Adipose tissue transplantation experiments may shed further light in this area; we and others have shown that transplantation of subcutaneous adipose tissue into the visceral compartment in mice causes reduction of overall adiposity and improved glucose tolerance/insulin sensitivity, whereas subcutaneous to subcutaneous, visceral to visceral or visceral to subcutaneous transfer had lesser or no benefit (63, 64) and mesenteric transplantation of visceral (epididymal) fat had a negative effect (54). These results raise the possibility of specific interaction of particular adipose tissue depots with neural or endothelial tissue, generating favorable systemic effects via humoral and/or central neural mechanisms.

Measurement of central abdominal fat by DXA, which measures all visceral fat but also a large proportion of abdominal subcutaneous fat, correlates as well, if not better, with insulin resistance than does visceral fat (20, 22) and reduction in DXA central abdominal fat correlates well with improved insulin sensitivity in overweight subjects during weight loss (65). This may be related to the fact that the DXA measurement includes a substantial amount of non-adipose tissue intracellular lipid, particularly hepatic lipid (see below) but could also relate to the fact that abdominal subcutaneous fat is larger in volume than visceral fat and is intermediate in metabolic characteristics between visceral fat and general subcutaneous fat, at least in regard to insulin and catecholamine modulation of lipolysis (66). Moreover it has been suggested that there are two functionally different layers of abdominal subcutaneous fat and the deep layer is more metabolically adverse and more related to insulin resistance (67). There is a relationship between central abdominal fat and fasting circulating free fatty acids (FFA) and both are independent predictors of insulin resistance under some circumstances (68), suggesting related influences on fatty acid flux. Moreover abdominally obese men showed reduced adipose tissue fatty acid uptake after feeding indicating diversion to ectopic sites (69).

**B. Liver fat**

Although liver fat content was not specifically measured in many earlier studies, it is usually greater in men than women and is certainly correlated with insulin resistance. One study of severely obese subjects (70) concluded that liver fat eliminated the correlation of visceral fat with insulin resistance but other studies of a broader cross section of subjects (36, 71) have suggested that intraabdominal and liver fat make similar and independent contributions to insulin resistance and dyslipidemia, while liver fat is more predictive of fasting blood glucose and, not surprisingly, abnormal liver function tests. These relationships may be affected by ethnicity as one study of obese adolescents found very low levels of hepatic lipid in Afro-Americans (72). Sex Hormone Binding Globulin (SHBG) has a strong inverse correlation with liver fat and is positively related to insulin sensitivity (73), but the nature of the links between SHBG, estrogen, liver and other fat depots with insulin sensitivity are not clear at this time.

Two further clinical conditions are relevant in regard to hepatic lipid. Hepatitis C causes insulin resistance, which is predominantly peripheral (muscle), rather than hepatic. There is a marked difference in hepatic lipid accumulation between two common genotypes, 1 and 3, but lipoprotein metabolism and possibly lipid flux are disturbed in both (74). Although genotype 3 is associated with substantially increased liver lipid, which does not occur with genotype 1, insulin sensitivity of liver and muscle is identical between the two genotypes; predictors of insulin resistance were viral load and subcutaneous (not visceral) fat and there was a trend ($p=0.096$) to elevation of basal circulating free fatty acids (FFA) (75). Hypobetalipoproteinemia is another uncommon clinical condition where there is markedly increased hepatic lipid not associated with insulin resistance. In both hepatitis C and hypobetalipoproteinemia there is alteration of lipoproteins and lipid flux, so it seems likely that the lipid flux rather than the amount of hepatic tissue triglyceride is the determining factor in changing insulin sensitivity. This hypothesis is further supported by the finding in animals that choline deficiency plus a high fat diet substantially increases liver fat accumulation while insulin sensitivity and glucose tolerance are improved rather than

worsened (76); these changes are associated with alterations in enzymes indicative of enhanced triglyceride synthesis, suggesting a "shunting" of fatty acids and related, metabolically-active, intermediates such as diacylglycerols (DAGs) into stored triglyceride. In fact DAGs through activation of PKC epsilon may interfere with insulin signalling and make an important contribution to hepatic insulin resistance (see 'lipid moieties' below, (77, 78)). Finally caloric reduction, especially with carbohydrate restriction, which would be expected to reduce liver fatty acid availability, can rapidly improve hepatic insulin sensitivity in obese subjects before any significant change in adipose tissue mass (65, 79) and short-term energy excess in non-obese healthy humans increased liver fat and insulin resistance by the surrogate HOMA-IR, reflecting induction of hepatic insulin resistance (80, 81).

While much has been written about liver fat as a contributor to insulin resistance and the Metabolic Syndrome, there is also evidence to suggest that insulin resistance with resulting hyperinsulinemia contributes to liver fat accumulation. It has been shown that in states of insulin resistance, in contrast to impaired post-receptor inhibition of insulin signalling affecting hepatic glucose production through PEPCK, the lipid synthesis pathway through SREBP1c remains 'insulin-sensitive' (82). Thus, insulin-stimulated lipid synthesis may be enhanced, while insulin-mediated glucose regulation is inhibited (83, 84). In other words liver lipid may be the result of, as well as the cause of, insulin resistance.

**C. Muscle fat; intra- and extramyocellular**

Intramyocellular triglyceride (IMTG) in muscle, measured chemically on biopsy or by MRS, correlates strongly with insulin resistance (85-88) and with central abdominal fat (89) in people who are not particularly physically active. However trained athletes, who are quite insulin sensitive, have relatively high levels of IMTG ("the athlete's paradox") (90). Interestingly, improvement in insulin sensitivity with exercise (91) or calorie restriction and weight loss (92) in sedentary overweight humans is associated with reduction in intraabdominal fat but not IMTG. Also, women may have more IMTG than men while having

greater muscle insulin sensitivity (45, 93). There is evidence to suggest that the disparities between IMTG and insulin sensitivity in muscle might be explained by the flux between DAGs, and perhaps long chain fatty acyl-CoA (LCACs), and IMTG and its regulation by DGAT (77); however a recent comparative study of endurance-trained and sedentary subjects showed, surprisingly, that total intramyocellular DAGs were lower in the insulin-resistant controls than the athletes, while ceramides and some individual DAG species were higher and therefore potential contributors to insulin resistance (94). Extramyocellular triglyceride (EMTG or intramuscular adipose tissue) also correlates with fasting plasma glucose, but not insulin (95). Interestingly, in HIV Lipodystrophy EMTG is decreased while IMTG is increased in association with the insulin resistance (96).

Paradoxically, and contrasting with the liver, muscle insulin sensitivity is reduced by short term fasting in both lean and obese subjects (97, 98).

**D. Subcutaneous fat**

A number of experimental clinical interventions or observations suggest that subcutaneous adipose tissue may not be directly implicated in the etiology of insulin resistance e.g. surgical removal of large amounts of subcutaneous fat (>10 kg) by liposuction in obese humans causes no improvement in insulin sensitivity or other metabolic benefit (99). Moreover, the thiazolidinedione group of PPAR-γ agonist compounds enhance insulin sensitivity while increasing subcutaneous, but not visceral, fat (100, 101); this effect may be heavily dependent on increased adiponectin secretion (102), but it is interesting that human subcutaneous preadipocytes differentiate in response to PPAR-γ agonists while omental preadipocytes do not (7). The ‘metabolically innocent’ characteristic of the subcutaneous adipose tissue is exhibited in the rare multiple symmetric lipomatosis syndrome (MSL) (see section V.). Nevertheless, abdominal subcutaneous fat, particularly its deep layer, may have characteristics intermediate between intraabdominal and other subcutaneous fat (discussed

under visceral fat) which may explain why measurement of this particular compartment can relate well to insulin resistance (e.g. (52)) and be predictive of diabetes risk (e.g. (103)). However the general subcutaneous fat depot, and especially gluteo-femoral fat, appears to play a 'buffering' role in taking up fatty acids and preventing the exposure of other insulin-sensitive tissues to their detrimental effects (104).

Human lipodystrophy syndromes also provide a unique example of the metabolic complications that arise from insufficient subcutaneous adipose tissue and the inability to partition lipid into adipose tissue stores. In addition to an inability to store triglycerides in adipocytes, a marked reduction in adipokine production (particularly leptin and adiponectin) may also contribute substantially to the metabolic derangement in lipodystrophy, as evidenced by the effectiveness of leptin therapy in reducing hyperglycemia, hypertriglyceridemia and hepatic steatosis in individuals with lipodystrophy syndromes (105-108), beyond that of reduced nutrient intake (106, 108) (see section V. A).

A number of studies have shed light on factors that govern subcutaneous adipose tissue expandability. Mature adipocytes are derived from preadipocytes, which in turn are derived from mesenchymal stem cells. Transcription factors such as ADD/SREB-1, C/EBP-α, -β, -δ and PPAR-γ are important in the control of adipogenesis. There are two isoforms of PPAR-γ, PPAR-γ1 that is expressed ubiquitously and PPAR-γ2 that is found almost exclusively in adipose tissue. A number of humans with heterozygous mutations in PPAR-γ have been identified. All have severe insulin resistance and many have a marked reduction in body fat (particularly affecting gluteal and peripheral limb deposits), hepatic steatosis and severe dyslipidemia (raised triglycerides, low high-density lipoprotein cholesterol) (109-111). These individuals are phenotypically similar to individuals with other congenital lipodystrophy syndromes, further supporting the concept that a limitation of subcutaneous adipose tissue expansion leads to insulin resistance and subsequent metabolic complications.

Information on the positive metabolic aspects of subcutaneous fat and the adverse consequences of its deficiency in experimental animals (112) or human lipodystrophy have led to a hypothesis of the desirability of subcutaneous adipose tissue "expandability" to accommodate excess lipid supply and avoid its spillover into "ectopic" sites (84, 113). It is interesting that some ethnic groups with a high susceptibility to Type 2 diabetes, including those from the Indian subcontinent (114) and Australian aborigines (115-117) have a naturally thin body habitus and a tendency to accumulate central (abdominal) fat with weight gain, as indicated by Waist/Hip Ratio, rather than expand their peripheral subcutaneous fat depots; in the case of the former group referred to as the "Asian Indian phenotype" (118) greater insulin resistance, as well as dyslipidemia, was found to be independent of BMI but related to abdominal and visceral fat (118, 119).

**E. Perivascular and pericardial fat**

These fat depots have been strongly linked to atherosclerosis and features of the Metabolic Syndrome and it has been suggested that both fatty acids and inflammatory adipokines are able to diffuse from these depots through the arterial wall and contribute to plaque formation (120). Much of the supportive data for this hypothesis comes from *in vitro* and small animal studies and it is not clear that the same scenario would operate in the thicker-walled arteries of humans. Nevertheless it is interesting that intramyocardial segments of human coronary arteries which do not have perivascular fat appear relatively protected from atheromatous lesions (120). In the Framingham Heart Study CT data on over 1000 subjects showed a relationship of peri-aortic fat with aortic and coronary calcification independent of other cardiovascular risk factors, however the relationship with features of the Metabolic Syndrome was eliminated by adjustment for visceral fat with which epicardial and perivascular fat are strongly correlated (121).

There is evidence that perivascular fat may influence vascular tone and blood pressure and it is possible that insulin sensitivity could be affected, either via adipokines or tissue blood flow, however a significant independent contribution of perivascular fat to human insulin resistance is not well supported at this time (120, 122).

## F. Pancreatic fat

Pancreatic steatosis is a relatively new clinical definition and studies that evaluate pancreatic fat by MRS in humans are emerging. These studies demonstrate a relationship between pancreatic fat and impaired glucose tolerance (123) and, as would be expected, an association between reduction in pancreatic fat and restoration of first phase insulin secretion by calorie restriction and weight loss in obese type 2 diabetes patients (124). Post-mortem data in eighty deceased males and females have suggested that pancreatic and hepatic steatosis were correlated, particularly in females; however, the relationship was attenuated when BMI was included in the model (125), suggesting that fatty liver and pancreas co-exist in obesity in humans. Further study will be needed to determine if pancreatic fat is a determinant of impaired insulin secretion.

## G. Brown fat (BAT) and "beiging" of subcutaneous fat

BAT differs from white adipose tissue by its high degree of vascularisation and sympathetic innervation and, most importantly, the expression of UCP-1. UCP-1 is a mitochondrial protein found in brown adipocytes that uncouples oxidative phosphorylation, resulting in inefficient production of ATP and release of energy as heat. Unlike white adipocytes which contain a single large lipid droplet surrounded by a thin layer of cytoplasm, brown adipocytes contain numerous lipid droplets and abundant cytoplasm with numerous mitochondria. It has long been established in animals that BAT is crucial for the process of non-shivering thermogenesis (126) and there is strong support for a beneficial effect on insulin sensitivity related mainly to increased fatty acid oxidation (127). Until recently, BAT was considered to be non-existent or non-functioning in human adults. Recent studies utilizing $^{18}F$ –

fluorodeoxyglucose ($^{18}$F –FDG) PET and CT have identified significant metabolic activity in BAT located in the neck, supraclavicular, mediastinal and paraspinal areas of adult humans (34, 35, 128-131). Formal proof that the areas contained functioning BAT has been provided by tissue biopsies, which reveal the morphological and molecular characteristics of brown adipose tissue, including expression of UCP1 (34, 35, 128, 130, 132, 133). These recent human brown adipose tissue studies suggest an inverse correlation between brown adipose tissue activity and BMI (34, 128, 130); moreover increased BAT metabolism may contribute significantly to energy expenditure during acute cold exposure in humans (134). However because of the relatively small amount of tissue and its inconsistent presence the impact of brown adipose tissue on thermogenesis, metabolism, insulin sensitivity and the development of obesity in humans under usual living conditions remains uncertain.

Recently, a population of brown fat–like adipocytes, having a multilocular morphology and expressing UCP-1, have been identified in white adipose tissue. These have been called adaptive or recruitable brown fat cells, brown in white ("brite") cells, or beige cells (135-137). These cells are distinct from brown adipocytes, which are derived from myogenic precursors expressing Myf-5 and are located in classic locations including the perinephric and interscapular fat pads (138, 139). Beige adipocytes do not express Myf-5 and are induced by prolonged cold exposure or in response to β3-selective adrenergic agonists (140-142). It remains to be determined whether mature white adipose cells, committed preadipocytes, or stem cells are the source of these brown fat-like cells. In numerous rodent models, browning of white adipose tissue depots is protective against diet-induced obesity (recent studies (143-145)). Increased *UCP1* gene expression in white adipose tissue in these models is induced by β-adrenergic - cAMP dependent pathways or the transcription factor PPAR-α. Browning of white adipose tissue in humans may have therapeutic potential. (See also IV. C re effects of Irisin).

## IV. Determinants of total adiposity and individual lipid depots

## A. Genetic and ethnic influences

### 1. Genetic

Twin studies (146, 147) have shown a major (>50%) genetic contribution to central distribution of adiposity, at least partly independent of the genetic determination of overall adiposity (147). However, until recently, responsible genes had not been identified, probably because of the difficulty of adequately measuring abdominal adiposity (e.g. by DXA, CT or MRI) in the very large cohorts required for genome wide association studies. However, such information is now starting to appear with recognition of new genetic loci associated with visceral adiposity (LYPLAL1 and, in women, THNSL2, (148)) and pericardial fat (TRIB2, (149)).The mechanistic pathways involved are as yet unclear. The FTO gene appears to have the strongest influence on overall adiposity and subcutaneous fat, although it only accounts for a relatively minor amount of weight gain in "affected" individuals (148, 150). In contrast, single-gene or monogenic obesity disorders result in severe early-onset obesity and insulin resistance, although the latter is usually at the level expected from the degree of adiposity of the affected individual. The relatively uncommon single gene variants causing obesity are not associated with major variation in adipose tissue distribution, with the exception of the loss of function variation in the PPAR-γ gene, which is not particularly associated with obesity, but displays substantial insulin resistance and loss of gluteofemoral fat (151) (see Section III D). Mutations in genes encoding key regulators of appetite in the hypothalamus, including leptin, the leptin receptor, pro-opiomelanocortin, prohormone convertase and the melanocortin 4 receptor (MC4R), have been identified in humans with severe, early-onset obesity (150). Most of these disorders are rare and inherited recessively, with the exception of MC4R deficiency, an autosomal dominant disorder accounting for 3-6% of severe obesity cases (152). MC4R deficiency is associated with milder but generalized adiposity, with a degree of insulin resistance compatible with the degree of adiposity (153).

### 2. Ethnic

Ethnicity is clearly an important issue in degree, distribution and metabolic effects of adiposity. The Asian Indian and Australian aboriginal "phenotype" where gain in adiposity is disproportionately central was discussed earlier (Section III. D) and it appears that waist measurement is a stronger predictor of insulin resistance in Asian Indians than Chinese or Malays (154). It has also proved necessary to set ethnic specific waist measurement criteria for the Metabolic Syndrome (155). Moreover it has been suggested that the BMI may indicate different degrees of adiposity in different ethnic groups with a BMI of 30 $kg/m^2$ in Caucasians being possibly equivalent to a BMI in the range of 27 $kg/m^2$ in some Asian populations (156). Such ethnic differences may be gender specific with Hispanic and Afro-American women having greater BMI and waist than Caucasians while Afro-American males have lower BMI and waist than their Hispanic and white counterparts (157).

In the DECODA and DECODE groups of over 50,000 subjects from 5 ethnic groups, prevalence of undiagnosed diabetes increased with increasing BMI and waist measurement similarly in all groups but to a lesser degree in Asian Indian women although this ethnic group had the highest overall prevalence (114).

Two ethnic groups with possibly the highest incidence in the world of obesity, insulin resistance and Type 2 diabetes are the Pima Indians in Arizona and the Micronesians of Nauru. In the case of the Nauruans the degree of insulin resistance appears to correspond with their adiposity when compared to Caucasians (158). Interestingly it has been possible to compare US Pimas to an ethnically and genetically similar population in Mexico with less obesity and diabetes, and substantially different life style; the greater insulin resistance of the US Pimas was accounted for in large part but not fully by their degree of obesity suggesting lifestyle, particularly degree of physical activity, is an important independent contributor (159).

There is not enough information at this time to determine the degree of genetic versus environmental contribution to ethnic differences but data on diabetes from different ethnic

572 groups in Mauritius (160) and emerging genome wide association data (e.g. (161)) suggest
573 genetic factors will be of importance although lifestyle change more so.
574
575 **B. Nutrition, including overfeeding and underfeeding**
576 Clearly when long term energy intake is greater than energy expended (outside childhood
577 growth) adiposity will increase and vice versa. Thus positive energy balance will affect and
578 increase the size of all adipose depots with the exception of BAT, but the variation in
579 response to short term change differs, with hepatic lipid changing most rapidly – even over
580 days with overfeeding (80) or calorie restriction (79). Preferential visceral adipose tissue loss
581 with calorie restriction is metabolically desirable and is suggested to occur in the initial phase
582 with modest weight loss (by low calorie diets; LCD) or with very low calorie diets (VLCD).
583 Longer term moderate caloric restriction with greater weight loss was not associated with a
584 preferential visceral fat loss (as reviewed in detail (162)). Similarly, in response to 28 days of
585 overfeeding and increased insulin resistance, non-obese men and women did not gain
586 proportionally more visceral compared to subcutaneous fat (81).
587
588 **C. Physical activity**
589 Physical activity clearly increases energy expenditure and favors weight loss and reduced
590 adiposity. In fact a high level of physical activity has been a strong characteristic of those
591 overweight people who have lost substantial weight and maintained the loss, whereas the
592 nature of the dietary regimen has been quite variable (163). Moreover calorie reduction
593 without exercise in overweight sedentary subjects may result in just as much loss of lean as
594 fat mass (65). On the other hand exercise alone has been only modestly successful in
595 generating and maintaining weight loss or reduction in abdominal fat (164, 165). However
596 long term physical activity has an important influence on fat depot size (166). A systematic
597 review has indicated exercise is particularly useful in reducing excess liver fat (167). Further,
598 a systematic review of weight loss intervention studies, including LCD and VLCD with or
599 without exercise or exercise alone reported no preferential visceral versus abdominal

subcutaneous fat loss from exercise beyond the magnitude of the weight loss achieved (162), however the type of exercise was not distinguished and a recent meta-analysis suggests aerobic rather than resistance exercise may be more beneficial in regard to visceral fat loss (168). In the context of bariatric surgery there is also evidence for an additive weight loss of 3-4 kg for subjects participating in exercise (169). A rather striking example of the effect of relatively extreme exercise is the study of Sumo wrestlers by Matsuzawa and co-workers (170); they found that active wrestlers with mean BMI 36 kg/m$^2$, who have an enormous energy intake but very strenuous training, have a large subcutaneous fat depot but relatively little visceral fat (Fig 1) and a moderately favorable metabolic phenotype; whereas after retirement and cessation of vigorous physical activity, their adipose tissue distribution and metabolic parameters deteriorate.

Enhancement of insulin sensitivity by physical activity is quite rapid, occurring within 2 to 3 days (91, 171), so this effect cannot be related to change in adipose depot size (though it could relate to intracellular lipid flux – see Section VI.D). It is likely that change in adipose depot size and perhaps function, particularly hepatic and visceral, contribute to the long term effects of exercise training on insulin sensitivity, although the relative importance of change in adipose depots versus the effect of exercise per se is unclear. In this context there is a fascinating new finding that a hormone, irisin, is released from muscle, under the influence of peroxisomal proliferator-activated receptor gamma coactivator-1α (PGC1-a), during exercise in mice and humans; in animals and *in vitro* irisin is capable of increasing UCP1 expression and thereby not only enhancing the activity of brown fat but also “browning” white adipose tissue, thus increasing metabolic rate and reducing obesity-induced insulin resistance (145). Irisin may well be an important mediator of the metabolic benefits of exercise in humans, so further human studies are awaited with interest.

### D. Effects of gut microbiota

The recognition that germ-free mice (i.e., raised in the absence of microorganisms) have 40% less total body fat than conventionally raised mice, even if their caloric intake is higher, provided the first evidence for a role of gut microbiota in regulating energy homeostasis and adiposity (172). Conventionalization of germ-free mice (i.e., colonization of their gut with a cecum-derived, distal microbial community) results in a marked increase in body fat content, hepatic triglycerides and insulin resistance within 10–14 days, despite no change in food intake or energy expenditure. Furthermore, germ-free mice are protected from diet-induced obesity, glucose intolerance and insulin resistance (173). A number of possible mechanisms account for the observed resistance of germ-free mice to diet-induced obesity. After conventionalization, the density of small intestinal villi capillaries doubles and monosaccharide uptake into the portal blood is enhanced. Fat accumulation in the liver and adipose tissue is promoted by carbohydrate response element binding protein (CREBP) – mediated and sterol REBP (SREBP) – mediated hepatic and adipose tissue lipogenesis. In comparison to their conventional counterparts, germ-free mice have increased levels of fasting-induced adipose factor (FIAF), a circulating lipoprotein lipase (LPL) inhibitor, whose expression is normally selectively suppressed in the gut epithelium by the microbiota. The suppression of LPL activity results in reduced uptake of fatty acids and triglyceride accumulation in adipocytes. FIAF also induces expression of PGC-1α, a key coactivator of nuclear receptors and enzymes involved in fatty acid oxidation. In addition, germ-free mice show increased fatty acid oxidation in liver and muscle, mediated by increased levels of phosphorylated AMPK and its downstream targets (acetylCoA carboxylase; carnitine-palmitoyl transferase) (173). Therefore, germ-free animals are protected from diet-induced obesity by two complementary, but independent mechanisms, which result in decreased fatty acid storage: (1) elevated levels of FIAF; and (2) increased AMPK activity.

In contrast to the protection against obesity conferred by a microbe-free gut, in animal models of obesity an altered microbiota composition has been associated with the development of obesity, insulin resistance and diabetes through several mechanisms. In animals fed an

obesogenic diet there is an alteration in the composition and functional properties of the gut microbiota, inducing enrichment in genes enabling energy harvest from otherwise indigestible components of the diet (174-176). Data from human studies investigating alterations in the composition of the gut microbiota in obesity have been generally consistent with animal models, but findings are more heterogeneous, likely related to the complexity of human lifestyle compared with a controlled experimental animal model (177-181). High-fat feeding increases the proportion of lipopolysaccharide (LPS) - containing microbiota in the gut and / or intestinal absorption of LPS, thereby increasing circulating LPS levels, which can trigger an inflammatory response by binding to the CD14 toll-like receptor-4 (TLR-4) complex at the surface of innate immune cells (182, 183). Alterations in gut microbiota in obesity can result in altered fatty acid metabolism and composition in adipose tissue and liver in mice (184-186), and may also modulate gut derived peptide secretion including Peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) secretion, impacting on gut transit time, energy harvest and satiety (187, 188). These animal data demonstrate that gut microbiota modulate energy homeostasis and adiposity through numerous mechanisms including energy harvest from the diet, energy storage as triglyceride, energy expenditure though fatty acid oxidation, LPS-induced chronic inflammation and gut-derived peptide secretion. However, a causal relationship between gut microbiota and the development of obesity in humans remains to be proven, and it is not clear that gut microbiota would influence distribution of lipid between different depots.

### E. Gender

Men and women differ in the incidence of obesity, fat deposition patterns, utilisation of fat as a metabolic fuel, serum lipid levels, genetic determination of metabolism related genes and health consequences of obesity. These differences may reflect evolved adaptive differences that stem from the differences in gender reproductive costs (189).

Women of all ethnicities and cultures have greater adipose stores than men, even after correcting for BMI, and this increased adiposity is present from birth, with female babies having greater subcutaneous fat than males for all gestational ages (190). Women have greater adipose stores in thighs and buttocks with males more likely to have abdominal adiposity. Furthermore, premenopausal women have a greater proportion of their abdominal fat in subcutaneous depots compared to males with males having more visceral fat for all values of BMI (189). Subcutaneous abdominal fat depots differ in the genders with women having 51% of the subcutaneous fat in the deep layer versus 66% for men (24). This distribution of fat, changes during the menopause transition; a longitudinal study using abdominal MRI to assess changes in fat depots through menopause showed no weight gain or change in BMI, however both abdominal subcutaneous and visceral fat increased, with no change in the relative distribution of fat in the abdomen (191). It has been suggested that estrogen depletion in the post menopause period may result in the increased deposition of body fat in the intra-abdominal region as administering hormone replacement therapy to post-menopausal women prevented an increase in abdominal fat (192).

Women also appear to utilize fat as an energy substrate during periods of sustained exertion more than men (189) and have higher rates of fat uptake into leg fat depots (193). Rates of fatty acid release from abdominal adipose tissue are higher in women than men, but they are lower from gluteal or femoral adipose tissue. After feeding, fatty acid uptake is higher in abdominal adipose tissue relative to gluteal or femoral in both men and women. However in women, the majority of the fatty acid uptake in abdominal adipose tissue is into subcutaneous fat, while in men a larger proportion goes into visceral fat. Turnover of visceral fat is higher in men compared with women. Men have greater rates of both lipolysis and lipogenesis in visceral fat compared with women, possibly due to fewer alpha adrenergic receptors in this fat depot. Furthermore, fatty acid uptake into this depot in the postprandial period is approximately7-fold higher in men than in women (194). Adrenergic stimulation increases

splanchnic fatty acid release in men but not in women suggesting that the effects of visceral fat on health may differ between the sexes as well (189). LPL is an enzyme that facilitates FFA uptake and premenopausal women have lower activity of this enzyme in their intra-abdominal tissue than men (195). In men abdominal fat is an important adipose tissue depot regulating muscle sympathetic nerve activity while in women, despite higher total body fat, this relationship is absent (196).

In the basal state, women matched to men for percentage body fat have higher rates of lipolysis. This may relate to higher insulin concentrations in men supressing lipolysis and a different set point and higher rate of fatty acid release in women in relation to their energy requirements (197). In the postprandial state, women are more sensitive to the inhibitory effect of insulin on lipolysis (198). This may compensate for the higher basal fatty acid flux to maintain fatty acid homeostasis (199). A recent study showed that women are more metabolically flexible than men despite more body fat i.e. they are able to transition between the utilization of fatty acids in the fed or insulin-stimulated state and regulate release of fatty acids from adipose tissue during fasting to the storage of fatty acids in the fed state (200). FFA were higher in women in the fasting state and higher in men in the insulin-stimulated state (200).

Lean and obese women have double the amount of IMTG as matched men (201, 202). Roepstorff, C et al. (203) and others have shown a net reduction in IMTG during prolonged submaximal exercise only in women. DAGs and ceramides have not been shown to be different in women and men (93) but further studies are required. Women appear to be more physiologically geared to use fat as a metabolic fuel under conditions of sustained increased demand, while men rely relatively more on glucose and protein metabolism.

Leptin and insulin are the only circulating hormones that act as adiposity signals. Leptin concentrations are more reflective of subcutaneous fat while insulin levels are more reflective of visceral fat (204). As these two fat stores differ between the genders, leptin is better correlated with total adipose mass in women and insulin is more correlated with total fat stores in men (205). Fat is linked to reproduction through leptin. Serum leptin concentration displays some persistent sex differences that begin even before birth. Circulating serum levels are higher in pregnancies where the foetus is female (206). Females have higher levels at birth and this difference persists throughout life. These differences cannot be fully accounted for by differences in total adipose tissue (women have higher levels of leptin for any given amount of fat mass (207)) or by relative amounts of adipose tissue in subcutaneous and visceral depots (208) and may be mediated by primary genetic effects on leptin production or gonadal hormones.

Metabolomic profiling and integration of whole-genome genetic association data have shown gender-specific differences in cell regulating processes with lower concentrations of most sphingomyelins in men than women (209).

Increased fatness, regardless of how measured, is associated with reduced peripheral insulin sensitivity. Despite women having more body fat than men, insulin sensitivity in women appears to be less affected by the amount of body fat. Increases in body fat among women are associated with smaller decreases in insulin sensitivity compared to men (210) and in lean women there may be no relation between adipose depots and insulin sensitivity (211).

## F. Hormones

### 1. Estrogen

As mentioned above, women have less intraabdominal fat than men and better insulin sensitivity; this would seem to be an estrogen, rather than lack of androgen, effect as this benefit is lost after menopause when insulin sensitivity is closely related to intraabdominal fat (212, 213). When given therapeutically oral, compared with transdermal, estrogen may cause a relative increase in adiposity and reduction in muscle mass apparently due to high concentrations of estrogen in the portal vein inhibiting IGF1 production (214).

**2. Testosterone**

Normal testosterone levels favor muscle maintenance and limit fat mass as evidenced by increased fat mass and reduced muscle mass with androgen deprivation therapy; this impairs insulin sensitivity and increases diabetes incidence even though there is probably little increase in intraabdominal fat (215, 216), moreover testosterone therapy in men with testosterone deficiency improves adiposity, insulin sensitivity and cardiovascular risk profile (217).

**3. Growth hormone**

GH deficiency also reduces muscle and increases fat mass, especially central fat, with impaired insulin action, although GH therapy, while improving adiposity, does not improve insulin sensitivity; likely due to GH's direct inhibition of insulin action (218, 219) with the result that there is no clear increase or decrease in risk of diabetes from GH therapy in GH deficient adults (220). Use of a GHRH analogue in patients with excess abdominal fat related to Human Immunodeficiency Virus and/or it's therapy has shown a clinically significant (15%) reduction in intraabdominal (by CT) but not subcutaneous abdominal fat associated with an improvement in triglycerides and cholesterol/HDL ratio without a benefit or deterioration in glycemia or insulin levels (221).

**4. Cortisol**

Cortisol excess is well recognized for its ability to increase central adiposity and gluconeogenesis and impair insulin action but Cushing's Syndrome is relatively uncommon. However there has been great interest in the role of 11β-hydroxysteroid dehydrogenase which converts (inactive) cortisone to (active) cortisol in tissues, including adipose tissue and liver, with data on cortisol metabolites suggesting this pathway is overactive in obesity. Such over activity could accentuate central adiposity, lipid synthesis, dyslipidemia, inflammation and insulin resistance (10) and there is evidence, mainly in animals but also in humans that inhibiting or genetically deleting this enzyme can remediate each of these abnormalities in obesity (222, 223).

### 5. Thyroid hormones

Although frank hyper- and hypothyroidism are associated with alterations in adiposity, whether more subtle changes in thyroid hormones are associated with insulin resistance, obesity and the Metabolic Syndrome is controversial; a detailed discussion is beyond the scope of this review. In some studies, humans with TSH values at the upper end of the normal range have higher BMI, higher triglyceride levels and a greater chance of being diagnosed with the Metabolic Syndrome compared to individuals with lower TSH values (224). An association between increasing TSH and waist circumference in overweight and obese women has also been demonstrated (225). However, other studies (226) have failed to confirm a significant effect of TSH elevation (subclinical hypothyroidism) on the risk of development of the Metabolic Syndrome in humans.

## G. Pharmacological agents

A number of medications have been shown to affect insulin sensitivity. On the positive side, metformin, a biguanide drug, has a modest weight reducing effect but is thought to predominantly improve insulin sensitivity in liver, and, to a lesser extent, muscle (227) via activation of AMPK (228). As mentioned previously, thiazolidinediones improve insulin sensitivity, increase adiponectin and expand the subcutaneous adipose tissue depot (101),

sequestering fatty acids and thereby minimizing exposure of insulin-sensitive tissues, such as muscle and liver. Another class of anti-diabetic agents, the GLP-1 receptor agonists, exerts a beneficial effect on insulin sensitivity, although this is largely dependent on the weight loss induced by these agents in some patients. Weight loss following activation of the GLP-1 receptor is thought to be due to the gastric decelerating properties of the GLP-1 receptor agonists, but may also be due to direct central effects on appetite and satiety (229).

Commentary on agents used primarily for weight loss is outside the scope of this review but there is no substantial data to suggest any of these agents cause preferential loss of fat from particular depots with the exception of the cannabinoid receptor antagonist, rimonabant, which caused a reduction in waist measurement, triglycerides and an increase in insulin sensitivity (HOMA) and HDL cholesterol which seemed disproportionate to the moderate weight loss, suggesting the possibility of preferential abdominal fat loss with resulting benefit on insulin sensitivity and lipids (230). However in the absence of a control group with equivalent weight loss this suggestion remains hypothetical. Rimonabant has been withdrawn because of concerns about depression and suicidal ideation but there is continuing work on similar agents which may have less central neural impact.

There are a number of drugs which adversely affect lipid depots and insulin sensitivity. HIV-positive patients treated with regimens including older protease inhibitors develop insulin resistance due to lipodystrophy, in association with relatively increased intraabdominal and intra-myocellular lipid deposition (96). Corticosteroids, particularly at high therapeutic doses, lead to hepatic and peripheral insulin resistance and, in some patients, type 2 diabetes at least partly mediated by increased total and central body fatness (231, 232). Recent evidence indicates that β-blockers reduce diet-induced thermogenesis and contribute to adiposity although there is no information on adipose tissue distribution (233); this is likely to be important in the modest diabetogenic effect of β-blockers. Finally, the antipsychotic class of medications, particularly the second generation agents, has been shown to be associated with

induction of insulin resistance, impairment of insulin secretion and promotion of increased adiposity, all of which contribute to a higher prevalence of type 2 diabetes and Metabolic Syndrome (234-236). This risk augments the already elevated risk of these metabolic disorders in patients with schizophrenia (237).

### H. Bariatric Surgery

As the role of bariatric surgery has very recently been reviewed in this journal (238) we will not deal with this subject in detail but various bariatric procedures generate improvements in insulin sensitivity (and glycemia in diabetic subjects) associated with weight and adipose tissue loss, although there seems to be little information on relative loss of adipose tissue versus lean mass or differential reduction of different adipose depots. It has been suggested that the improvement in insulin sensitivity may be disproportionate to changes in adiposity, at least for some procedures, and that altered secretion of gut hormones could be an important contributor to improved insulin secretion and insulin sensitivity (239).

## V. Other conditions of fat depletion or excess

### A. Lipodystrophies

Human lipodystrophy syndromes are comprised of a heterogeneous group of congenital and acquired disorders characterized by a partial or near complete absence of subcutaneous adipose tissue, but a relative increase in visceral fat. Patients with lipodystrophy have marked insulin resistance, hepatic steatosis and dyslipidemia, suggesting that subcutaneous fat is an important organ for storing lipid “out of harm’s way” (84). They also have reduced leptin and adiponectin levels. One form of lipodystrophy that has become increasingly common is HIV-related lipodystrophy (240, 241); as with other forms of lipodystrophy, there is loss of subcutaneous fat, but relative increase in visceral fat (96). HIV Lipodystrophy is associated with a substantially increased diabetes risk (241) and an increase in cardiovascular events commensurate with the adverse metabolic profile, particularly lipids (242). Fortunately the syndrome, which was associated with earlier antiviral agents, especially protease inhibitors, is

less commonly seen with newer antiviral agents which have been screened for these adverse metabolic effects (242).

### B. Lipomatosis

Multiple Symmetrical Lipomatosis (MSL) is a rare condition associated with adenomatous change in upper body subcutaneous fat and in a way represents the converse of the lipodystrophies. Observations in MSL patients include improved insulin sensitivity (243, 244) accompanied by decreased lipid in leg and liver (243), increased circulating adiponectin, decreased adipocyte size and adipose tissue mRNA expression of pro-inflammatory cytokines (244) compared with matched obese individuals without the condition.

## VI. Mediation of effects on insulin sensitivity

### A. Fat cell size and number

Whilst total adiposity and adipose tissue distribution are important determinants of insulin resistance and type 2 diabetes, the size of adipocytes within adipose tissue depots also plays a contributing role. This is illustrated in Pima Indians, in whom the presence of anatomically larger subcutaneous adipocytes is a better predictor of the onset of type 2 diabetes than the presence of obesity alone (245). Similarly individuals from South East Asia, where there is a high prevalence of type 2 diabetes, have a lower number of adipocytes and increased adipocyte size in addition to an increase in the relative amount of visceral fat. This may account for the increase in metabolic disease in Asians compared with Caucasians at the same level of BMI (246). In adult humans, adipose tissue expansion occurs as a result of adipocyte hypertrophy and the recruitment and proliferation of preadipocytes (adipogenesis) (247). During the development of obesity, the initial enlargement of adipocytes triggers the production of a number of paracrine adipogenic growth factors, resulting in the proliferation of new fat cells – that is an increase in fat cell size precedes an increase in fat cell number (247-249). Therefore, variations in adipocyte size may be related to a genetically (or otherwise) determined ability for adipogenesis - if adipogenesis is impaired during positive

energy balance, then existing adipocytes continue to undergo hypertrophy to store excessive energy. It has recently been shown that a low generation rate of new adipocytes associates with adipose hypertrophy, whereas a high generation rate of new adipocytes associates with the more benign adipose hyperplasia (250).

Increased adipocyte size correlates with serum insulin concentrations, insulin resistance, and increased risk of developing type 2 diabetes (251-256). Furthermore, adipocyte hypertrophy is associated with inflammation with the pro-inflammatory factors IL-6, TNF-$\alpha$ and CRP being positively correlated with adipocyte size (257-259). Conversely, the anti-inflammatory factor adiponectin is inversely correlated with adipocyte size (257). Hypertrophic fat cells display distinct differences in gene expression (260) and are more prone to cell death in response to mechanical stress, with subsequent inflammation, when compared with small adipocytes (261).

In contrast, an increased number of small adipocytes has a beneficial impact on metabolism. PPAR-$\gamma$ agonists are an effective therapy in type 2 diabetes as they promote the recruitment and proliferation of small adipocytes, as well as decreasing the ratio of visceral to subcutaneous adipose tissue (262-264). Severely obese individuals with a healthy metabolic profile have smaller adipocytes than obese individuals with metabolic disease (265).

The correlation between adipocyte size and insulin resistance has led to the adipocyte overflow hypothesis which suggests that an adipocyte undergoes hypertrophy until it is no longer able to store further lipid, causing an ‘overflow’ of fatty acids into ectopic sites such as liver and muscle, resulting in insulin resistance. If this hypothesis was correct then individuals with a reduced capacity to generate new adipocytes would be susceptible to metabolic disease at a lower level of body fat than individuals with better lipid storing potential (266).

**B. Inflammation.** ***Is inflammation the 'missing link'?***

Increased adiposity is associated with accumulation of macrophages in both visceral and subcutaneous fat (56, 267); moreover increased LPS absorption from the gut related to changes in microbiota can activate immune cells (183). Thus in rodents inflammation is clearly important in generating insulin resistance (268, 269). So could the degree of inflammation, rather than the level of tissue lipids be the critical factor in human insulin resistance? Several studies would suggest that this is not the case. Obese insulin-resistant subjects have higher CRP levels than obese insulin- sensitive subjects but the obese sensitive have significantly higher CRP than a non-obese group with similar insulin sensitivity (270). Moreover, insulin resistance may appear in relatives of type 2 diabetes patients without evidence of inflammation (271).

While weight loss in obese and morbidly obese humans by calorie restriction (272-274) and/or exercise (275, 276) or bariatric surgery (277) results in a drastic reduction in circulating pro-inflammatory cytokines and mRNA expression of inflammatory genes in subcutaneous adipose tissue biopsy samples, it remains unclear whether improvement in insulin resistance is a consequence of the reduction in adipose tissue inflammation. Improvement or deterioration in insulin sensitivity in healthy non-obese humans with weight loss (278) or high fat overfeeding and weight gain (279, 280), respectively was not accompanied by changes in subcutaneous mRNA expression of genes associated with inflammation or macrophage count in adipose tissue (278-280) or change in the ratio of pro (M1)- to anti (M2)-inflammatory macrophage phenotype (279), suggesting that adipose tissue inflammation is secondary to obesity and/or insulin resistance in humans. In support of this argument are studies that administered anti-inflammatory agents to obese diabetic and non-diabetic individuals and assessed the effect on insulin sensitivity, secretion and glycemic control (Table 2). Specifically, clinical trials that studied the effect of TNFα inhibition (281-283) found no effect on insulin sensitivity by i.v. insulin tolerance test (281), HOMA-IR (282, 283) or hyperinsulinemic-euglycemic clamp (282) (Table 2). Inconsistent improvements in

insulin sensitivity with TNFα inhibition have been seen in patients with inflammatory arthritidies (284), with a tendency for greater improvement in those with more severe disease; but if there was a benefit it is unclear whether it was a direct effect of TNFα inhibition or an indirect effect of disease improvement. Similarly infusion of TNFα itself in humans does generate a modest impairment of insulin action in muscle along with an elevation of IL-6 and FFA but circulating TNFα levels were above those seen in obesity/diabetes (285).

Inhibition of IL-1 receptor by IL-1r antagonist in obese type 2 diabetic (286) or non-diabetic (287) men and women also did not affect insulin sensitivity (by HOMA-IR, hyperinsulinemic-euglycemic clamp or insulin sensitivity index) (Table 2). Studies of salicylate administration in overweight and obese diabetic (288-290) and non-diabetic (291, 292) patients showed improved glycaemia (288, 291), with a concomitant increase in adiponectin and reduction of circulating FFA (288, 289). It was suggested that insulin sensitivity had been improved, but the elevation of insulin levels (mainly related to reduced clearance) seemed to fully explain the increased glucose disposal during hyperinsulinemia (289, 292) (Table 2). For the higher dose of salicylate, clamp insulin levels were increased by approximately 75% while glucose disposal was increased by 44% (289). Similarly, in non-diabetic obese subjects, it was suggested that insulin sensitivity was improved based on a HOMA IR C-peptide calculation (291). However, if HOMA-IR had been calculated in the usual manner (with insulin levels) there would have been no improvement (290). Likewise, fenofibrate reduced CRP and IL-6 by approximately 50% and 30% respectively without changing insulin sensitivity by hyperinsulinemic-euglycemic clamp in subjects with Metabolic Syndrome (293).

One way in which this apparent conflict between animal and human data could be reconciled is an important influence on insulin signalling by the NFkB pathway (Fig 2). This pathway is present in muscle and liver as well as immune cells and can be activated by saturated fatty acids via TLR4 (294) as well as by inflammatory molecules. Also deletion of TLR2 protects

against hepatic insulin resistance in mice (295). It could be that inflammation is the more important influence on NFkB activity in obese rodents, while fatty acid mediation is more important in obese humans – in both cases the end result being an inhibition of insulin signalling, possibly at the level of IRS-1 (296).

### C. Adipokines

The influence of fat depots on insulin sensitivity has close connections with the levels and activity of adipose tissue derived hormones although the cause and effect relationships and mechanisms involved in humans await further clarification. Both leptin and adiponectin activate AMPK and increase fat oxidation but are otherwise different in their actions (Fig 2).

#### 1. Leptin

Leptin, which is secreted more from subcutaneous than visceral fat (297) reduces appetite and increases metabolic rate (298). One might expect that leptin would have a feedback effect to limit adiposity and insulin resistance but this is not the case as, while leptin levels rise, leptin action is inhibited ("leptin resistance"). The cause of leptin resistance is poorly understood but may involve impairment of receptor signalling and reduced passage across the blood-brain barrier (299). One possibility is that expanded adipose tissue sends a humoral message which inhibits leptin action; this seems unlikely as leptin administration is highly effective in very obese leptin-deficient animals or humans (300, 301). A second possibility is that a leptin-resistance mechanism is integral to the genetic predisposition to obesity; this also seems unlikely to be a common mechanism as diet induced adiposity induces leptin resistance in rodents (302). A third and likely possibility is that chronic elevation of leptin levels induces impaired leptin activity; this would be compatible with much *in vivo* data and it is noteworthy that one of the phosphorylation/activation sites on the leptin receptor induces feedback inhibition of leptin signalling (303) which might provide a credible mechanism.

#### 2. Adiponectin

Adiponectin, especially the high molecular weight (HMW) form, also preferentially secreted by subcutaneous fat (304), is anti-inflammatory and has protective effects in relation to atheromatous cardiovascular disease (102, 298, 305, 306). This hormone also fails to compensate for adiposity as adiponectin levels, including the HMW form, fall with increasing adiposity. The decrease in adiponectin levels is particularly related to increased intraabdominal fat (298); the mechanisms involved are not well understood but may include suppressive effects of inflammatory cytokines, and/or downregulation by hyperinsulinemia or lipid accumulation in adipocytes (298, 307, 308). However the likely importance in regard to insulin sensitivity is attested in adiponectin knock out and transgenic animals, and the already mentioned dependence of the insulin sensitizing effects of thiazolidinediones on increased adiponectin levels (102).

**3. Interleukin-6 (IL-6)**

IL-6 is released from muscle in response to exercise and has an important role in mobilizing myocyte fatty acids and hepatic glucose output to supply energy to muscle (309) but in the non-exercising state adipose tissue is thought to be an important source; levels are modestly elevated in obesity and reduced by exercise training. While it has been suggested that IL-6 may contribute to insulin resistance by increasing fatty acid flux or by contributing to inflammation via CRP release (310), infusion of IL-6 in humans increases rather than decreases insulin mediated glucose disposal (309).Thus IL-6 does not seem to be an important player in human insulin resistance.

**4. Adipocyte Fatty Acid Binding Protein (AFABP, also known as aP2 and FABP4)**

AFABP is produced in adipocytes, and to a lesser extent in macrophages (311) and it's blockade or disruption benefits insulin resistance, dyslipidemia and liver steatosis in obese or fat fed animals (312). In humans it has also been elevated in and predictive of Type 2 Diabetes and the Metabolic Syndrome (313-315) and predictive of liver inflammation and fibrosis in non-alcoholic fatty liver disease (316); moreover AFABP gene variants are

associated with obesity and insulin resistance (317). Thus AFABP, either by enhancing availability of fatty acids to tissues or as part of a macrophage inflammatory response (318) is a potentially important player in regard to insulin resistance and the Metabolic Syndrome (319).

**5. Retinol Binding Protein 4 (RBP4)**

RBP4, secreted from adipose tissue and liver, has been proposed as an important contributor to insulin resistance (320) but a number of subsequent human studies have not supported this (315, 316, 321, 322); also there has been concern about whether different assays give different circulating levels. At this time its role in insulin resistance is also uncertain.

**6. Resistin**

Resistin is a member of a family of closely related peptides. It is secreted preferentially by intraabdominal fat (but also expressed in leukocytes, macrophages, spleen and bone marrow) and has been shown in animals to cause hepatic insulin resistance and to be a potential contributor to cardiovascular disease (323, 324) but it's role in human insulin resistance is unclear at this time (325).

**7. Visfatin**

Visfatin was originally identified from visceral fat and is upregulated in obesity but may be the product of macrophages in adipose tissue; it is also produced by leukocytes, myocytes and hepatocytes. The contribution, if any, of visfatin to human insulin resistance is uncertain (298).

**8. Omentin**

Omentin is another adipokine preferentially secreted by visceral fat (but also expressed in heart, lungs, ovary and placenta) with lower circulating levels in obesity and insulin resistance; as it has insulin sensitizing and anti-inflammatory effects in animals its impaired

secretion is also a potential contributor to insulin resistance but further work is needed to clarify its importance in humans (326).

**D. Fatty acid supply and metabolically active lipid moieties**

Although it has been commonly believed that circulating FFA are elevated in obesity-induced insulin resistance, a recent review (327) has challenged this notion in non-diabetic subjects but has supported the idea of an increased fatty acid diversion to non-adipose tissues in obese insulin-resistant subjects, so the contribution of fatty acids and their metabolically active products may occur mainly at the tissue/cell level. Randle (328) first demonstrated that increased fatty acid supply and oxidation could inhibit glucose oxidation by mechanisms particularly involving pyruvate dehydrogenase. Although this mechanism may contribute to impairment of insulin-mediated glucose disposal it does not account for the well-established inhibition of GLUT4 translocation and glucose transport which characterize insulin resistance in animals and humans (88) (mechanisms by which fatty acids may impair glucose transport are considered below).

In obese type 2 diabetic humans it has been shown that identical (11%) weight loss achieved by a 1674 k/day or a 4185 kj/day diet (over a longer time) resulted in a greater improvement in insulin sensitivity with the more negative energy balance suggesting that negative caloric balance has a benefit independent of adipose tissue mass (329) which could well be related to reduced availability of active lipid moieties such as DAGs, LCACs or ceramides.

It is also relevant that circulating triglycerides with lower carbon number and double bonds are associated with insulin resistance and epidemiologically with increased diabetes risk (330); it is unclear whether this is a causative relationship but it is possible that corresponding triglyceride-derived DAGs or ceramides could have a greater impact on insulin signalling

In animal studies, feeding a high-fat diet to rats increases liver lipid and causes reduced hepatic insulin sensitivity after 3 days. By 3 weeks there is increased lipid in muscle and impaired muscle insulin action (331). This insulin resistance due to high-fat feeding can be reversed in less than 24 hours by fasting, exercise or carbohydrate feeding (332, 333). On the other hand, choline deficiency can greatly increase hepatic lipid without a reduction in glucose tolerance or insulin sensitivity, with data suggesting this is related to shunting of FFA into triglyceride stores (76). Conversely, inhibition of triglyceride accumulation by over 50% in the Ob/Ob mouse due to glycerol-3-phosphate acyltransferase 1 deficiency did not improve insulin sensitivity or fasting glucose levels (334). Similarly in overweight humans, calorie restriction coupled with improvement in insulin sensitivity was not accompanied by reduction in triglycerides in skeletal muscle (92).

All these findings could be explained if the critical factor in creating insulin resistance is an "active" lipid moiety such as DAG, LCAC or ceramide, rather than triglyceride itself. Thus, acute caloric restriction could reduce tissue availability (especially in liver and muscle) of these active metabolites before a significant depletion of triglyceride stores. Conversely, fatty acid flux could be increased without necessarily having increased tissue lipid content. Athletes may be very good at holding their fatty acids in IMTG stores in muscle until commencing exercise. Both ceramide and DAG have been reported to impair insulin action in muscle and liver (78, 335, 336). Data from cross sectional studies of insulin-resistant and insulin-sensitive humans that evaluated skeletal muscle lipid species have been conflicting. Specifically, elevated DAG (93) and ceramide (93, 337, 338) were reported in obese diabetic, obese non-diabetic and insulin-resistant lean individuals compared with insulin-sensitive lean individuals, but this was not confirmed in other studies (339, 340). Interestingly, when obese insulin-sensitive were compared with obese insulin-resistant women, some ceramide, but not DAG, species were significantly elevated in the insulin-resistant group (341), emphasizing the potential importance of ceramide species to the underlying insulin resistance phenotype, irrespective of obesity. Interestingly, a small randomized study of weight loss intervention in

obese men and women found an improvement in insulin sensitivity with either calorie restriction or exercise with a concomitant decrease in all DAG species in muscle, but the change in ceramide species was intervention-dependent, with 6 out of 8 measured species decreasing with exercise and 3 decreasing and *1 increasing* with calorie restriction (342), suggesting that different ceramide species may be involved in the insulin sensitizing effect of calorie restriction and exercise and that specific ceramide species may be beneficial to insulin sensitivity. Further lifestyle intervention studies in humans are warranted.

Unlike skeletal muscle, it may well be that DAG species in liver play a role in hepatic insulin resistance. Two recent studies in severely obese individuals that collected liver samples during bariatric surgeries have reported significant associations between liver DAG and suppression of endogenous glucose production during hyperinsulinemic clamp (343) or the surrogate HOMA-IR (344).

## VII. The connection between insulin resistance, adiposity and the cardiovascular manifestations of the Metabolic Syndrome

The Metabolic Syndrome or Insulin Resistance Syndrome (345) has been variously defined (155, 346, 347) but represents an association between central adiposity (population-specific waist circumference), insulin resistance, dysglycemia, hypertension and dyslipidemia, particularly elevated triglycerides and low HDL cholesterol. It has been used as a concept to advance research and understanding of the relationship of metabolic disturbances with cardiovascular disease (348), but also as a medical diagnosis in individual management.

Much has been written about the usefulness of the Metabolic Syndrome as a diagnosis. It appears to signify a doubling or more of diabetes risk even when blood glucose levels are normal (347, 349) but whether it carries cardiovascular prognostic information of more value than can be derived from its component criteria is controversial (347, 349-351). As this issue has been well reviewed (e.g. (347)) we will not deal with it further here, but will discuss

briefly the mechanisms by which insulin resistance and central adiposity could increase cardiovascular risk.

As indicated earlier insulin resistance is “selective” and does not impair insulin-stimulated hepatic lipogenesis (82). Since insulin resistance is accompanied by hyperinsulinemia (until the development of diabetes) there will be increased insulin-stimulated hepatic lipogenesis resulting in increased intrahepatic triglyceride and increased export as circulating triglycerides with consequent reduction of HDL cholesterol. The increased flux of fatty acids to non-adipose tissue, including liver, associated with central adiposity (327) would be expected to aggravate this problem, especially if this includes a flow of fatty acids through the portal vein to the liver from increased visceral fat.

There is controversy as to the importance of inflammation in the generation of insulin resistance in humans but there is no doubt of the association of obesity with inflammation (269, 352) and inflammation is a well-established marker of, and likely contributor to, cardiovascular disease (353), so this would seem a second candidate pathway to adverse cardiovascular outcomes. In addition the possible role of perivascular fat has already been mentioned.

Obesity also contributes to cardiovascular risk by raising blood pressure by mechanisms that appear to be predominantly related to neurohormonal activation but are incompletely understood (354); the importance of this issue is evidenced by the increased medication required by obese hypertensive subjects and the benefit of weight loss in management of hypertension, at least when the weight loss is substantial (354).

Finally, altered adipokine secretion is another likely contributor to cardiovascular risk (298) as central adiposity and insulin resistance are associated with reduced adiponectin levels and

this adipokine has been shown in humans to correlate inversely with arterial disease (355) and in mouse transgenic studies to have significant anti-atherogenic properties (306).

**VIII. Summary**

In summary the various adipose depots in humans appear to affect insulin action firstly by influencing the tissue supply of fatty acids (Fig 2) and their metabolically active derivatives, DAGs, LCACs and ceramides. In this regard intraabdominal, liver and intramyocellular fat probably play a more important role, while subcutaneous fat could be partially protective by acting as a reservoir to quarantine excess lipid "out of harm's way". Clearly a deficient subcutaneous fat depot, as in lipodystrophies, increases the fatty acid supply to non-adipose tissues and simulates the metabolic profile of severe obesity.

When considering the pathogenic contribution of liver fat to insulin resistance it is important to remember that the lipogenic action of insulin is not impaired in insulin resistance, so the compensatory hyperinsulinemia would overstimulate lipogenesis; thus increased hepatic lipid could be a consequence as well as a cause of insulin resistance.

Visceral fat appears capable of contributing to insulin resistance (3), in part by a poorly understood downregulation of adiponectin secretion, and its surgical removal benefits insulin action in rats (46), but less consistently in humans.

The newly recognized presence of brown fat in humans is interesting and it could clearly contribute to increased metabolic rate, fat oxidation and thereby insulin sensitivity. However it's quantitative importance is likely to be limited in view of the relatively small and inconsistent amounts in humans.

Perivascular and pericardial fat clearly have a relationship, which may or may not be causative, to atheromatous disease but a contribution to insulin resistance is uncertain.

Adipose tissue may also influence insulin sensitivity by its secretions, adipokines from adipocytes themselves or cytokines from adipocytes and infiltrating immune cells whose number increase with adiposity (Fig 2). There is certainly an association between elevated TNFα, CRP and other inflammatory cytokines with insulin resistance and, in rodents, evidence for an important pathogenic contribution. However data from human studies does not support a major role at this stage although an alternative pathway to NFkB stimulation and impaired insulin signalling could be activated by fatty acids through the toll-like receptors. On the other hand, leptin and adiponectin are clearly important players that should act to ameliorate obesity and insulin resistance but fail to do so; adiponectin because it's secretion is paradoxically reduced in obesity and leptin because of the phenomenon of leptin resistance.

Further understanding of the particular contributions and mechanisms of different fat depots to the metabolic derangements of obesity may help develop improved approaches to limit the epidemic of obesity or at least lessen its adverse metabolic consequences.

**Acknowledgements**

We would like to thank Miss Suzanne Emery for administrative assistance with this manuscript.

**Figure Legends**

Fig 1

Abdominal CT scan of an active Sumo wrestler (right) showing a large amount of subcutaneous fat with relatively little visceral fat compared with a person of similar adiposity (left). Kind permission of Prof Y. Matsuzawa and Obesity Research (pending) (356).

Fig 2

A diagrammatic representation of the influence of adipose tissue on insulin responsive tissues in the lean (A) and obese (B) states beyond effects via the Randle cycle. In obesity leptin resistance, reduced adiponectin levels, increased FFA supply and increased cytokines may all contribute to insulin resistance (S or V indicates relatively greater contribution from subcutaneous or visceral fat). FFA supply may impact on insulin signaling via DAGs, ceramide and PKCs via toll like receptors and NFkB.

**Table 1:** Possible mechanism by which intraabdominal fat contributes to insulin resistance

| | **Mechanism** |
|---|---|
| 1. | More labile fatty acid release (lipolysis more sensitive to catecholamines and less sensitive to inhibition by insulin) |
| 2. | Direct flow of fatty acids to the liver via portal vein (only for omental fat) |
| 3. | More accumulation of inflammatory cells |
| 4. | Strong relationship to reduced circulating adiponectin levels |
| 5. | Less responsiveness to PPAR-γ agonism |
| 6. | Correlated with, and possible mediator of, inflammation in liver and kidney |

1249

**Table 2:** The effect of anti-inflammatory agents on glucose homeostasis in patients with the Metabolic Syndrome

| | | | | **Effect of the treatment** | | | |
|---|---|---|---|---|---|---|---|
| *Agent* | *Treatment duration* | *Study design* | *Cohort* | *Glycemic control* | *Fasting glucose* | *Insulin secretion / β-cell function* | *Insulin sensitivity* |
| Anti-TNFα antibody (CDP571). Single dose of 5 mg/kg body weight at baseline (281) | 6-weeks | Randomized double-blind placebo-controlled | Type 2 diabetes overweight-obese men and women *n* = 21 | Not evaluated | No change | No change by fasting insulin and C-peptide concentrations | No change by insulin tolerance test |
| TNFα antagonist etanercept 50 mg twice weekly (283) | 6-months | Randomized double-blind placebo-controlled | Non-diabetic obese men and women *n* = 40 | Not evaluated | Decreased | Not evaluated | No change by HOMA-IR |
| TNFα antagonist etanercept 25 mg twice weekly (282) | 4-weeks | Randomized open-label | Type 2 diabetes obese men and women *n* = 20 | No change in HbA1c | No change | Tendency to increase by IVGTT insulin (*P*=0.07) | No change by hyperinsulinemic-euglycemic clamp and HOMA-IR |
| IL-1-receptor antagonist anakinra 100 mg once daily (286) | 13-weeks | Randomized double-blind placebo-controlled | Type 2 diabetes overweight-obese men and women *n* = 70 | HbA1c decreased | Decreased (both fasting and 2-h OGTT) | Increased C-peptide AUC (OGTT and IVGTT) | No change by hyperinsulinemic-euglycemic clamp |
| IL-1-receptor antagonist anakinra 150 mg once daily (287) | 4-weeks | Randomized double blind crossover | Non diabetic obese men and women *n* = 13 | No change in HbA1c | No change | ° Increased by the disposition index (change in insulin divided by change | No change by hyperinsulinemic-euglycemic clamp |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | in glucose during the first 30 min of OGTT)<br>° No change by C-peptide AUC during OGTT | |
| Salicylate 4 g daily (291) | 4-weeks | Randomized double-blind placebo-controlled | Non-diabetic obese men and women *n* = 20 | Glycated albumin decreased | Decreased (both fasting and AUC of OGTT) | Decreased by fasting and AUC of OGTT C-peptide | ° No change by HOMA-IR<br>° Improved by HOMA-IR$_{C\text{-peptide}}$ |
| Salicylate 3 or 4.5 g daily (289) | 2 weeks | Open label | Glucose intolerant and type 2 diabetes obese men and women (n = 9 3 g/d; n = 9 4.5 g/d) | Glycated albumin decreased (4.5 g/d only) | Decreased by both salicylate doses | Insulin and C-peptide concentrations increased in the first phase (10 min) IVGTT with 4.5 g/d treatment. Insulin, but not C-peptide remained increased in the 2$^{nd}$ phase (10-180 min IVGTT) due to reduced insulin clearance (4.5 g/d) | Increased glucose disposal (*Rd*) accompanied by decreased insulin clearance with treatment. |
| Salicylate 3, 3.5 or 4 g daily (288) | 13-weeks | Randomized double-blind placebo-controlled | Type 2 diabetes obese men and women *n* = 128 | HbA1c and glycated albumin decreased by all salicylate doses | Decreased by all salicylate doses | Not evaluated | Not evaluated |
| Salicylate 3 g daily (292) | 7-days | Randomized double-blind placebo-controlled | Non-diabetic obese men and women *n* = 40 | | Decreased (both fasting and OGTT AUC) | | Increased glucose disposal (*Rd*) accompanied by decreased insulin |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | clearance with treatment. The effect on insulin sensitivity was abolished after normalizing to steady state insulin concentration post treatment. |
| Salicylate 3 g daily (290) | 12-weeks | Randomized double-blind placebo-controlled | Type 2 diabetes overweight-obese men and women *n* = 60 | No change in HbA1c | Fasting glucose decreased, 2-h OGTT not changed | Not evaluated | No change by HOMA-IR, non-significant increase in fasting insulin concentrations |

**References**


1. **Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G** 1985 Relationship between degree of obesity and in vivo insulin action in man. Am J Physiol 248:E286-291
2. **Gan SK, Kriketos AD, Poynten AM, Furler SM, Thompson CH, Kraegen EW, Campbell LV, Chisholm DJ** 2003 Insulin action, regional fat, and myocyte lipid: altered relationships with increased adiposity. Obes Res 11:1295-1305
3. **Montague CT, O'Rahilly S** 2000 The perils of portliness: causes and consequences of visceral adiposity. Diabetes 49:883-888
4. **Vague J** 1947 La differenciation sexuelle, facteur determinant des formes de l'obesite. Presse Med 55:339-340
5. **Gesta S, Bluher M, Yamamoto Y, Norris AW, Berndt J, Kralisch S, Boucher J, Lewis C, Kahn CR** 2006 Evidence for a role of developmental genes in the origin of obesity and body fat distribution. Proc Natl Acad Sci U S A 103:6676-6681
6. **Hocking SL, Wu LE, Guilhaus M, Chisholm DJ, James DE** 2010 Intrinsic depot-specific differences in the secretome of adipose tissue, preadipocytes, and adipose tissue-derived microvascular endothelial cells. Diabetes 59:3008-3016
7. **Adams M, Montague CT, Prins JB, Holder JC, Smith SA, Sanders L, Digby JE, Sewter CP, Lazar MA, Chatterjee VK, O'Rahilly S** 1997 Activators of peroxisome proliferator-activated receptor gamma have depot-specific effects on human preadipocyte differentiation. J Clin Invest 100:3149-3153
8. **Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K** 2006 Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 116:1784-1792
9. **Hotamisligil GS** 1999 The role of TNFalpha and TNF receptors in obesity and insulin resistance. J Intern Med 245:621-625
10. **Cooper MS, Stewart PM** 2009 11Beta-hydroxysteroid dehydrogenase type 1 and its role in the hypothalamus-pituitary-adrenal axis, metabolic syndrome, and inflammation. J Clin Endocrinol Metab 94:4645-4654
11. **Ashwell M, Cole TJ, Dixon AK** 1985 Obesity: new insight into the anthropometric classification of fat distribution shown by computed tomography. Br Med J (Clin Res Ed) 290:1692-1694
12. **Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ** 1994 Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. The American journal of cardiology 73:460-468
13. **Onat A, Avci GS, Barlan MM, Uyarel H, Uzunlar B, Sansoy V** 2004 Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 28:1018-1025
14. **Bengtsson C, Bjorkelund C, Lapidus L, Lissner L** 1993 Associations of serum lipid concentrations and obesity with mortality in women: 20 year follow up of participants in prospective population study in Gothenburg, Sweden. Bmj 307:1385-1388
15. **Lyssenko V, Jorgensen T, Gerwien RW, Hansen T, Rowe MW, McKenna MP, Kolberg J, Pedersen O, Borch-Johnsen K, Groop L** 2012 Validation of a multi-marker model for the prediction of incident type 2 diabetes mellitus: combined results of the Inter99 and Botnia studies. Diab Vasc Dis Res 9:59-67
16. **Kahn HS, Cheng YJ, Thompson TJ, Imperatore G, Gregg EW** 2009 Two Risk-Scoring Systems for Predicting Incident Diabetes Mellitus in U.S. Adults Age 45 to 64 Years. Annals of Internal Medicine 150:741-751

17. **Lee CM, Huxley RR, Wildman RP, Woodward M** 2008 Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. Journal of clinical epidemiology 61:646-653
18. **Ashwell M, Gunn P, Gibson S** 2012 Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity 13:275-286
19. **Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gomez J, Lilienthal Heitmann B, Kent-Smith L, Melchior JC, Pirlich M, Scharfetter H, A MWJS, Pichard C** 2004 Bioelectrical impedance analysis-part II: utilization in clinical practice. Clinical nutrition 23:1430-1453
20. **Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ** 1996 Abdominal fat and insulin resistance in normal and overweight women: Direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. Diabetes 45:633-638
21. **Bertin E, Marcus C, Ruiz JC, Eschard JP, Leutenegger M** 2000 Measurement of visceral adipose tissue by DXA combined with anthropometry in obese humans. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 24:263-270
22. **Paradisi G, Smith L, Burtner C, Leaming R, Garvey WT, Hook G, Johnson A, Cronin J, Steinberg HO, Baron AD** 1999 Dual energy X-ray absorptiometry assessment of fat mass distribution and its association with the insulin resistance syndrome. Diabetes Care 22:1310-1317
23. **Seidell JC, Bakker CJ, van der Kooy K** 1990 Imaging techniques for measuring adipose-tissue distribution--a comparison between computed tomography and 1.5-T magnetic resonance. Am J Clin Nutr 51:953-957
24. **Smith SR, Lovejoy JC, Greenway F, Ryan D, deJonge L, de la Bretonne J, Volafova J, Bray GA** 2001 Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. Metabolism 50:425-435
25. **Greenfield JR, Samaras K, Chisholm DJ, Campbell LV** 2002 Regional intra-subject variability in abdominal adiposity limits usefulness of computed tomography. Obes Res 10:260-265
26. **Abate N, Burns D, Peshock RM, Garg A, Grundy SM** 1994 Estimation of adipose tissue mass by magnetic resonance imaging: validation against dissection in human cadavers. Journal of lipid research 35:1490-1496
27. **Szczepaniak LS, Babcock EE, Schick F, Dobbins RL, Garg A, Burns DK, McGarry JD, Stein DT** 1999 Measurement of intracellular triglyceride stores by H spectroscopy: validation in vivo. Am J Physiol 276:E977-989
28. **Szczepaniak LS, Dobbins RL, Metzger GJ, Sartoni-D'Ambrosia G, Arbique D, Vongpatanasin W, Unger R, Victor RG** 2003 Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 49:417-423
29. **Lingvay I, Esser V, Legendre JL, Price AL, Wertz KM, Adams-Huet B, Zhang S, Unger RH, Szczepaniak LS** 2009 Noninvasive quantification of pancreatic fat in humans. J Clin Endocrinol Metab 94:4070-4076
30. **Park SH, Kim PN, Kim KW, Lee SW, Yoon SE, Park SW, Ha HK, Lee MG, Hwang S, Lee SG, Yu ES, Cho EY** 2006 Macrovesicular hepatic steatosis in living liver donors: use of CT for quantitative and qualitative assessment. Radiology 239:105-112
31. **Gorter PM, van Lindert AS, de Vos AM, Meijs MF, van der Graaf Y, Doevendans PA, Prokop M, Visseren FL** 2008 Quantification of epicardial and peri-coronary fat using cardiac computed tomography; reproducibility and relation

with obesity and metabolic syndrome in patients suspected of coronary artery disease. Atherosclerosis 197:896-903

32. **van der Meer RW, Lamb HJ, Smit JWA, de Roos A** 2012 MR Imaging Evaluation of Cardiovascular Risk in Metabolic Syndrome. Radiology 264:21-37
33. **Iacobellis G, Willens HJ** 2009 Echocardiographic epicardial fat: a review of research and clinical applications. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 22:1311-1319; quiz 1417-1318
34. **Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR** 2009 Identification and importance of brown adipose tissue in adult humans. The New England journal of medicine 360:1509-1517
35. **Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, Nuutila P** 2009 Functional brown adipose tissue in healthy adults. The New England journal of medicine 360:1518-1525
36. **Kotronen A, Yki-Jarvinen H, Sevastianova K, Bergholm R, Hakkarainen A, Pietilainen KH, Juurinen L, Lundbom N, Sorensen TI** 2011 Comparison of the relative contributions of intra-abdominal and liver fat to components of the metabolic syndrome. Obesity (Silver Spring) 19:23-28
37. **Indulekha K, Anjana RM, Surendar J, Mohan V** 2011 Association of visceral and subcutaneous fat with glucose intolerance, insulin resistance, adipocytokines and inflammatory markers in Asian Indians (CURES-113). Clin Biochem 44:281-287
38. **Gastaldelli A, Miyazaki Y, Pettiti M, Matsuda M, Mahankali S, Santini E, DeFronzo RA, Ferrannini E** 2002 Metabolic effects of visceral fat accumulation in type 2 diabetes. J Clin Endocrinol Metab 87:5098-5103
39. **Ohlson LO, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, Bjorntorp P, Tibblin G** 1985 The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 34:1055-1058
40. **Dalton M, Cameron AJ, Zimmet PZ, Shaw JE, Jolley D, Dunstan DW, Welborn TA** 2003 Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. J Intern Med 254:555-563
41. **Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP** 1993 Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. Am J Clin Nutr 58:463-467
42. **Donahue RP, Prineas RJ, DeCarlo Donahue R, Bean JA, Skyler JS** 1996 The female 'insulin advantage' in a biracial cohort: results from the Miami Community Health Study. Int J Obes Relat Metab Disord 20:76-82
43. **Nuutila P, Knuuti MJ, Maki M, Laine H, Ruotsalainen U, Teras M, Haaparanta M, Solin O, Yki-Jarvinen H** 1995 Gender and insulin sensitivity in the heart and in skeletal muscles. Studies using positron emission tomography. Diabetes 44:31-36
44. **Sumner AE, Kushner H, Sherif KD, Tulenko TN, Falkner B, Marsh JB** 1999 Sex differences in African-Americans regarding sensitivity to insulin's glucoregulatory and antilipolytic actions. Diabetes Care 22:71-77
45. **Hoeg L, Roepstorff C, Thiele M, Richter EA, Wojtaszewski JF, Kiens B** 2009 Higher intramuscular triacylglycerol in women does not impair insulin sensitivity and proximal insulin signaling. J Appl Physiol 107:824-831
46. **Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, Scherer P, Rossetti L, Barzilai N** 2002 Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? Diabetes 51:2951-2958
47. **Csendes A, Maluenda F, Burgos AM** 2009 A prospective randomized study comparing patients with morbid obesity submitted to laparotomic gastric bypass with or without omentectomy. Obesity surgery 19:490-494

48. **Fabbrini E, Tamboli RA, Magkos F, Marks-Shulman PA, Eckhauser AW, Richards WO, Klein S, Abumrad NN** 2010 Surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults. Gastroenterology 139:448-455
49. **Herrera MF, Pantoja JP, Velazquez-Fernandez D, Cabiedes J, Aguilar-Salinas C, Garcia-Garcia E, Rivas A, Villeda C, Hernandez-Ramirez DF, Davila A, Zarain A** 2010 Potential additional effect of omentectomy on metabolic syndrome, acute-phase reactants, and inflammatory mediators in grade III obese patients undergoing laparoscopic Roux-en-Y gastric bypass: a randomized trial. Diabetes Care 33:1413-1418
50. **Klein S** 2010 Is visceral fat responsible for the metabolic abnormalities associated with obesity?: implications of omentectomy. Diabetes Care 33:1693-1694
51. **Samocha-Bonet D, Chisholm DJ, Tonks K, Campbell LV, Greenfield JR** 2012 Insulin-sensitive obesity in humans a favorable fat phenotype? Trends Endocrinol Metab 23:116-124
52. **Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM** 1995 Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest 96:88-98
53. **Chan DC, Watts GF, Sussekov AV, Barrett PH, Yang Z, Hua J, Song S** 2004 Adipose tissue compartments and insulin resistance in overweight-obese Caucasian men. Diabetes Res Clin Pract 63:77-85
54. **Rytka JM, Wueest S, Schoenle EJ, Konrad D** 2011 The portal theory supported by venous drainage-selective fat transplantation. Diabetes 60:56-63
55. **Curat CA, Wegner V, Sengenes C, Miranville A, Tonus C, Busse R, Bouloumie A** 2006 Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia 49:744-747
56. **Harman-Boehm I, Bluher M, Redel H, Sion-Vardy N, Ovadia S, Avinoach E, Shai I, Kloting N, Stumvoll M, Bashan N, Rudich A** 2007 Macrophage infiltration into omental versus subcutaneous fat across different populations: effect of regional adiposity and the comorbidities of obesity. The Journal of clinical endocrinology and metabolism 92:2240-2247
57. **Gauthier MS, O'Brien EL, Bigornia S, Mott M, Cacicedo JM, Xu XJ, Gokce N, Apovian C, Ruderman N** 2011 Decreased AMP-activated protein kinase activity is associated with increased inflammation in visceral adipose tissue and with whole-body insulin resistance in morbidly obese humans. Biochem Biophys Res Commun 404:382-387
58. **Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD** 2004 Splanchnic lipolysis in human obesity. J Clin Invest 113:1582-1588
59. **van der Poorten D, Milner KL, Hui J, Hodge A, Trenell MI, Kench JG, London R, Peduto T, Chisholm DJ, George J** 2008 Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology 48:449-457
60. **Foster MC, Hwang SJ, Massaro JM, Hoffmann U, DeBoer IH, Robins SJ, Vasan RS, Fox CS** 2011 Association of subcutaneous and visceral adiposity with albuminuria: the Framingham Heart Study. Obesity (Silver Spring) 19:1284-1289
61. **Yatagai T, Nagasaka S, Taniguchi A, Fukushima M, Nakamura T, Kuroe A, Nakai Y, Ishibashi S** 2003 Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in Japanese men with type 2 diabetes mellitus. Metabolism 52:1274-1278
62. **Rosen ED, Spiegelman BM** 2006 Adipocytes as regulators of energy balance and glucose homeostasis. Nature 444:847-853
63. **Hocking SL, Chisholm DJ, James DE** 2008 Studies of regional adipose transplantation reveal a unique and beneficial interaction between subcutaneous adipose tissue and the intra-abdominal compartment. Diabetologia 51:900-902
64. **Tran TT, Yamamoto Y, Gesta S, Kahn CR** 2008 Beneficial effects of subcutaneous fat transplantation on metabolism. Cell Metab 7:410-420

65. **Markovic TP, Jenkins AB, Campbell LV, Furler SM, Kraegen EW, Chisholm DJ** 1998 The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM. Diabetes Care 21:687-694
66. **Goldrick RB, McLoughlin GM** 1970 Lipolysis and lipogenesis from glucose in human fat cells of different sizes. Effects of insulin, epinephrine, and theophylline. J Clin Invest 49:1213-1223
67. **Kelley DE, Thaete FL, Troost F, Huwe T, Goodpaster BH** 2000 Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance. Am J Physiol Endocrinol Metab 278:E941-948
68. **Poynten AM, Gan SK, Kriketos AD, Campbell LV, Chisholm DJ** 2005 Circulating fatty acids, non-high density lipoprotein cholesterol, and insulin-infused fat oxidation acutely influence whole body insulin sensitivity in nondiabetic men. J Clin Endocrinol Metab 90:1035-1040
69. **McQuaid SE, Hodson L, Neville MJ, Dennis AL, Cheeseman J, Humphreys SM, Ruge T, Gilbert M, Fielding BA, Frayn KN, Karpe F** 2011 Downregulation of adipose tissue fatty acid trafficking in obesity: a driver for ectopic fat deposition? Diabetes 60:47-55
70. **Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, Okunade A, Klein S** 2009 Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proc Natl Acad Sci U S A 106:15430-15435
71. **Kotronen A, Juurinen L, Tiikkainen M, Vehkavaara S, Yki-Jarvinen H** 2008 Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes. Gastroenterology 135:122-130
72. **Liska D, Dufour S, Zern TL, Taksali S, Cali AM, Dziura J, Shulman GI, Pierpont BM, Caprio S** 2007 Interethnic differences in muscle, liver and abdominal fat partitioning in obese adolescents. PLoS One 2:e569
73. **Peter A, Kantartzis K, Machann J, Schick F, Staiger H, Machicao F, Schleicher E, Fritsche A, Haring HU, Stefan N** 2010 Relationships of circulating sex hormone-binding globulin with metabolic traits in humans. Diabetes 59:3167-3173
74. **Nielsen SU, Bassendine MF, Burt AD, Martin C, Pumeechockchai W, Toms GL** 2006 Association between hepatitis C virus and very-low-density lipoprotein (VLDL)/LDL analyzed in iodixanol density gradients. J Virol 80:2418-2428
75. **Milner KL, van der Poorten D, Trenell M, Jenkins AB, Xu A, Smythe G, Dore GJ, Zekry A, Weltman M, Fragomeli V, George J, Chisholm DJ** 2010 Chronic hepatitis C is associated with peripheral rather than hepatic insulin resistance. Gastroenterology 138:932-941 e931-933
76. **Raubenheimer PJ, Nyirenda MJ, Walker BR** 2006 A choline-deficient diet exacerbates fatty liver but attenuates insulin resistance and glucose intolerance in mice fed a high-fat diet. Diabetes 55:2015-2020
77. **Samuel VT, Petersen KF, Shulman GI** 2010 Lipid-induced insulin resistance: unravelling the mechanism. Lancet 375:2267-2277
78. **Jornayvaz FR, Shulman GI** 2012 Diacylglycerol activation of protein kinase cepsilon and hepatic insulin resistance. Cell metabolism 15:574-584
79. **Kirk E, Reeds DN, Finck BN, Mayurranjan SM, Patterson BW, Klein S** 2009 Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. Gastroenterology 136:1552-1560
80. **van der Meer RW, Hammer S, Lamb HJ, Frolich M, Diamant M, Rijzewijk LJ, de Roos A, Romijn JA, Smit JW** 2008 Effects of short-term high-fat, high-energy diet on hepatic and myocardial triglyceride content in healthy men. J Clin Endocrinol Metab 93:2702-2708
81. **Samocha-Bonet D, Campbell LV, Viardot A, Freund J, Tam CS, Greenfield JR, Heilbronn LK** 2010 A family history of type 2 diabetes increases risk factors associated with overfeeding. Diabetologia 53:1700-1708
82. **Brown MS, Goldstein JL** 2008 Selective versus total insulin resistance: a pathogenic paradox. Cell Metab 7:95-96

83. **Semple RK, Sleigh A, Murgatroyd PR, Adams CA, Bluck L, Jackson S, Vottero A, Kanabar D, Charlton-Menys V, Durrington P, Soos MA, Carpenter TA, Lomas DJ, Cochran EK, Gorden P, O'Rahilly S, Savage DB** 2009 Postreceptor insulin resistance contributes to human dyslipidemia and hepatic steatosis. J Clin Invest 119:315-322
84. **Huang-Doran I, Sleigh A, Rochford JJ, O'Rahilly S, Savage DB** 2010 Lipodystrophy: metabolic insights from a rare disorder. J Endocrinol 207:245-255
85. **Pan DA, Lillioja S, Kriketos AD, Milner MR, Baur LA, Bogardus C, Jenkins AB, Storlien LH** 1997 Skeletal muscle triglyceride levels are inversely related to insulin action. Diabetes 46:983-988
86. **Krssak M, Falk Petersen K, Dresner A, DiPietro L, Vogel SM, Rothman DL, Roden M, Shulman GI** 1999 Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. Diabetologia 42:113-116
87. **Perseghin G, Scifo P, De Cobelli F, Pagliato E, Battezzati A, Arcelloni C, Vanzulli A, Testolin G, Pozza G, Del Maschio A, Luzi L** 1999 Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a 1H-13C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. Diabetes 48:1600-1606
88. **Savage DB, Petersen KF, Shulman GI** 2007 Disordered lipid metabolism and the pathogenesis of insulin resistance. Physiol Rev 87:507-520
89. **Kriketos AD, Furler SM, Gan SK, Poynten AM, Chisholm DJ, Campbell LV** 2003 Multiple indexes of lipid availability are independently related to whole body insulin action in healthy humans. J Clin Endocrinol Metab 88:793-798
90. **Goodpaster BH, He J, Watkins S, Kelley DE** 2001 Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab 86:5755-5761
91. **Gan SK, Kriketos AD, Ellis BA, Thompson CH, Kraegen EW, Chisholm DJ** 2003 Changes in aerobic capacity and visceral fat but not myocyte lipid levels predict increased insulin action after exercise in overweight and obese men. Diabetes Care 26:1706-1713
92. **Larson-Meyer DE, Heilbronn LK, Redman LM, Newcomer BR, Frisard MI, Anton S, Smith SR, Alfonso A, Ravussin E** 2006 Effect of calorie restriction with or without exercise on insulin sensitivity, beta-cell function, fat cell size, and ectopic lipid in overweight subjects. Diabetes Care 29:1337-1344
93. **Moro C, Galgani JE, Luu L, Pasarica M, Mairal A, Bajpeyi S, Schmitz G, Langin D, Liebisch G, Smith SR** 2009 Influence of gender, obesity, and muscle lipase activity on intramyocellular lipids in sedentary individuals. J Clin Endocrinol Metab 94:3440-3447
94. **Amati F, Dube JJ, Alvarez-Carnero E, Edreira MM, Chomentowski P, Coen PM, Switzer GE, Bickel PE, Stefanovic-Racic M, Toledo FG, Goodpaster BH** 2011 Skeletal muscle triglycerides, diacylglycerols, and ceramides in insulin resistance: another paradox in endurance-trained athletes? Diabetes 60:2588-2597
95. **Yim JE, Heshka S, Albu J, Heymsfield S, Kuznia P, Harris T, Gallagher D** 2007 Intermuscular adipose tissue rivals visceral adipose tissue in independent associations with cardiovascular risk. Int J Obes (Lond) 31:1400-1405
96. **Gan SK, Samaras K, Thompson CH, Kraegen EW, Carr A, Cooper DA, Chisholm DJ** 2002 Altered myocellular and abdominal fat partitioning predict disturbance in insulin action in HIV protease inhibitor-related lipodystrophy. Diabetes 51:3163-3169
97. **Bergman BC, Cornier MA, Horton TJ, Bessesen DH** 2007 Effects of fasting on insulin action and glucose kinetics in lean and obese men and women. Am J Physiol Endocrinol Metab 293:E1103-1111
98. **Hoeks J, van Herpen NA, Mensink M, Moonen-Kornips E, van Beurden D, Hesselink MK, Schrauwen P** 2010 Prolonged fasting identifies skeletal muscle

mitochondrial dysfunction as consequence rather than cause of human insulin resistance. Diabetes 59:2117-2125

99. **Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, Mohammed BS** 2004 Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. The New England journal of medicine 350:2549-2557
100. **Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, Mandarino LJ, DeFronzo RA** 2002 Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 87:2784-2791
101. **Carey DG, Cowin GJ, Galloway GJ, Jones NP, Richards JC, Biswas N, Doddrell DM** 2002 Effect of rosiglitazone on insulin sensitivity and body composition in type 2 diabetic patients [corrected]. Obes Res 10:1008-1015
102. **Kadowaki T, Yamauchi T** 2005 Adiponectin and adiponectin receptors. Endocr Rev 26:439-451
103. **Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE** 1997 Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes 46:1579-1585
104. **Manolopoulos KN, Karpe F, Frayn KN** 2010 Gluteofemoral body fat as a determinant of metabolic health. Int J Obes (Lond) 34:949-959
105. **Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, Cline GW, DePaoli AM, Taylor SI, Gorden P, Shulman GI** 2002 Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest 109:1345-1350
106. **Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gorden P, Garg A** 2002 Leptin-replacement therapy for lipodystrophy. The New England journal of medicine 346:570-578
107. **Simha V, Szczepaniak LS, Wagner AJ, DePaoli AM, Garg A** 2003 Effect of leptin replacement on intrahepatic and intramyocellular lipid content in patients with generalized lipodystrophy. Diabetes Care 26:30-35
108. **Chong AY, Lupsa BC, Cochran EK, Gorden P** 2010 Efficacy of leptin therapy in the different forms of human lipodystrophy. Diabetologia 53:27-35
109. **Barroso I, Gurnell M, Crowley VEF, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TDM, Lewis H, Schafer AJ, Chatterjee VKK, O'Rahilly S** 1999 Dominant negative mutations in human PPAR[gamma] associated with severe insulin resistance, diabetes mellitus and hypertension. Nature 402:880-883
110. **Savage DB, Tan GD, Acerini CL, Jebb SA, Agostini M, Gurnell M, Williams RL, Umpleby AM, Thomas EL, Bell JD, Dixon AK, Dunne F, Boiani R, Cinti S, Vidal-Puig A, Karpe F, Chatterjee VKV, O'Rahilly S** 2003 Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor-Œ≥. Diabetes 52:910-917
111. **Agostini M, Schoenmakers E, Mitchell C, Szatmari I, Savage D, Smith A, Rajanayagam O, Semple R, Luan Ja, Bath L, Zalin A, Labib M, Kumar S, Simpson H, Blom D, Marais D, Schwabe J, Barroso I, Trembath R, Wareham N, Nagy L, Gurnell M, O'Rahilly S, Chatterjee K** 2006 Non-DNA binding, dominant-negative, human PPAR[gamma] mutations cause lipodystrophic insulin resistance. Cell Metabolism 4:303-311
112. **Kim JK, Gavrilova O, Chen Y, Reitman ML, Shulman GI** 2000 Mechanism of insulin resistance in A-ZIP/F-1 fatless mice. J Biol Chem 275:8456-8460
113. **Virtue S, Vidal-Puig A** 2008 It's not how fat you are, it's what you do with it that counts. PLoS Biol 6:e237
114. **Nyamdorj R, Pitkaniemi J, Tuomilehto J, Hammar N, Stehouwer CD, Lam TH, Ramachandran A, Janus ED, Mohan V, Soderberg S, Laatikainen T, Gabriel R, Qiao Q** 2010 Ethnic comparison of the association of undiagnosed diabetes with obesity. Int J Obes (Lond) 34:332-339

115. **Piers LS, Rowley KG, Soares MJ, O'Dea K** 2003 Relation of adiposity and body fat distribution to body mass index in Australians of Aboriginal and European ancestry. Eur J Clin Nutr 57:956-963
116. **Kondalsamy-Chennakesavan S, Hoy WE, Wang Z, Briganti E, Polkinghorne K, Chadban S, Shaw J** 2008 Anthropometric measurements of Australian Aboriginal adults living in remote areas: comparison with nationally representative findings. Am J Hum Biol 20:317-324
117. **Kondalsamy-Chennakesavan S, Hoy WE, Wang Z, Shaw J** 2008 Quantifying the excess risk of type 2 diabetes by body habitus measurements among Australian aborigines living in remote areas. Diabetes Care 31:585-586
118. **Sandeep S, Gokulakrishnan K, Velmurugan K, Deepa M, Mohan V** 2010 Visceral & subcutaneous abdominal fat in relation to insulin resistance & metabolic syndrome in non-diabetic south Indians. Indian J Med Res 131:629-635
119. **Raji A, Seely EW, Arky RA, Simonson DC** 2001 Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. J Clin Endocrinol Metab 86:5366-5371
120. **Verhagen SN, Visseren FL** 2011 Perivascular adipose tissue as a cause of atherosclerosis. Atherosclerosis 214:3-10
121. **Lehman SJ, Massaro JM, Schlett CL, O'Donnell CJ, Hoffmann U, Fox CS** 2010 Peri-aortic fat, cardiovascular disease risk factors, and aortic calcification: the Framingham Heart Study. Atherosclerosis 210:656-661
122. **Eringa EC, Bakker W, Smulders YM, Serne EH, Yudkin JS, Stehouwer CD** 2007 Regulation of vascular function and insulin sensitivity by adipose tissue: focus on perivascular adipose tissue. Microcirculation 14:389-402
123. **van der Zijl NJ, Goossens GH, Moors CC, van Raalte DH, Muskiet MH, Pouwels PJ, Blaak EE, Diamant M** 2011 Ectopic fat storage in the pancreas, liver, and abdominal fat depots: impact on beta-cell function in individuals with impaired glucose metabolism. J Clin Endocrinol Metab 96:459-467
124. **Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R** 2011 Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 54:2506-2514
125. **van Geenen EJM, Smits MM, Schreuder TCMA, van der Peet DL, Bloemena E, Mulder CJJ** 2010 Nonalcoholic Fatty Liver Disease Is Related to Nonalcoholic Fatty Pancreas Disease. Pancreas 39:1185-1190
126. **Cannon B, Nedergaard J** 2004 Brown adipose tissue: function and physiological significance. Physiol Rev 84:277-359
127. **Kim H, Pennisi PA, Gavrilova O, Pack S, Jou W, Setser-Portas J, East-Palmer J, Tang Y, Manganiello VC, Leroith D** 2006 Effect of adipocyte beta3-adrenergic receptor activation on the type 2 diabetic MKR mice. Am J Physiol Endocrinol Metab 290:E1227-1236
128. **van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ** 2009 Cold-activated brown adipose tissue in healthy men. The New England journal of medicine 360:1500-1508
129. **Nedergaard J, Bengtsson T, Cannon B** 2007 Unexpected evidence for active brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab 293:E444-452
130. **Saito M, Okamatsu-Ogura Y, Matsushita M, Watanabe K, Yoneshiro T, Nio-Kobayashi J, Iwanaga T, Miyagawa M, Kameya T, Nakada K, Kawai Y, Tsujisaki M** 2009 High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. Diabetes 58:1526-1531
131. **Zingaretti MC, Crosta F, Vitali A, Guerrieri M, Frontini A, Cannon B, Nedergaard J, Cinti S** 2009 The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue. FASEB J 23:3113-3120

132. **Lee P, Zhao JT, Swarbrick MM, Gracie G, Bova R, Greenfield JR, Freund J, Ho KK** 2011 High prevalence of brown adipose tissue in adult humans. J Clin Endocrinol Metab 96:2450-2455
133. **Lee P, Greenfield JR, Ho KK, Fulham MJ** 2010 A critical appraisal of the prevalence and metabolic significance of brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab 299:E601-606
134. **Ouellet V, Labbe SM, Blondin DP, Phoenix S, Guerin B, Haman F, Turcotte EE, Richard D, Carpentier AC** 2012 Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. J Clin Invest 122:545-552
135. **Enerback S** 2009 The origins of brown adipose tissue. The New England journal of medicine 360:2021-2023
136. **Ishibashi J, Seale P** 2010 Medicine. Beige can be slimming. Science 328:1113-1114
137. **Petrovic N, Walden TB, Shabalina IG, Timmons JA, Cannon B, Nedergaard J** 2010 Chronic peroxisome proliferator-activated receptor gamma (PPARgamma) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocytes. J Biol Chem 285:7153-7164
138. **Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, Scime A, Devarakonda S, Conroe HM, Erdjument-Bromage H, Tempst P, Rudnicki MA, Beier DR, Spiegelman BM** 2008 PRDM16 controls a brown fat/skeletal muscle switch. Nature 454:961-967
139. **Laharrague P, Casteilla L** 2010 The emergence of adipocytes. Endocr Dev 19:21-30
140. **Cousin B, Cinti S, Morroni M, Raimbault S, Ricquier D, Penicaud L, Casteilla L** 1992 Occurrence of brown adipocytes in rat white adipose tissue: molecular and morphological characterization. J Cell Sci 103 ( Pt 4):931-942
141. **Ghorbani M, Himms-Hagen J** 1997 Appearance of brown adipocytes in white adipose tissue during CL 316,243-induced reversal of obesity and diabetes in Zucker fa/fa rats. Int J Obes Relat Metab Disord 21:465-475
142. **Himms-Hagen J, Melnyk A, Zingaretti MC, Ceresi E, Barbatelli G, Cinti S** 2000 Multilocular fat cells in WAT of CL-316243-treated rats derive directly from white adipocytes. Am J Physiol Cell Physiol 279:C670-681
143. **Cao L, Choi EY, Liu X, Martin A, Wang C, Xu X, During MJ** 2011 White to brown fat phenotypic switch induced by genetic and environmental activation of a hypothalamic-adipocyte axis. Cell Metab 14:324-338
144. **Seale P, Conroe HM, Estall J, Kajimura S, Frontini A, Ishibashi J, Cohen P, Cinti S, Spiegelman BM** 2011 Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. J Clin Invest 121:96-105
145. **Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Bostrom EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Hojlund K, Gygi SP, Spiegelman BM** 2012 A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481:463-468
146. **Carey DG, Nguyen TV, Campbell LV, Chisholm DJ, Kelly P** 1996 Genetic influences on central abdominal fat: a twin study. Int J Obes Relat Metab Disord 20:722-726
147. **Samaras K, Spector TD, Nguyen TV, Baan K, Campbell LV, Kelly PJ** 1997 Independent genetic factors determine the amount and distribution of fat in women after the menopause. J Clin Endocrinol Metab 82:781-785
148. **Fox CS, Liu Y, White CC, Feitosa M, Smith AV, Heard-Costa N, Lohman K, Johnson AD, Foster MC, Greenawalt DM, Griffin P, Ding J, Newman AB, Tylavsky F, Miljkovic I, Kritchevsky SB, Launer L, Garcia M, Eiriksdottir G, Carr JJ, Gudnason V, Harris TB, Cupples LA, Borecki IB** 2012 Genome-wide

association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women. PLoS Genet 8:e1002695

149. **Fox CS, White CC, Lohman K, Heard-Costa N, Cohen P, Zhang Y, Johnson AD, Emilsson V, Liu CT, Chen YD, Taylor KD, Allison M, Budoff M, Rotter JI, Carr JJ, Hoffmann U, Ding J, Cupples LA, Liu Y** 2012 Genome-Wide Association of Pericardial Fat Identifies a Unique Locus for Ectopic Fat. PLoS Genet 8:e1002705
150. **O'Rahilly S, Farooqi IS** 2008 Human obesity as a heritable disorder of the central control of energy balance. Int J Obes (Lond) 32 Suppl 7:S55-61
151. **Semple RK, Chatterjee VK, O'Rahilly S** 2006 PPAR gamma and human metabolic disease. J Clin Invest 116:581-589
152. **Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S** 2003 Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. The New England journal of medicine 348:1085-1095
153. **Greenfield JR, Miller JW, Keogh JM, Henning E, Satterwhite JH, Cameron GS, Astruc B, Mayer JP, Brage S, See TC, Lomas DJ, O'Rahilly S, Farooqi IS** 2009 Modulation of blood pressure by central melanocortinergic pathways. The New England journal of medicine 360:44-52
154. **Gao H, Salim A, Lee J, Tai ES, van Dam RM** 2011 Can body fat distribution, adiponectin levels and inflammation explain differences in insulin resistance between ethnic Chinese, Malays and Asian Indians? Int J Obes (Lond)
155. **Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr.** 2009 Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120:1640-1645
156. 2004 Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363:157-163
157. **Deboer MD** 2011 Ethnicity, obesity and the metabolic syndrome: implications on assessing risk and targeting intervention. Expert Rev Endocrinol Metab 6:279-289
158. **Garcia-Webb P, Zimmet P, Bonser A, King H, Bottomley S** 1984 Factors affecting fasting serum C-peptide levels in Micronesians: comparison with a Caucasoid population. Diabetologia 27:23-26
159. **Esparza-Romero J, Valencia ME, Martinez ME, Ravussin E, Schulz LO, Bennett PH** 2010 Differences in insulin resistance in Mexican and U.S. Pima Indians with normal glucose tolerance. The Journal of clinical endocrinology and metabolism 95:E358-362
160. **Magliano DJ, Soderberg S, Zimmet PZ, Chen L, Joonas N, Kowlessur S, Larhubarbe J, Gaoneadry D, Pauvaday V, Tuomilehto J, Alberti KG, Shaw JE** 2012 Explaining the increase of diabetes prevalence and plasma glucose in Mauritius. Diabetes Care 35:87-91
161. **Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L, Chen CH, Delahanty RJ, Okada Y, Tabara Y, Gu D, Zhu D, Haiman CA, Mo Z, Gao YT, Saw SM, Go MJ, Takeuchi F, Chang LC, Kokubo Y, Liang J, Hao M, Le Marchand L, Zhang Y, Hu Y, Wong TY, Long J, Han BG, Kubo M, Yamamoto K, Su MH, Miki T, Henderson BE, Song H, Tan A, He J, Ng DP, Cai Q, Tsunoda T, Tsai FJ, Iwai N, Chen GK, Shi J, Xu J, Sim X, Xiang YB, Maeda S, Ong RT, Li C, Nakamura Y, Aung T, Kamatani N, Liu JJ, Lu W, Yokota M, Seielstad M, Fann CS, Wu JY, Lee JY, Hu FB, Tanaka T, Tai ES, Shu XO** 2012 Meta-analysis identifies common variants associated with body mass index in east Asians. Nat Genet 44:307-311
162. **Chaston TB, Dixon JB** 2008 Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. Int J Obes (Lond) 32:619-628

163. **Ogden LG, Stroebele N, Wyatt HR, Catenacci VA, Peters JC, Stuht J, Wing RR, Hill JO** 2012 Cluster analysis of the National Weight Control Registry to identify distinct subgroups maintaining successful weight loss. Obesity (Silver Spring)
164. **Thorogood A, Mottillo S, Shimony A, Filion KB, Joseph L, Genest J, Pilote L, Poirier P, Schiffrin EL, Eisenberg MJ** 2011 Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. Am J Med 124:747-755
165. **Kay SJ, Fiatarone Singh MA** 2006 The influence of physical activity on abdominal fat: a systematic review of the literature. Obes Rev 7:183-200
166. **Samaras K, Kelly PJ, Chiano MN, Spector TD, Campbell LV** 1999 Genetic and environmental influences on total-body and central abdominal fat: the effect of physical activity in female twins. Ann Intern Med 130:873-882
167. **Keating SE, Hackett DA, George J, Johnson NA** 2012 Exercise and non-alcoholic fatty liver disease: A systematic review and meta-analysis. J Hepatol
168. **Ismail I, Keating SE, Baker MK, Johnson NA** 2012 A systematic review and meta-analysis of the effect of aerobic vs. resistance exercise training on visceral fat. Obes Rev 13:68-91
169. **Egberts K, Brown WA, Brennan L, O'Brien PE** 2012 Does exercise improve weight loss after bariatric surgery? A systematic review. Obesity surgery 22:335-341
170. **Matsuzawa Y** 2008 The role of fat topology in the risk of disease. Int J Obes (Lond) 32 Suppl 7:S83-92
171. **King DS, Baldus PJ, Sharp RL, Kesl LD, Feltmeyer TL, Riddle MS** 1995 Time course for exercise-induced alterations in insulin action and glucose tolerance in middle-aged people. J Appl Physiol 78:17-22
172. **Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI** 2004 The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A 101:15718-15723
173. **Backhed F, Manchester JK, Semenkovich CF, Gordon JI** 2007 Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci U S A 104:979-984
174. **Turnbaugh PJ, Backhed F, Fulton L, Gordon JI** 2008 Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe 3:213-223
175. **Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI** 2006 An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444:1027-1031
176. **Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI** 2009 The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med 1:6ra14
177. **Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI** 2009 A core gut microbiome in obese and lean twins. Nature 457:480-484
178. **Ley RE, Turnbaugh PJ, Klein S, Gordon JI** 2006 Microbial ecology: human gut microbes associated with obesity. Nature 444:1022-1023
179. **Duncan SH, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, Flint HJ** 2008 Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes (Lond) 32:1720-1724
180. **Santacruz A, Marcos A, Warnberg J, Marti A, Martin-Matillas M, Campoy C, Moreno LA, Veiga O, Redondo-Figuero C, Garagorri JM, Azcona C, Delgado M, Garcia-Fuentes M, Collado MC, Sanz Y** 2009 Interplay between weight loss and gut microbiota composition in overweight adolescents. Obesity (Silver Spring) 17:1906-1915
181. **Nadal I, Santacruz A, Marcos A, Warnberg J, Garagorri M, Moreno LA, Martin-Matillas M, Campoy C, Marti A, Moleres A, Delgado M, Veiga OL,**

**Garcia-Fuentes M, Redondo CG, Sanz Y** 2009 Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. Int J Obes (Lond) 33:758-767

182. **Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmee E, Cousin B, Sulpice T, Chamontin B, Ferrieres J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R** 2007 Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 56:1761-1772
183. **Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM** 2009 Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut 58:1091-1103
184. **Martin FP, Wang Y, Sprenger N, Yap IK, Lundstedt T, Lek P, Rezzi S, Ramadan Z, van Bladeren P, Fay LB, Kochhar S, Lindon JC, Holmes E, Nicholson JK** 2008 Probiotic modulation of symbiotic gut microbial-host metabolic interactions in a humanized microbiome mouse model. Mol Syst Biol 4:157
185. **Dumas ME, Barton RH, Toye A, Cloarec O, Blancher C, Rothwell A, Fearnside J, Tatoud R, Blanc V, Lindon JC, Mitchell SC, Holmes E, McCarthy MI, Scott J, Gauguier D, Nicholson JK** 2006 Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. Proc Natl Acad Sci U S A 103:12511-12516
186. **Wall R, Ross RP, Shanahan F, O'Mahony L, O'Mahony C, Coakley M, Hart O, Lawlor P, Quigley EM, Kiely B, Fitzgerald GF, Stanton C** 2009 Metabolic activity of the enteric microbiota influences the fatty acid composition of murine and porcine liver and adipose tissues. Am J Clin Nutr 89:1393-1401
187. **Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, Gordon JI** 2008 Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci U S A 105:16767-16772
188. **Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, De Backer F, Neyrinck AM, Delzenne NM** 2009 Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. Am J Clin Nutr 90:1236-1243
189. **Power ML, Schulkin J** 2008 Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. The British journal of nutrition 99:931-940
190. **Rodriguez G, Samper MP, Olivares JL, Ventura P, Moreno LA, Perez-Gonzalez JM** 2005 Skinfold measurements at birth: sex and anthropometric influence. Archives of disease in childhood Fetal and neonatal edition 90:F273-275
191. **Franklin RM, Ploutz-Snyder L, Kanaley JA** 2009 Longitudinal changes in abdominal fat distribution with menopause. Metabolism 58:311-315
192. **Haarbo J, Marslew U, Gotfredsen A, Christiansen C** 1991 Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. Metabolism: clinical and experimental 40:1323-1326
193. **Votruba SB, Jensen MD** 2006 Sex-specific differences in leg fat uptake are revealed with a high-fat meal. American journal of physiology Endocrinology and metabolism 291:E1115-1123
194. **Williams CM** 2004 Lipid metabolism in women. The Proceedings of the Nutrition Society 63:153-160
195. **Rebuffe-Scrive M, Andersson B, Olbe L, Bjorntorp P** 1989 Metabolism of adipose tissue in intraabdominal depots of nonobese men and women. Metabolism: clinical and experimental 38:453-458
196. **Tank J, Heusser K, Diedrich A, Hering D, Luft FC, Busjahn A, Narkiewicz K, Jordan J** 2008 Influences of gender on the interaction between sympathetic nerve

traffic and central adiposity. The Journal of clinical endocrinology and metabolism 93:4974-4978

197. **Nielsen S, Guo Z, Albu JB, Klein S, O'Brien PC, Jensen MD** 2003 Energy expenditure, sex, and endogenous fuel availability in humans. The Journal of clinical investigation 111:981-988
198. **Jensen MD** 1997 Lipolysis: contribution from regional fat. Annual review of nutrition 17:127-139
199. **Mittendorfer B** 2005 Sexual dimorphism in human lipid metabolism. The Journal of nutrition 135:681-686
200. **Sparks LM, Pasarica M, Sereda O, deJonge L, Thomas S, Loggins H, Xie H, Miles JM, Smith SR** 2009 Effect of adipose tissue on the sexual dimorphism in metabolic flexibility. Metabolism: clinical and experimental 58:1564-1571
201. **Tarnopolsky MA, Rennie CD, Robertshaw HA, Fedak-Tarnopolsky SN, Devries MC, Hamadeh MJ** 2007 Influence of endurance exercise training and sex on intramyocellular lipid and mitochondrial ultrastructure, substrate use, and mitochondrial enzyme activity. American journal of physiology Regulatory, integrative and comparative physiology 292:R1271-1278
202. **Haugaard SB, Mu H, Vaag A, Madsbad S** 2009 Intramyocellular triglyceride content in man, influence of sex, obesity and glycaemic control. European journal of endocrinology / European Federation of Endocrine Societies 161:57-64
203. **Roepstorff C, Donsmark M, Thiele M, Vistisen B, Stewart G, Vissing K, Schjerling P, Hardie DG, Galbo H, Kiens B** 2006 Sex differences in hormone-sensitive lipase expression, activity, and phosphorylation in skeletal muscle at rest and during exercise. American journal of physiology Endocrinology and metabolism 291:E1106-1114
204. **Dua A, Hennes MI, Hoffmann RG, Maas DL, Krakower GR, Sonnenberg GE, Kissebah AH** 1996 Leptin: a significant indicator of total body fat but not of visceral fat and insulin insensitivity in African-American women. Diabetes 45:1635-1637
205. **Woods SC, Gotoh K, Clegg DJ** 2003 Gender differences in the control of energy homeostasis. Experimental biology and medicine 228:1175-1180
206. **Alexe DM, Syridou G, Petridou ET** 2006 Determinants of early life leptin levels and later life degenerative outcomes. Clin Med Res 4:326-335
207. **Kennedy A, Gettys TW, Watson P, Wallace P, Ganaway E, Pan Q, Garvey WT** 1997 The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. J Clin Endocrinol Metab 82:1293-1300
208. **Rosenbaum M, Pietrobelli A, Vasselli JR, Heymsfield SB, Leibel RL** 2001 Sexual dimorphism in circulating leptin concentrations is not accounted for by differences in adipose tissue distribution. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 25:1365-1371
209. **Mittelstrass K, Ried JS, Yu Z, Krumsiek J, Gieger C, Prehn C, Roemisch-Margl W, Polonikov A, Peters A, Theis FJ, Meitinger T, Kronenberg F, Weidinger S, Wichmann HE, Suhre K, Wang-Sattler R, Adamski J, Illig T** 2011 Discovery of sexual dimorphisms in metabolic and genetic biomarkers. PLoS genetics 7:e1002215
210. **Sierra-Johnson J, Johnson BD, Bailey KR, Turner ST** 2004 Relationships between insulin sensitivity and measures of body fat in asymptomatic men and women. Obesity research 12:2070-2077
211. **Masharani U, Goldfine ID, Youngren JF** 2009 Influence of gender on the relationship between insulin sensitivity, adiposity, and plasma lipids in lean nondiabetic subjects. Metabolism 58:1602-1608
212. **Poehlman ET, Toth MJ, Gardner AW** 1995 Changes in energy balance and body composition at menopause: a controlled longitudinal study. Ann Intern Med 123:673-675

213. **Brochu M, Starling RD, Tchernof A, Matthews DE, Garcia-Rubi E, Poehlman ET** 2000 Visceral adipose tissue is an independent correlate of glucose disposal in older obese postmenopausal women. J Clin Endocrinol Metab 85:2378-2384
214. **O'Sullivan AJ, Crampton LJ, Freund J, Ho KK** 1998 The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in postmenopausal women. J Clin Invest 102:1035-1040
215. **Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, Kantoff PW** 2002 Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 87:599-603
216. **Keating NL, O'Malley AJ, Smith MR** 2006 Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 24:4448-4456
217. **Saad F, Aversa A, Isidori AM, Gooren LJ** 2012 Testosterone as potential effective therapy in treatment of obesity in men with testosterone deficiency: a review. Curr Diabetes Rev 8:131-143
218. **Ho KK, O'Sullivan AJ, Hoffman DM** 1996 Metabolic actions of growth hormone in man. Endocr J 43 Suppl:S57-63
219. **Alford FP, Hew FL, Christopher MC, Rantzau C** 1999 Insulin sensitivity in growth hormone (GH)-deficient adults and effect of GH replacement therapy. J Endocrinol Invest 22:28-32
220. **Attanasio AF, Jung H, Mo D, Chanson P, Bouillon R, Ho KK, Lamberts SW, Clemmons DR** 2011 Prevalence and incidence of diabetes mellitus in adult patients on growth hormone replacement for growth hormone deficiency: a surveillance database analysis. J Clin Endocrinol Metab 96:2255-2261
221. **Falutz J, Mamputu JC, Potvin D, Moyle G, Soulban G, Loughrey H, Marsolais C, Turner R, Grinspoon S** 2010 Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. J Clin Endocrinol Metab 95:4291-4304
222. **Gathercole LL, Stewart PM** 2010 Targeting the pre-receptor metabolism of cortisol as a novel therapy in obesity and diabetes. J Steroid Biochem Mol Biol 122:21-27
223. **Wamil M, Battle JH, Turban S, Kipari T, Seguret D, de Sousa Peixoto R, Nelson YB, Nowakowska D, Ferenbach D, Ramage L, Chapman KE, Hughes J, Dunbar DR, Seckl JR, Morton NM** 2011 Novel fat depot-specific mechanisms underlie resistance to visceral obesity and inflammation in 11 beta-hydroxysteroid dehydrogenase type 1-deficient mice. Diabetes 60:1158-1167
224. **Ruhla S, Weickert MO, Arafat AM, Osterhoff M, Isken F, Spranger J, Schofl C, Pfeiffer AF, Mohlig M** 2010 A high normal TSH is associated with the metabolic syndrome. Clin Endocrinol (Oxf) 72:696-701
225. **De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R** 2007 Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. Clin Endocrinol (Oxf) 67:265-269
226. **Liu C, Scherbaum WA, Schott M, Schinner S** 2011 Subclinical hypothyroidism and the prevalence of the metabolic syndrome. Horm Metab Res 43:417-421
227. **Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI** 1998 Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. The New England journal of medicine 338:867-872
228. **Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE** 2001 Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 108:1167-1174
229. **Williams DL** 2009 Minireview: finding the sweet spot: peripheral versus central glucagon-like peptide 1 action in feeding and glucose homeostasis. Endocrinology 150:2997-3001

230. **Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J** 2006 Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 295:761-775
231. **Burt MG, Willenberg VM, Petersons CJ, Smith MD, Ahern MJ, Stranks SN** 2012 Screening for diabetes in patients with inflammatory rheumatological disease administered long-term prednisolone: a cross-sectional study. Rheumatology (Oxford) 51:1112-1119
232. **Andrews RC, Walker BR** 1999 Glucocorticoids and insulin resistance: old hormones, new targets. Clin Sci (Lond) 96:513-523
233. **Lee P, Kengne AP, Greenfield JR, Day RO, Chalmers J, Ho KK** 2011 Metabolic sequelae of beta-blocker therapy: weighing in on the obesity epidemic? Int J Obes (Lond) 35:1395-1403
234. **Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK** 2009 Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA 302:1765-1773
235. **Bergman RN, Ader M** 2005 Atypical antipsychotics and glucose homeostasis. J Clin Psychiatry 66:504-514
236. **Ader M, Kim SP, Catalano KJ, Ionut V, Hucking K, Richey JM, Kabir M, Bergman RN** 2005 Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease: a placebo-controlled study of olanzapine and risperidone in dogs. Diabetes 54:862-871
237. **Peet M** 2004 Diet, diabetes and schizophrenia: review and hypothesis. Br J Psychiatry Suppl 47:S102-105
238. **Stefater MA, Wilson-Perez HE, Chambers AP, Sandoval DA, Seeley RJ** 2012 All Bariatric Surgeries Are Not Created Equal: Insights from Mechanistic Comparisons. Endocr Rev
239. **Rubino F, R'Bibo S L, del Genio F, Mazumdar M, McGraw TE** 2010 Metabolic surgery: the role of the gastrointestinal tract in diabetes mellitus. Nat Rev Endocrinol 6:102-109
240. **Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA** 1998 A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 12:F51-58
241. **Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA** 1999 Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. Lancet 353:2093-2099
242. **Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, Thiebaut R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD** 2007 Class of antiretroviral drugs and the risk of myocardial infarction. The New England journal of medicine 356:1723-1735
243. **Haap M, Siewecke C, Thamer C, Machann J, Schick F, Haring HU, Szeimies RM, Stumvoll M** 2004 Multiple symmetric lipomatosis: a paradigm of metabolically innocent obesity? Diabetes care 27:794-795
244. **Chen K, Xie Y, Hu P, Zhao S, Mo Z** 2010 Multiple symmetric lipomatosis: substantial subcutaneous adipose tissue accumulation did not induce glucose and lipid metabolism dysfunction. Annals of nutrition & metabolism 57:68-73
245. **Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE** 2000 Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. Diabetologia 43:1498-1506
246. **Smith J, Al-Amri M, Dorairaj P, Sniderman A** 2006 The adipocyte life cycle hypothesis. Clin Sci (Lond) 110:1-9
247. **Hausman DB, DiGirolamo M, Bartness TJ, Hausman GJ, Martin RJ** 2001 The biology of white adipocyte proliferation. Obes Rev 2:239-254

248. **Marques BG, Hausman DB, Martin RJ** 1998 Association of fat cell size and paracrine growth factors in development of hyperplastic obesity. Am J Physiol 275:R1898-1908
249. **van Harmelen V, Skurk T, Rohrig K, Lee YM, Halbleib M, Aprath-Husmann I, Hauner H** 2003 Effect of BMI and age on adipose tissue cellularity and differentiation capacity in women. Int J Obes Relat Metab Disord 27:889-895
250. **Arner E, Westermark PO, Spalding KL, Britton T, Ryden M, Frisen J, Bernard S, Arner P** 2010 Adipocyte turnover: relevance to human adipose tissue morphology. Diabetes 59:105-109
251. **Bjorntorp P** 1971 Sjostrom L,+SJOSTROM L: Number and size of adipose tissue fat cells in relation to metabolism in human obesity. Metabolism 20:703-713
252. **Bjorntorp P, Bengtsson C, Blohme G, Jonsson A, Sjostrom L, Tibblin E, Tibblin G, Wilhelmsen L** 1971 Adipose tissue fat cell size and number in relation to metabolism in randomly selected middle-aged men and women. Metabolism 20:927-935
253. **Ktotkiewski M, Sjostrom L, Bjorntorp P, Smith U** 1975 Regional adipose tissue cellularity in relation to metabolism in young and middle-aged women. Metabolism 24:703-710
254. **Lundgren M, Svensson M, Lindmark S, Renstrom F, Ruge T, Eriksson JW** 2007 Fat cell enlargement is an independent marker of insulin resistance and 'hyperleptinaemia'. Diabetologia 50:625-633
255. **Stern JS, Batchelor BR, Hollander N, Cohn CK, Hirsch J** 1972 Adipose-cell size and immunoreactive insulin levels in obese and normal-weight adults. Lancet 2:948-951
256. **Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U** 1983 Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. J Clin Invest 72:1150-1162
257. **Bahceci M, Gokalp D, Bahceci S, Tuzcu A, Atmaca S, Arikan S** 2007 The correlation between adiposity and adiponectin, tumor necrosis factor alpha, interleukin-6 and high sensitivity C-reactive protein levels. Is adipocyte size associated with inflammation in adults? J Endocrinol Invest 30:210-214
258. **Ronti T, Lupattelli G, Mannarino E** 2006 The endocrine function of adipose tissue: an update. Clin Endocrinol (Oxf) 64:355-365
259. **Skurk T, Alberti-Huber C, Herder C, Hauner H** 2007 Relationship between adipocyte size and adipokine expression and secretion. J Clin Endocrinol Metab 92:1023-1033
260. **Jernas M, Palming J, Sjoholm K, Jennische E, Svensson PA, Gabrielsson BG, Levin M, Sjogren A, Rudemo M, Lystig TC, Carlsson B, Carlsson LM, Lonn M** 2006 Separation of human adipocytes by size: hypertrophic fat cells display distinct gene expression. FASEB J 20:1540-1542
261. **Monteiro R, de Castro PM, Calhau C, Azevedo I** 2006 Adipocyte size and liability to cell death. Obesity surgery 16:804-806
262. **Larsen TM, Toubro S, Astrup A** 2003 PPARgamma agonists in the treatment of type II diabetes: is increased fatness commensurate with long-term efficacy? Int J Obes Relat Metab Disord 27:147-161
263. **Bays H, Blonde L, Rosenson R** 2006 Adiposopathy: how do diet, exercise and weight loss drug therapies improve metabolic disease in overweight patients? Expert Rev Cardiovasc Ther 4:871-895
264. **Bays H, Mandarino L, DeFronzo RA** 2004 Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. J Clin Endocrinol Metab 89:463-478
265. **O'Connell J, Lynch L, Cawood TJ, Kwasnik A, Nolan N, Geoghegan J, McCormick A, O'Farrelly C, O'Shea D** 2010 The relationship of omental and

subcutaneous adipocyte size to metabolic disease in severe obesity. PLoS One 5:e9997

266. **Sniderman AD, Bhopal R, Prabhakaran D, Sarrafzadegan N, Tchernof A** 2007 Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis. Int J Epidemiol 36:220-225
267. **Klimcakova E, Roussel B, Kovacova Z, Kovacikova M, Siklova-Vitkova M, Combes M, Hejnova J, Decaunes P, Maoret JJ, Vedral T, Viguerie N, Bourlier V, Bouloumie A, Stich V, Langin D** 2011 Macrophage gene expression is related to obesity and the metabolic syndrome in human subcutaneous fat as well as in visceral fat. Diabetologia 54:876-887
268. **Donath MY, Shoelson SE** 2011 Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 11:98-107
269. **Olefsky JM, Glass CK** 2010 Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 72:219-246
270. **Romano M, Guagnano MT, Pacini G, Vigneri S, Falco A, Marinopiccoli M, Manigrasso MR, Basili S, Davi G** 2003 Association of inflammation markers with impaired insulin sensitivity and coagulative activation in obese healthy women. J Clin Endocrinol Metab 88:5321-5326
271. **Kriketos AD, Greenfield JR, Peake PW, Furler SM, Denyer GS, Charlesworth JA, Campbell LV** 2004 Inflammation, insulin resistance, and adiposity: a study of first-degree relatives of type 2 diabetic subjects. Diabetes Care 27:2033-2040
272. **Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Giugliano D** 2003 Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA : the journal of the American Medical Association 289:1799-1804
273. **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** 2004 Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. FASEB J 18:1657-1669
274. **Christiansen T, Richelsen B, Bruun JM** 2005 Monocyte chemoattractant protein-1 is produced in isolated adipocytes, associated with adiposity and reduced after weight loss in morbid obese subjects. Int J Obes (Lond) 29:146-150
275. **Bruun JM, Helge JW, Richelsen B, Stallknecht B** 2006 Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. American journal of physiology Endocrinology and metabolism 290:E961-967
276. **Christiansen T, Paulsen SK, Bruun JM, Pedersen SB, Richelsen B** 2010 Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study. American journal of physiology Endocrinology and metabolism 298:E824-831
277. **Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumie A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clement K** 2005 Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes 54:2277-2286
278. **Tam CS, Covington JD, Ravussin E, Redman LM** 2012 Little evidence of systemic and adipose tissue inflammation in overweight individuals(dagger). Frontiers in genetics 3:58
279. **Tam CS, Viardot A, Clement K, Tordjman J, Tonks K, Greenfield JR, Campbell LV, Samocha-Bonet D, Heilbronn LK** 2010 Short-term overfeeding may induce peripheral insulin resistance without altering subcutaneous adipose tissue macrophages in humans. Diabetes 59:2164-2170
280. **Alligier M, Meugnier E, Debard C, Lambert-Porcheron S, Chanseaume E, Sothier M, Loizon E, Hssain AA, Brozek J, Scoazec JY, Morio B, Vidal H,**

**Laville M** 2012 Subcutaneous adipose tissue remodeling during the initial phase of weight gain induced by overfeeding in humans. J Clin Endocrinol Metab 97:E183-192

281. **Ofei F, Hurel S, Newkirk J, Sopwith M, Taylor R** 1996 Effects of an engineered human anti-TNF-alpha antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. Diabetes 45:881-885
282. **Dominguez H, Storgaard H, Rask-Madsen C, Steffen Hermann T, Ihlemann N, Baunbjerg Nielsen D, Spohr C, Kober L, Vaag A, Torp-Pedersen C** 2005 Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. Journal of vascular research 42:517-525
283. **Stanley TL, Zanni MV, Johnsen S, Rasheed S, Makimura H, Lee H, Khor VK, Ahima RS, Grinspoon SK** 2011 TNF-alpha antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. J Clin Endocrinol Metab 96:E146-150
284. **Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Llorca J** 2010 Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-alpha therapy. Ann N Y Acad Sci 1193:153-159
285. **Plomgaard P, Bouzakri K, Krogh-Madsen R, Mittendorfer B, Zierath JR, Pedersen BK** 2005 Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. Diabetes 54:2939-2945
286. **Larsen CM, Faulenbach M, Vaag A, Volund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY** 2007 Interleukin-1-receptor antagonist in type 2 diabetes mellitus. The New England journal of medicine 356:1517-1526
287. **van Asseldonk EJ, Stienstra R, Koenen TB, Joosten LA, Netea MG, Tack CJ** 2011 Treatment with Anakinra improves disposition index but not insulin sensitivity in nondiabetic subjects with the metabolic syndrome: a randomized, double-blind, placebo-controlled study. The Journal of clinical endocrinology and metabolism 96:2119-2126
288. **Goldfine AB, Fonseca V, Jablonski KA, Pyle L, Staten MA, Shoelson SE** 2010 The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. Ann Intern Med 152:346-357
289. **Goldfine AB, Silver R, Aldhahi W, Cai D, Tatro E, Lee J, Shoelson SE** 2008 Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. Clin Transl Sci 1:36-43
290. **Faghihimani E, Aminorroaya A, Rezvanian H, Adibi P, Ismail-Beigi F, Amini M** 2011 Salsalate improves glycemic control in patients with newly diagnosed type 2 diabetes. Acta diabetologica
291. **Fleischman A, Shoelson SE, Bernier R, Goldfine AB** 2008 Salsalate improves glycemia and inflammatory parameters in obese young adults. Diabetes Care 31:289-294
292. **Koska J, Ortega E, Bunt JC, Gasser A, Impson J, Hanson RL, Forbes J, de Courten B, Krakoff J** 2009 The effect of salsalate on insulin action and glucose tolerance in obese non-diabetic patients: results of a randomised double-blind placebo-controlled study. Diabetologia 52:385-393
293. **Belfort R, Berria R, Cornell J, Cusi K** 2010 Fenofibrate reduces systemic inflammation markers independent of its effects on lipid and glucose metabolism in patients with the metabolic syndrome. J Clin Endocrinol Metab 95:829-836
294. **Reyna SM, Ghosh S, Tantiwong P, Meka CS, Eagan P, Jenkinson CP, Cersosimo E, Defronzo RA, Coletta DK, Sriwijitkamol A, Musi N** 2008 Elevated toll-like receptor 4 expression and signaling in muscle from insulin-resistant subjects. Diabetes 57:2595-2602

295. **Kuo LH, Tsai PJ, Jiang MJ, Chuang YL, Yu L, Lai KT, Tsai YS** 2011 Toll-like receptor 2 deficiency improves insulin sensitivity and hepatic insulin signalling in the mouse. Diabetologia 54:168-179
296. **Konner AC, Bruning JC** 2011 Toll-like receptors: linking inflammation to metabolism. Trends Endocrinol Metab 22:16-23
297. **Montague CT, Prins JB, Sanders L, Digby JE, O'Rahilly S** 1997 Depot- and sex-specific differences in human leptin mRNA expression: implications for the control of regional fat distribution. Diabetes 46:342-347
298. **Deng Y, Scherer PE** 2010 Adipokines as novel biomarkers and regulators of the metabolic syndrome. Ann N Y Acad Sci 1212:E1-E19
299. **Schulz C, Paulus K, Johren O, Lehnert H** 2012 Intranasal leptin reduces appetite and induces weight loss in rats with diet-induced obesity (DIO). Endocrinology 153:143-153
300. **Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F** 1995 Effects of the obese gene product on body weight regulation in ob/ob mice. Science 269:540-543
301. **Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, O'Rahilly S** 1999 Effects of recombinant leptin therapy in a child with congenital leptin deficiency. The New England journal of medicine 341:879-884
302. **Enriori PJ, Evans AE, Sinnayah P, Jobst EE, Tonelli-Lemos L, Billes SK, Glavas MM, Grayson BE, Perello M, Nillni EA, Grove KL, Cowley MA** 2007 Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. Cell Metab 5:181-194
303. **Myers MG, Jr.** 2010 Outstanding Scientific Achievement Award Lecture 2010: deconstructing leptin: from signals to circuits. Diabetes 59:2708-2714
304. **Lihn AS, Bruun JM, He G, Pedersen SB, Jensen PF, Richelsen B** 2004 Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. Mol Cell Endocrinol 219:9-15
305. **Kadowaki T, Yamauchi T** 2011 Adiponectin receptor signaling: a new layer to the current model. Cell Metab 13:123-124
306. **Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J, Takata M, Eto K, Terauchi Y, Komeda K, Tsunoda M, Murakami K, Ohnishi Y, Naitoh T, Yamamura K, Ueyama Y, Froguel P, Kimura S, Nagai R, Kadowaki T** 2003 Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem 278:2461-2468
307. **Fried SK, Bunkin DA, Greenberg AS** 1998 Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 83:847-850
308. **Basu R, Pajvani UB, Rizza RA, Scherer PE** 2007 Selective downregulation of the high molecular weight form of adiponectin in hyperinsulinemia and in type 2 diabetes: differential regulation from nondiabetic subjects. Diabetes 56:2174-2177
309. **Pedersen BK, Febbraio MA** 2012 Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol
310. **Taylor AW, Ku NO, Mortensen RF** 1990 Regulation of cytokine-induced human C-reactive protein production by transforming growth factor-beta. J Immunol 145:2507-2513
311. **Furuhashi M, Hotamisligil GS** 2008 Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. Nat Rev Drug Discov 7:489-503
312. **Maeda K, Cao H, Kono K, Gorgun CZ, Furuhashi M, Uysal KT, Cao Q, Atsumi G, Malone H, Krishnan B, Minokoshi Y, Kahn BB, Parker RA, Hotamisligil GS** 2005 Adipocyte/macrophage fatty acid binding proteins control integrated metabolic responses in obesity and diabetes. Cell Metab 1:107-119

313. **Tso AW, Xu A, Sham PC, Wat NM, Wang Y, Fong CH, Cheung BM, Janus ED, Lam KS** 2007 Serum adipocyte fatty acid binding protein as a new biomarker predicting the development of type 2 diabetes: a 10-year prospective study in a Chinese cohort. Diabetes Care 30:2667-2672
314. **Xu A, Tso AW, Cheung BM, Wang Y, Wat NM, Fong CH, Yeung DC, Janus ED, Sham PC, Lam KS** 2007 Circulating adipocyte-fatty acid binding protein levels predict the development of the metabolic syndrome: a 5-year prospective study. Circulation 115:1537-1543
315. **Choi KM, Yannakoulia M, Park MS, Cho GJ, Kim JH, Lee SH, Hwang TG, Yang SJ, Kim TN, Yoo HJ, Baik SH, Kim SM, Mantzoros CS** 2011 Serum adipocyte fatty acid-binding protein, retinol-binding protein 4, and adiponectin concentrations in relation to the development of the metabolic syndrome in Korean boys: a 3-y prospective cohort study. Am J Clin Nutr 93:19-26
316. **Milner KL, van der Poorten D, Xu A, Bugianesi E, Kench JG, Lam KS, Chisholm DJ, George J** 2009 Adipocyte fatty acid binding protein levels relate to inflammation and fibrosis in nonalcoholic fatty liver disease. Hepatology 49:1926-1934
317. **Khalyfa A, Bhushan B, Hegazi M, Kim J, Kheirandish-Gozal L, Bhattacharjee R, Capdevila OS, Gozal D** 2010 Fatty-acid binding protein 4 gene variants and childhood obesity: potential implications for insulin sensitivity and CRP levels. Lipids Health Dis 9:18
318. **Makowski L, Brittingham KC, Reynolds JM, Suttles J, Hotamisligil GS** 2005 The fatty acid-binding protein, aP2, coordinates macrophage cholesterol trafficking and inflammatory activity. Macrophage expression of aP2 impacts peroxisome proliferator-activated receptor gamma and IkappaB kinase activities. J Biol Chem 280:12888-12895
319. **Furuhashi M, Tuncman G, Gorgun CZ, Makowski L, Atsumi G, Vaillancourt E, Kono K, Babaev VR, Fazio S, Linton MF, Sulsky R, Robl JA, Parker RA, Hotamisligil GS** 2007 Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2. Nature 447:959-965
320. **Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, Wason CJ, Oberbach A, Jansson PA, Smith U, Kahn BB** 2006 Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. The New England journal of medicine 354:2552-2563
321. **Takashima N, Tomoike H, Iwai N** 2006 Retinol-binding protein 4 and insulin resistance. The New England journal of medicine 355:1392; author reply 1394-1395
322. **Janke J, Engeli S, Boschmann M, Adams F, Bohnke J, Luft FC, Sharma AM, Jordan J** 2006 Retinol-binding protein 4 in human obesity. Diabetes 55:2805-2810
323. **Jamaluddin MS, Weakley SM, Yao Q, Chen C** 2012 Resistin: functional roles and therapeutic considerations for cardiovascular disease. Br J Pharmacol 165:622-632
324. **Schwartz DR, Lazar MA** 2011 Human resistin: found in translation from mouse to man. Trends Endocrinol Metab 22:259-265
325. **Kotnik P, Fischer-Posovszky P, Wabitsch M** 2011 RBP4: a controversial adipokine. Eur J Endocrinol 165:703-711
326. **Tan BK, Adya R, Randeva HS** 2010 Omentin: a novel link between inflammation, diabesity, and cardiovascular disease. Trends Cardiovasc Med 20:143-148
327. **Karpe F, Dickmann JR, Frayn KN** 2011 Fatty acids, obesity, and insulin resistance: time for a reevaluation. Diabetes 60:2441-2449
328. **Randle PJ, Garland PB, Hales CN, Newsholme EA** 1963 The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785-789
329. **Wing RR, Blair EH, Bononi P, Marcus MD, Watanabe R, Bergman RN** 1994 Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. Diabetes Care 17:30-36

330. **Rhee EP, Cheng S, Larson MG, Walford GA, Lewis GD, McCabe E, Yang E, Farrell L, Fox CS, O'Donnell CJ, Carr SA, Vasan RS, Florez JC, Clish CB, Wang TJ, Gerszten RE** 2011 Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. J Clin Invest 121:1402-1411
331. **Kraegen EW, Clark PW, Jenkins AB, Daley EA, Chisholm DJ, Storlien LH** 1991 Development of muscle insulin resistance after liver insulin resistance in high-fat-fed rats. Diabetes 40:1397-1403
332. **Oakes ND, Bell KS, Furler SM, Camilleri S, Saha AK, Ruderman NB, Chisholm DJ, Kraegen EW** 1997 Diet-induced muscle insulin resistance in rats is ameliorated by acute dietary lipid withdrawal or a single bout of exercise: parallel relationship between insulin stimulation of glucose uptake and suppression of long-chain fatty acyl-CoA. Diabetes 46:2022-2028
333. **Bell KS, Schmitz-Peiffer C, Lim-Fraser M, Biden TJ, Cooney GJ, Kraegen EW** 2000 Acute reversal of lipid-induced muscle insulin resistance is associated with rapid alteration in PKC-theta localization. Am J Physiol Endocrinol Metab 279:E1196-1201
334. **Wendel AA, Li LO, Li Y, Cline GW, Shulman GI, Coleman RA** 2010 Glycerol-3-phosphate acyltransferase 1 deficiency in ob/ob mice diminishes hepatic steatosis but does not protect against insulin resistance or obesity. Diabetes 59:1321-1329
335. **Bikman BT, Summers SA** 2011 Ceramides as modulators of cellular and whole-body metabolism. J Clin Invest 121:4222-4230
336. **Schmitz-Peiffer C, Craig DL, Biden TJ** 1999 Evidence for the involvement of ceramide in the inhibition of insulin action by palmitate in mouse C2C12 skeletal muscle cells. Diabetes 48:A331-A331
337. **Adams JM, 2nd, Pratipanawatr T, Berria R, Wang E, DeFronzo RA, Sullards MC, Mandarino LJ** 2004 Ceramide content is increased in skeletal muscle from obese insulin-resistant humans. Diabetes 53:25-31
338. **Straczkowski M, Kowalska I, Baranowski M, Nikolajuk A, Otziomek E, Zabielski P, Adamska A, Blachnio A, Gorski J, Gorska M** 2007 Increased skeletal muscle ceramide level in men at risk of developing type 2 diabetes. Diabetologia 50:2366-2373
339. **Skovbro M, Baranowski M, Skov-Jensen C, Flint A, Dela F, Gorski J, Helge JW** 2008 Human skeletal muscle ceramide content is not a major factor in muscle insulin sensitivity. Diabetologia 51:1253-1260
340. **Anastasiou CA, Kavouras SA, Lentzas Y, Gova A, Sidossis LS, Melidonis A** 2009 Diabetes mellitus is associated with increased intramyocellular triglyceride, but not diglyceride, content in obese humans. Metabolism 58:1636-1642
341. **Coen PM, Dube JJ, Amati F, Stefanovic-Racic M, Ferrell RE, Toledo FG, Goodpaster BH** 2010 Insulin resistance is associated with higher intramyocellular triglycerides in type I but not type II myocytes concomitant with higher ceramide content. Diabetes 59:80-88
342. **Dube JJ, Amati F, Toledo FG, Stefanovic-Racic M, Rossi A, Coen P, Goodpaster BH** 2011 Effects of weight loss and exercise on insulin resistance, and intramyocellular triacylglycerol, diacylglycerol and ceramide. Diabetologia 54:1147-1156
343. **Magkos F, Su X, Bradley D, Fabbrini E, Conte C, Eagon JC, Varela JE, Brunt EM, Patterson BW, Klein S** Intrahepatic Diacylglycerol Content is Associated with Hepatic Insulin Resistance in Obese Subjects. Gastroenterology
344. **Kumashiro N, Erion DM, Zhang D, Kahn M, Beddow SA, Chu X, Still CD, Gerhard GS, Han X, Dziura J, Petersen KF, Samuel VT, Shulman GI** 2011 Cellular mechanism of insulin resistance in nonalcoholic fatty liver disease. Proc Natl Acad Sci U S A 108:16381-16385
345. **Reaven GM** 1988 Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37:1595-1607

346. **Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., Spertus JA, Costa F** 2005 Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112:2735-2752
347. **Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH** 2008 The metabolic syndrome. Endocr Rev 29:777-822
348. **Matsuzawa Y, Funahashi T, Nakamura T** 2011 The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism. J Atheroscler Thromb 18:629-639
349. **Lorenzo C, Williams K, Hunt KJ, Haffner SM** 2007 The National Cholesterol Education Program - Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 30:8-13
350. **Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM** 2004 Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 27:2676-2681
351. **Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ** 2010 The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 56:1113-1132
352. **Hotamisligil GS** 2006 Inflammation and metabolic disorders. Nature 444:860-867
353. **Libby P, Ridker PM, Hansson GK** 2011 Progress and challenges in translating the biology of atherosclerosis. Nature 473:317-325
354. **Jordan J, Yumuk V, Schlaich M, Nilsson PM, Zahorska-Markiewicz B, Grassi G, Schmieder RE, Engeli S, Finer N** 2012 Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: obesity and difficult to treat arterial hypertension. J Hypertens 30:1047-1055
355. **Ho DY, Cook NR, Britton KA, Kim E, Creager MA, Ridker PM, Pradhan AD** 2011 High-molecular-weight and total adiponectin levels and incident symptomatic peripheral artery disease in women: a prospective investigation. Circulation 124:2303-2311
356. **Matsuzawa Y, Shimomura I, Nakamura T, Keno Y, Kotani K, Tokunaga K** 1995 Pathophysiology and pathogenesis of visceral fat obesity. Obes Res 3 Suppl 2:187S-194S

Figure

Click here to download Figure: Figure 1.pptx

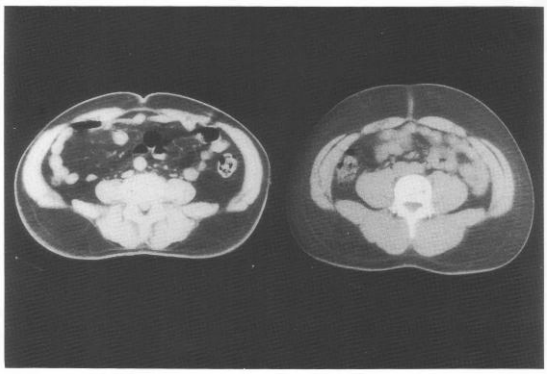
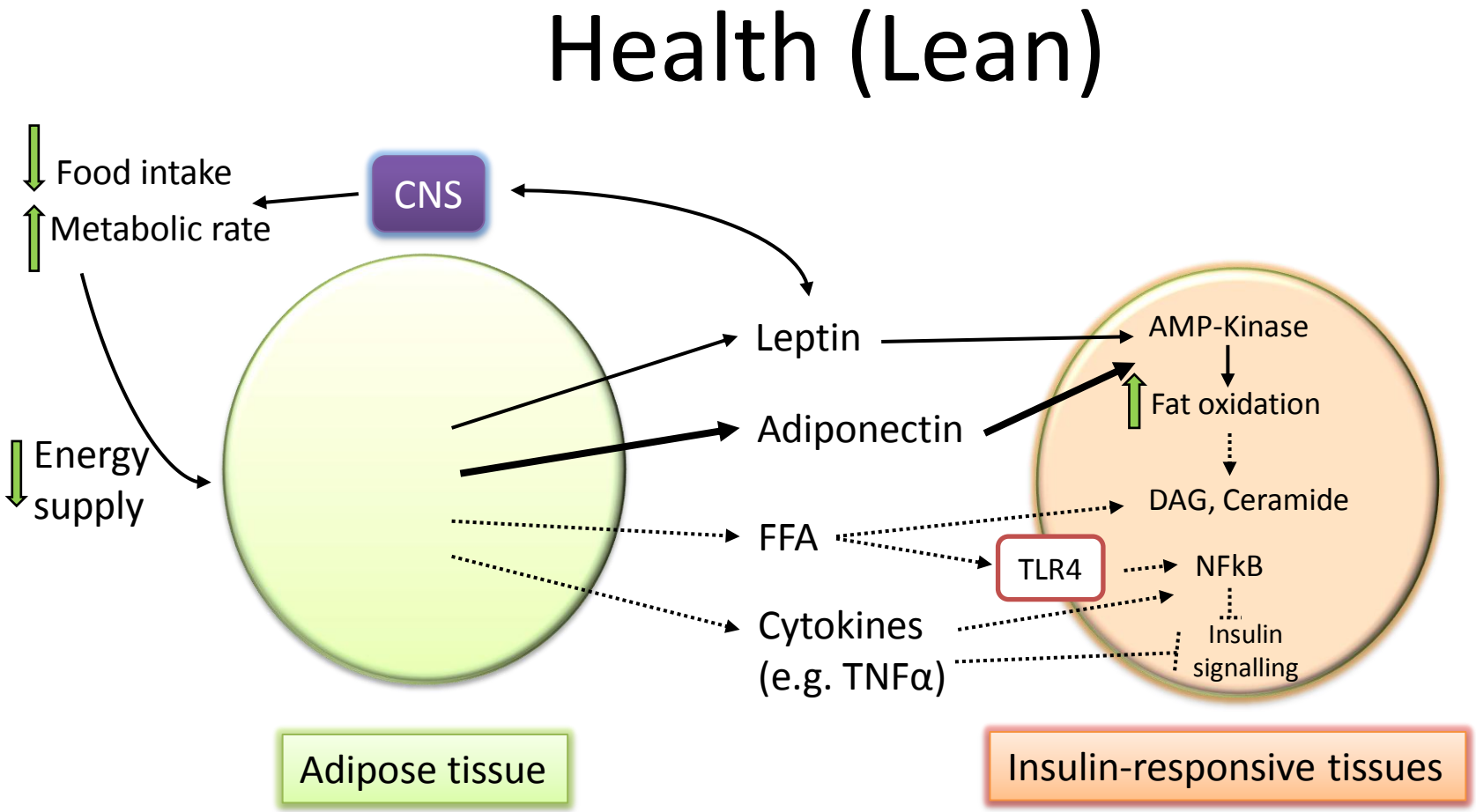
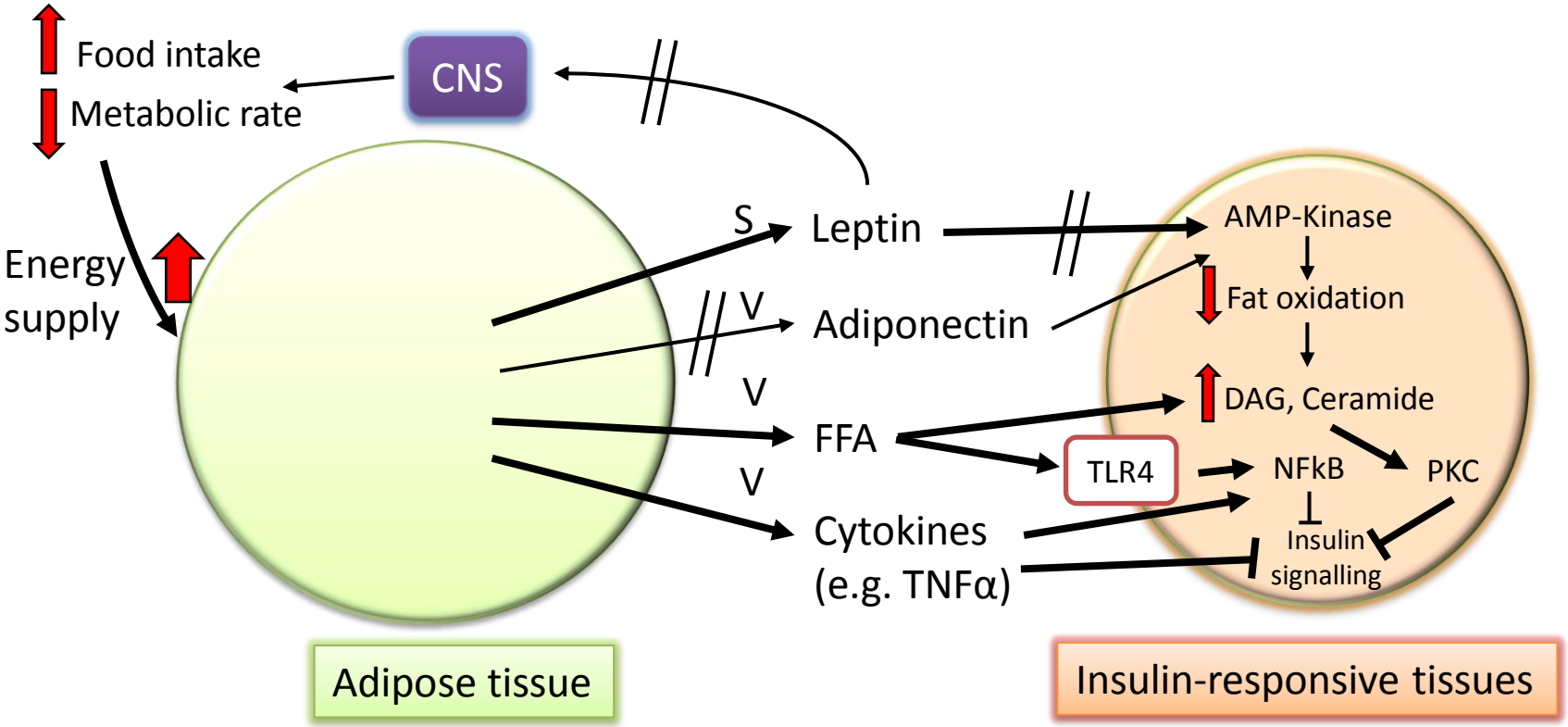


**Figure 1.**

Figure
Click here to download Figure: Figure 2.pptx



# Obesity


Food intake
Metabolic rate
CNS
Energy supply
S
Leptin
V
Adiponectin
V
FFA
V
Cytokines
(e.g. TNFα)
AMP-Kinase
Fat oxidation
DAG, Ceramide
TLR4
NFkB
PKC
Insulin signalling
Adipose tissue
Insulin-responsive tissues