Published in final edited form as:

J Matern Fetal Neonatal Med. 2008 November ; 21(11): 796–815. doi:10.1080/14767050802266881.

Adiponectin Multimers in Normal Pregnancy

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Abstract

Objective—Adiponectin is an anti-diabetic, anti-atherogenic, anti-inflammatory and angiogenic adipokine that circulates in oligomeric complexes including: low-molecular-weight (LMW) trimers, medium-molecular-weight (MMW) hexamers and high-molecular-weight (HMW) isoforms. The aim of this study was to determine whether there are changes in adiponectin multimers in pregnancy and as a function of maternal weight.

Study design—In this cross-sectional study, serum concentrations of total, HMW, MMW and LMW adiponectin were determined in women included in three groups: 1) normal pregnant women of normal body mass index (BMI) (n=466); 2) overweight/obese pregnant women (BMI ≥ 25 ; n=257); and 3) non-pregnant women of normal weight (n=40). Blood samples were collected once from each pregnant woman between 11 and 42 weeks of gestation. Serum adiponectin multimers concentrations were determined by ELISA. Non-parametric statistics were used for analysis.

Results—1) The median HMW adiponectin concentration and the median HMW/Total adiponectin ratio were significantly higher and the median LMW adiponectin concentration was significantly lower in pregnant than in non-pregnant women; 2) among pregnant women, the median serum concentration of total, HMW and MMW adiponectin was significantly higher in normal weight women than in overweight/obese patients; 3) HMW adiponectin was the most prevalent multimer in maternal serum regardless of gestational age or BMI status; 4) there were no significant differences in the median concentration of total, MMW, LMW adiponectin, and their relative distribution with advancing gestation.

Conclusion—Human pregnancy is characterized by quantitative and qualitative changes in adiponectin multimers, especially of the most active isoform, HMW adiponectin.

Keywords

Adiponectin; Adipokines; Pregnancy; High molecular weight (HMW) adiponectin; Medium molecular weight (MMW) adiponectin; Low molecular weight (LMW) adiponectin; BMI

Introduction

Insulin resistance is one of the hallmarks of human pregnancy [1–14]. Teleologically, an increased maternal resistance to insulin and the amplified production of glucose are aimed to ensure adequate glucose transport to the developing fetus [15–17]. The ephemeral nature of this metabolic alteration during pregnancy, as well as empirical findings [18–24], led to the conventional view that this physiologic adaptation stems from the “diabetogenic” effect of the placental hormones.

Adipose tissue has emerged as a powerful endocrine organ [25–37] that can exert autocrine, paracrine and endocrine effects by the production and secretion of a variety of adipokines including: adiponectin [38–46], leptin [6,47–51], tumor necrosis factor (TNF) – α [46,52–55], and resistin [56–60]. These highly active peptides and proteins [30,31,61,62] have been implicated in the pathophysiology of the most common metabolic complications such as insulin resistance [25,63–70], obesity [71–75], and the metabolic syndrome [43,70,76–81]. An abundance of evidence demonstrates that adipokines play an important role in the metabolic homeostasis during normal gestation [82–89], as well as in complications of pregnancy such as gestational diabetes mellitus [63,90–100] and preeclampsia [101–112].

Adiponectin, identified independently by four groups [40,42,44,45], is the most abundant gene (*AMP1*) product of adipose tissue; it circulates at relatively high concentrations [38,40,71,74, 113,114] and accounts for 0.01% of the total serum proteins. The serum concentrations of adiponectin are paradoxically lower in obese than in non-obese individuals [38,40]. In addition, weight reduction is associated with an increase in serum adiponectin concentration [72,74], suggesting that adipose tissue exerts a negative feedback on adiponectin production or secretion. Adiponectin has an important role in the pathophysiology of insulin resistance and diabetes [115–122], atherosclerosis [77–79,123,124], hypertension [80,125,126], dyslipidemia [127–129] and angiogenesis [130,131]. Moreover, adiponectin has been suggested to play a regulatory role in the metabolic adaptation during human pregnancy [25,65,83,84], as well as in the pathophysiology of both gestational diabetes mellitus (GDM) [90,92–94,96] and preeclampsia [101–109].

Adiponectin circulates in human serum in distinct forms: 1) low-molecular-weight (LMW) trimers; 2) medium-molecular-weight (MMW) hexamers; and 3) high-molecular-weight (HMW) oligomers (12 to 18 subunits) [38,45,132–138]. These adiponectin multimers can exert distinct biological effects [133–140], activate different single transduction pathways [133, 138] and may have different affinities to the adiponectin receptors [141]. In particular, the adiponectin sensitivity index (S_A) [137], which is the ratio of HMW to total adiponectin, has been reported to be a more sensitive marker of the biological activity of adiponectin [134, 135,137,139,140,142–161]. Indeed, S_A has a better correlation with insulin resistance [134, 135,137,140,142–146], obesity [147–150], cardiovascular diseases [134,139,151,152] and other impaired metabolic states [153–161] than total adiponectin.

Only a handful of studies have addressed the changes in maternal adiponectin multimers concentrations and their relative concentration during human pregnancy [25,162–165]. Moreover, data regarding the concentrations of the HMW, MMW and LMW adiponectin isoforms in each trimester as well as the association between maternal weight and the relative distribution of adiponectin multimers has not been reported. Thus, the aim of this study was to determine whether there are changes in adiponectin multimers in pregnancy and as a function of maternal body mass index (BMI).

Materials and methods

Study design and population

A cross-sectional study was conducted using samples and data retrieved from the bank of biological samples and clinical database of the Perinatology Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The following groups of subjects were included: 1) normal pregnant women of normal BMI (n=466); 2) overweight/obese pregnant women with normal pregnancy (n=257); and 3) non-pregnant women of normal weight (n=40) with no prior or current medical or metabolic conditions and who were not using oral contraceptives.

The inclusion criteria for normal pregnant women were: singleton gestation, no prior diabetes mellitus, no maternal or fetal complications during pregnancy, normal serum glucose concentrations in the first trimester, normal oral glucose challenge test, and delivery at term of a healthy neonate with a birthweight above the 10th percentile for gestational age. Maternal blood samples were collected once from each woman in the following gestational ages: 11–14 weeks (n=84), 15–18 weeks (n=93), 19–22 weeks (n=93), 23–26 weeks (n=94), 27–30 weeks (n=95), 31–34 weeks (n=86) and term (≥ 37 weeks) in labor (n=98) and not in labor (n=80). The BMI was calculated according to the formula: weight (kg)/height (m^2). Normal weight women were defined as those with a BMI of 18.5–25 kg/m^2 according to the definitions of the World Health Organization (WHO) [166]. Pregnant women were classified according to their first trimester BMI into two groups: normal weight and overweight/obese ($BMI \geq 25 kg/m^2$) and by the gestational age at sample collection.

Written informed consent was obtained from all participants after approval by the Institutional Review Board of both the Sotero del Rio Hospital (Chile) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (Bethesda, Maryland, USA).

Sample collection

Maternal serum samples were collected from each pregnant woman. Many of these samples were used previously to study the biology of inflammation, hemostasis, angiogenesis regulation and growth factors concentrations in non-pregnant and normal pregnant women.

Quantitative determination of multimeric forms of adiponectin in maternal serum—Sensitive enzyme-linked immunoassays were used to determine the concentrations of adiponectin multimeric forms in maternal serum. Immunoassays were purchased from ALPCO Diagnostics (Salem, NH, USA). The assays were run according to the manufacturer's recommendations. To detect HMW adiponectin, serum samples were pretreated with a specific protease that selectively digested MMW and LMW adiponectin. We were also able to determine the combined HMW and MMW adiponectin concentrations by pretreating the samples with a protease that specifically digested LMW adiponectin. Maternal serum samples were assayed directly to determine total adiponectin concentrations. Briefly, untreated and pretreated maternal serum samples were incubated in duplicate wells of the micro titer plates, which had been pre-coated with a monoclonal antibody specific for adiponectin. During this incubation any adiponectin present in the standards and untreated or pretreated maternal serum samples was bound by the immobilized antibodies. After repeated washing and aspiration to remove all unbound substances, an enzyme-linked polyclonal antibody specific for adiponectin was added to the wells. Unbound materials were removed with repeated washing and a substrate solution was added to the wells and color developed in proportion to the amount of adiponectin bound in the initial step. The color development was stopped with the addition of an acid solution and the intensity of color was read using a programmable spectrophotometer.

(SpectraMax M2, Molecular Devices, Sunnyvale, CA, USA). The concentration of adiponectin in untreated and treated maternal serum samples was determined by interpolation from individual standard curves composed of human adiponectin. Total, HMW, and HMW-MMW adiponectin concentrations were derived directly from the assay plates. MMW adiponectin concentrations were obtained by subtracting HMW adiponectin value from the combined HMW-MMW value. Finally, the LMW adiponectin value was computed by subtracting HMW and MMW adiponectin values from the total adiponectin values. The calculated inter- and intra-assay coefficients of variation for adiponectin multimers immunoassays in our laboratory were 2.2% and 4.2%. The sensitivity was calculated to be 0.04 ng/mL.

Statistical analysis—Normality of the data was tested using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Serum multimeric adiponectin isoforms concentrations were not normally distributed; thus, non-parametric methods were used to perform the statistical analysis. Correlation between the various adiponectin multimers and gestational age, maternal age, BMI and birthweight was conducted with the Spearman's rank correlation.

Comparison of the median concentration of adiponectin multimers among the gestational age groups was performed by Kruskal-Wallis test with post-hoc analyses with Mann-Whitney *U*-test and Bonferroni correction for the calculated *p*-value in order to maintain the significance level below 0.05. The statistical package used was SPSS 14.0 (SPSS, Inc., Chicago, IL, USA).

Results

Table I displays the maternal demographic and clinical characteristics of all pregnant women according to BMI. Overweight/obese pregnant women were older compared to normal weight pregnant women. There were no significant differences in parity, gestational age at sampling or gestational age at delivery between normal weight and overweight/obese women. Table II displays the maternal demographic and clinical characteristics of normal and overweight/obese according to the different gestational age groups. There were no significant differences in maternal age, parity, BMI or gestational age at delivery between the various gestational age groups.

When all pregnant women were pooled together, total adiponectin concentrations were negatively correlated with gestational age at sampling ($r=-0.11$, $p<0.01$). HMW adiponectin concentrations were negatively correlated with BMI at sampling only in overweight/obese patients ($r=-0.15$, $p=0.01$). HMW/Total adiponectin ratio was negatively correlated with BMI at sampling in both normal weight ($r=-0.10$, $p=0.03$) and overweight/obese ($r=-0.12$, $p=0.04$) pregnant women.

Reference tables of the normal serum adiponectin concentrations for each gestational age, including the 10th, 25th, 50th, 75th and 90th percentiles, in normal weight and overweight/obese pregnant women, are presented in tables III and IV, respectively.

Adiponectin multimers concentrations and relative distribution in non-pregnant vs. pregnant women

When all pregnant women were pooled together (except those in labor), the median maternal concentration of HMW adiponectin was significantly higher in pregnant women than in non-pregnant women (median: 3554 ng/mL, range: 52–17548 ng/mL vs. median: 2812 ng/mL, range: 801–8937 ng/mL; $p=0.01$). Similarly, pregnant women had a higher median HMW/Total adiponectin ratio than non-pregnant women (median: 56.3%, range: 2–88% vs. median: 46.0%, range: 25–81%, respectively; $p<0.01$). In contrast, the median maternal serum concentration of LMW adiponectin was lower in pregnant than non-pregnant women (median: 1235 ng/mL, range: 56–6112 ng/mL vs. median: 1883 ng/mL, range: 766–3976 ng/mL;

$p < 0.01$). The median maternal serum concentrations of total and MMW adiponectin did not differ between the two groups.

The median total adiponectin concentration was comparable between the different gestational age groups. Similarly, the median ratio of HMW, MMW and LMW to total adiponectin did not change significantly with advancing gestation. The median HMW adiponectin concentration was significantly higher than the median concentrations of MMW ($p < 0.01$) and LMW ($p < 0.01$) adiponectin at any gestational age. The median concentrations of MMW and LMW adiponectin did not differ with advancing gestation.

Among non-pregnant women, the median HMW adiponectin concentration was significantly higher than the median concentrations of MMW and LMW adiponectin ($p < 0.01$, for both comparisons), while the median concentration of LMW was significantly higher than the median serum MMW adiponectin concentration ($p < 0.01$) (Figure 1).

Changes in adiponectin multimers serum concentrations of non-pregnant and pregnant women according to BMI

Compared to non-pregnant women, normal weight pregnant women had a higher median concentration of HMW adiponectin (3949 ng/mL, range: 945–17548 ng/mL vs. median: 2812 ng/mL, range: 801–8937 ng/mL; $p < 0.01$) and a lower median concentration of LMW adiponectin (1217 ng/mL, range: 56–6112 ng/mL vs. median: 1883 ng/mL, range: 766–3976 ng/mL; $p < 0.01$). In contrast, overweight/obese patients had a median concentration of LMW adiponectin lower only than non-pregnant women (1260 ng/mL, range: 85–4009 ng/mL vs. median: 1883 ng/mL, range: 766–3976 ng/mL; $p < 0.01$).

Compared to overweight/obese pregnant women, those with normal weight had higher median serum concentrations of total adiponectin (median: 6792 ng/mL, range: 2442–21956 ng/mL vs. median: 5577 ng/mL, range: 2180–16301 ng/mL; $p < 0.01$, Figure 1), HMW adiponectin (median: 3949 ng/mL, range: 945–17548 ng/mL vs. median: 2934 ng/mL, range: 52–11954 ng/mL; $p < 0.01$) and MMW adiponectin (median: 1452 ng/mL, range: 220–5158 ng/mL vs. median: 1280 ng/mL, range: 174–11272 ng/mL; $p < 0.01$, Figure 1). The median concentrations of LMW adiponectin were comparable between normal weight and overweight/obese pregnant women (1217 ng/mL, range: 56–6112 ng/mL vs. 1260 ng/mL, range: 85–4009 ng/mL, respectively; $p = 0.7$).

The ratio between of adiponectin multimers in non-pregnant women and pregnant women

The median HMW/Total adiponectin ratio was higher in normal weight than in overweight/obese pregnant women (median: 0.57, range: 0.33–0.86 vs. median: 0.53, range: 0.02–0.88; $p < 0.01$). This ratio was also higher in overweight/obese patients compared to non-pregnant women (median: 0.53, range: 0.02–0.88 vs. median: 0.46, range: 0.25–0.81; $p < 0.01$) (Figure 2). In contrast, the LMW to total adiponectin ratio was higher in non-pregnant women than in overweight/obese pregnant women (median: 0.33, range: 0.10–0.53 vs. median: 0.21, range: 0.01–0.9; $p < 0.01$) and as well as in the latter group compared to normal weight pregnant (median: 0.21, range: 0.01–0.9 vs. median: 0.19, range: 0.01–0.83; $p < 0.01$) (Figure 2).

Adiponectin multimers concentrations and their relative distribution with advancing gestation in normal and overweight/obese pregnant women

The median maternal serum concentration of total adiponectin was higher in normal weight than overweight/obese women between 11–14 weeks of gestation (median: 6578 ng/mL, range: 3293–18887 ng/mL vs. median: 5831 ng/mL, range: 2180–12554 ng/mL; $p = 0.02$, Figure 3a), 19–22 weeks of gestation (median: 6697 ng/mL, range: 3446–21954 ng/mL vs. median: 5868 ng/mL, range: 2909–14988 ng/mL; $p = 0.01$, Figure 3a) and between 31–34 weeks of gestation

(median: 7304 ng/mL, range: 3415–16504 ng/mL vs. median: 5056 ng/mL, range: 3060–11260 ng/mL; $p=0.01$, Figure 3a)

The median maternal serum concentration of HMW adiponectin was higher in normal weight than in overweight/obese women between 11–14 weeks of gestation (median: 3961 ng/mL, range: 1281–13384 ng/mL vs. median: 2723 ng/mL, range: 412–6584 ng/mL; $p<0.01$, Figure 3b), 19–22 weeks of gestation (median: 3674 ng/mL, range: 1462–17548 ng/mL vs. median: 2795 ng/mL, range: 52–11954 ng/mL; $p<0.01$, Figure 3b), 31–34 weeks of gestation (median: 4084 ng/mL, range: 1553–14196 ng/mL vs. median: 2672 ng/mL, range: 372–7592 ng/mL; $p=0.01$, Figure 3b) and at term (median: 3916 ng/mL, range: 945–7928 ng/mL vs. median: 2946 ng/mL, range: 1423–8589 ng/mL; $p=0.01$, Figure 3b)

The median maternal serum concentration of MMW adiponectin was higher in normal weight than overweight/obese women between 19–22 weeks of gestation (median: 1467 ng/mL, range: 268–4644 ng/mL vs. median: 1171 ng/mL, range: 263–2559 ng/mL; $p<0.01$, Figure 3c) and between 31–34 weeks of gestation MMW adiponectin (1551 ng/mL, range: 552–4227 ng/mL vs. 1204 ng/mL, range: 322–2129 ng/mL; $p<0.01$, Figure 3c). Serum LMW adiponectin did not differ between normal and overweight/obese pregnant women (Figure 3d).

The median maternal HMW/Total adiponectin ratio was higher in normal weight than overweight/obese women between 11–14 weeks of gestation (median: 0.58, range: 0.33–0.76 vs. median: 0.51, range: 0.18–0.81, respectively; $p<0.01$, Figure 4a) and between 19–22 weeks of gestation (median: 0.57, range: 0.4–0.82 vs. 0.52, range: 0.02–0.82, respectively; $p=0.03$, Figure 4b).

The effect of labor on adiponectin multimers concentrations

Women at term in labor had a higher median concentration of HMW adiponectin than women at term not in labor (median: 4051 ng/mL, range: 182–9204 ng/mL vs. median: 3392 ng/mL, range: 945–8589 ng/mL; $p=0.02$, Figure 5). In addition, labor was associated with an increased median HMW/Total adiponectin ratio (58.6%, range: 6–82% vs. 53.9%, range: 34–75%; $p=0.01$) and a decreased LMW to total adiponectin ratio (17.7%, range: 3–83% vs. 20.0%, range: 2–39%, respectively; $p=0.03$).

Among pregnant women at term, in labor and not in labor, the median serum concentration of HMW adiponectin was higher than the median concentrations of LMW ($p<0.01$) and MMW ($p<0.01$) adiponectin. The latter was higher than the median LMW adiponectin concentrations ($p<0.01$) (Figure 5).

Normal weight women at term, not in labor, had a higher median concentration of HMW adiponectin than overweight/obese patients. Among women in labor, those with normal weight had a higher median concentration of total adiponectin (median: 7080 ng/mL, range: 2844–13701 ng/mL vs. median: 5983 ng/mL, range: 2395–11367 ng/mL; $p<0.01$), HMW adiponectin (median: 4405 ng/mL, range: 182–9204 ng/mL vs. median: 3358 ng/mL, range: 1046–8130 ng/mL; $p=0.01$) and MMW adiponectin (median: 1657 ng/mL, range: 288–2772 ng/mL vs. median: 1331 ng/mL, range: 388–2796 ng/mL; $p=0.03$) than overweight/obese women.

Discussion

Principal findings of the study

1) HMW was the most prevalent adiponectin isoform, regardless of gestational age or BMI status; 2) the median HMW adiponectin concentration and HMW/Total adiponectin ratio were significantly higher, and the median LMW adiponectin concentration was lower, in pregnant than in non-pregnant women; 3) among pregnant women, the median concentration of total,

HMW and MMW adiponectin were significantly higher in normal weight compared to overweight/obese women; and 4) the median concentrations of total, MMW and LMW adiponectin as well as their relative distribution were comparable for each gestational age group.

What is the rationale in assessing maternal circulating adiponectin?

Adiponectin is a member of a growing group of peptides and proteins secreted by adipose tissue, termed adipokines. In contrast to the other adipokines whose concentrations increase with the accumulation of fat mass, adiponectin concentrations are lower in overweight/obese and obese patients than in normal weight subjects [38,40,84,167,168]. The insulin sensitizing [115,116,121,169–174], anti-atherogenic [78–80,124,175–178] and the anti-inflammatory [126,179–183] properties of adiponectin have provided a mechanistic basis for the association between adiposity and metabolic complication. Indeed, low adiponectin concentrations were reported in type-2 diabetes mellitus and insulin resistance [115–122,182,184–189], cardiovascular disease [118,190,191] dyslipidemia [70,81,192–198] and atherosclerosis [43, 78,79,123,124,139,175,176,199,200]. Thus, the concept of the protective role of adiponectin has evolved [41,46,201–204].

Several factors prompted the investigation of adiponectin in human pregnancy: 1) the unique combination of its biological properties, including insulin sensitizing [115,116,121,169–174], anti-atherogenic [78–80,124,175–178], anti-inflammatory [126,179–183] and anti-angiogenic [130,131,205–207] effects; 2) physiologic adaptation to pregnancy is characterized by insulin resistance [1–12,14] and a remarkable fat depot [208–213]; and 3) the association between insulin resistance and increased adipose depots as well as angiogenesis in common pregnancy complications such as gestational diabetes [29,210,214–217] and preeclampsia [217–224].

The role of adiponectin in human pregnancy

A solid body of evidence supports the role of adiponectin in normal gestation and pregnancy complications: 1) circulating maternal adiponectin concentrations correlate with insulin resistance indices during pregnancy [25,64–66]; 2) patients with GDM have a lower concentrations of adiponectin compared to those without GDM [90,92–94,96]; 3) women with adiponectin concentrations less than 6.4 µg/ml in first or early second trimester experienced a 4.6-fold increased risk of GDM, compared to those with higher concentrations [95]; 4) overweight/obese pregnant patients have lower adiponectin concentrations than normal weight pregnant women [84]; 5) preeclampsia is associated with altered maternal adiponectin concentrations. Both higher [101,104–109] and lower [102,225,226] adiponectin concentrations in patients with preeclampsia compared to normal pregnant women were reported. Collectively, these findings suggest that adiponectin plays a regulatory role in metabolic and vascular complications of pregnancy.

Multimerization as a method of regulation: adiponectin isoforms regulate its pleiotropic effects

The structural diversity of adiponectin multimers has been proposed to be associated with its pleiotropic effects. Structurally, adiponectin belongs to the complement 1q family, which is known to form characteristic multimers [227–229]. This adipokine undergoes post-translational modification [230–231] within adipocytes into multimeric forms, including: LMW trimers, MMW hexamers, and HMW oligomers (12–18 monomers) [44,45,132,133, 136,138,232]. The multimeric forms do not interchange with each other after secretion, neither *in-vivo*, nor *in vitro* [136]. It has been suggested that the various adiponectin isoforms have distinct biological activities: 1) *in vitro*, HMW and MMW adiponectin have pro-inflammatory properties such as induction of IL-6 from human monocytes and activation of nuclear factor (NF)-κB [138,233–235], whereas LMW adiponectin inhibits the release of IL-6 [160,236], a

pro-inflammatory cytokine and increase the secretion of IL-10 [236], an anti-inflammatory cytokine. In addition, only HMW adiponectin has been shown to suppress apoptosis of endothelial cells [139]; 2) MMW and HMW can activate NF- κ B, while LMW adiponectin activates AMP-activated protein kinase (AMPK) in skeletal muscle [138]. These findings represent a novel paradigm where multimerization state of a hormone can regulate a specific signal; 3) administration of HMW, but not LMW, adiponectin multimers to adiponectin knockout mice, results in a dose-dependent reduction in serum glucose concentrations [137]; 4) mutations in the collagen domain are associated with type-2 diabetes mellitus and extremely low concentrations of HMW adiponectin [117,133,237]; 5) the serum HMW/Total adiponectin ratio has a better correlation with insulin resistance indices (e.g. HOMA-IR) compared to total adiponectin concentrations and the HMW/Total adiponectin ratio was lower in patients with diabetes compared to non-diabetic subjects [137,139,142,144,146,157]; 6) absolute concentrations of HMW adiponectin have a better correlation with metabolic indices (e.g. HDL cholesterol, total cholesterol concentrations), and endothelial dysfunction than total adiponectin [135,155,165,238,239]. Thus, HMW adiponectin concentrations may be the superior biomarker for insulin resistance and the metabolic syndrome; and 7) weight reduction and treatment with insulin sensitizing drugs (e.g. thiazolidinedione) preferentially elevates the HMW adiponectin concentrations compared to the other two isoforms [137,139,140] or to total adiponectin concentration [149,150,152]. In addition, re-feeding of patients with anorexia nervosa was associated with a decrease in HMW adiponectin concentrations [158,240].

Collectively, these data suggest that multimerization of adiponectin plays an important role in its metabolic and anti-inflammatory functions. In addition, those reports highlight the importance of the relative distribution of adiponectin multimers as more precise determinant governing adiponectin's protective properties against metabolic, inflammatory, and atherogenic disorders.

Determination of circulating adiponectin multimers - The pros and cons of the available methods

Several methods have been developed to identify and measure the various adiponectin isoforms such as gel filtration chromatography [38,132,136] and SDS-PAGE [133,137,138]. Recently, an ELISA assay specific to adiponectin multimers has been developed [241–243]. ELISA has several advantages over the previously used methods: 1) formerly, determination of circulating adiponectin multimers were only semi-quantitative and required size fraction by velocity sedimentation followed by SDS-PAGE and Western blotting [135,137,139,155,244]; 2) although reproducible, those methods are time consuming and laborious and thus essentially precludes clinical implantation of their use. The use of ELISA, on the other hand, is accurate and negates the need for arduous laboratory work [241–243]. The current literature indicates that adiponectin isoforms differ in their biological activity. Therefore, to better understand the effects of this hormone, not only the absolute amount but also the distribution of its isoforms has to be considered. Applications of the measurements of the different adiponectin isoforms in maternal circulation have been limited, mostly due to the lack of high-throughput assays. However, the new ELISA assays provide a potential solution to this limitation.

Human pregnancy is characterized by quantitative and qualitative alterations in adiponectin concentration

Only a handful of studies have addressed the maternal adiponectin multimers concentrations and their relative distribution [25,162–165]. Catalano et al. [25] conducted a longitudinal study in which total, HMW and LMW adiponectin were measured in 10 normal lean women, before pregnancy, in both early (12–14 weeks) and in late gestation (34–36 weeks). The authors reported that maternal circulating HMW adiponectin and HMW/Total adiponectin ratio were lower in late gestation than in non-pregnant state, and that there were no significant differences

in circulating adiponectin multimers between early and late gestation. Ong et al.[162] found a negative correlation between third trimester HMW/Total adiponectin ratio and birthweight in 58 patients. In addition, changes in maternal adiponectin multimers concentrations were reported in complications of pregnancy. Retnakaran et al.[165] reported a lower HMW adiponectin concentration in patients with GDM (n=41) compared to third trimester normal pregnant women (n=80). In study conducted by the same group [163] the HMW/Total adiponectin ratio, measured between 28 to 31 weeks of gestation, was decreased in pregnant women of Indo-Asian descent (n=30) as compared to Caucasian women (n=65). Takemura et al. [164] described a higher maternal concentration of HMW adiponectin and an elevated HMW/Total adiponectin ratio in patients with preeclampsia (n=14) than in normal pregnant women (n=14). Of note, ELISA assay was used only the latter study.

The findings reported herein are in accordance with previous studies [65,84,102,245] in which total adiponectin concentration did not differ between pregnant and non-pregnant women. However, our results indicate that pregnancy is associated with a higher median HMW adiponectin concentration and HMW/Total adiponectin ratio, as well as a lower median LMW adiponectin concentration as compared to the non-pregnant state. The discrepancy in the findings reported herein and those previously reported [25] may result from differences in the study design, the definition of adiponectin multimers, and the methods to determine serum adiponectin isoforms. In particular, our study was cross-sectional, included a large number of women at a wide range of gestational ages, both lean and overweight/obese, determined the adiponectin total concentrations and its isoforms by ELISA assay and distinguished in the analysis between MMW and LMW adiponectin isoforms.

Human pregnancy is characterized by a shift from LMW adiponectin to HMW adiponectin species

The increase in the median HMW adiponectin concentration and the median HMW/Total adiponectin ratio and the parallel decrease in the median LMW adiponectin concentration in pregnant than in non-pregnant women are novel. There can be several explanations for these findings:

1. Compensatory reaction to metabolic alterations of pregnancy—The shift from LMW adiponectin to HMW adiponectin and the consequently higher HMW/Total adiponectin ratio in pregnant than in non-pregnant state may represent a compensatory response. Human pregnancy can be viewed as a *forme frusta* of the metabolic syndrome, as the maternal physiological adaptation to normal pregnancy includes core components of this conditions including: weight gain and increase in fat deposition [25,208–213], hyperlipidemia [246–249] and insulin resistance [1–14]. The current literature indicates that HMW adiponectin has a prominent protective role, particularly against metabolic complications such as insulin resistance [137,142,144,146,155,157,239] and hyperlipidemia [135,152,238]. Total adiponectin concentrations are comparable between non-pregnant and pregnant women. However, gestation is characterized by a shift from a less active (LMW) to a more active isoform (HMW) of adiponectin suggesting that the higher HMW adiponectin concentrations may be a counter-regulatory response to the metabolic changes (e.g. insulin resistance, hyperlipidemia) associated with a normal pregnancy.

2. Adipogenesis during pregnancy favors production and secretion of HMW adiponectin—An alternative explanation for the elevated HMW adiponectin observed in women with normal pregnancy can be the significant weight gain and increased fat depot that accompanies normal gestation [25,208–213]. Previously, the mechanism for increased fat mass in normal and obese individuals was attributed exclusively to adipocyte hypertrophy; however, adipose tissue accretion during pregnancy is now known to be associated also with adipocyte

hyperplasia [250–255]. This finding is supported by reports demonstrating the effect of peroxisome proliferator-activated receptor (PPAR)- γ agonist on adipose tissue. Treatment with PPAR- γ agonist (e.g. Thiazolidinediones), results in distinct increase in the number of newly differentiated small adipocytes [256], as well as body weight gain, and increase serum adiponectin concentrations [232,257–263]. Treatment with PPAR- γ agonist (in mice and human) has resulted in a decreased insulin resistance and a dramatic increase in circulating adiponectin concentration, mostly due to the elevation in HMW adiponectin [137,140]. In conclusion, adipogenesis can contribute to the shift towards HMW adiponectin in pregnant women. It is important to note in this context that the major role of the HMW multimers has been highlighted in the context of the effect of PPAR- γ .

Adiponectin multimers concentrations and advancing gestation

When normal weight and overweight/obese patients were pooled together, the median total adiponectin concentration, the median concentration of adiponectin multimers and their relative distribution did not change with advancing gestational age. HMW adiponectin was the most prevalent adiponectin species regardless of gestational age or BMI. These findings are in agreement with the report by Catalano et al. [25] in which maternal HMW and LMW adiponectin concentrations did not differ between 12–14 and 34–36 weeks of gestation. This present study extends the available data by showing comparable concentrations of adiponectin concentrations with advancing gestation. Moreover, the nomogram (Tables III and IV) presented herein should be beneficial to those investigating the intriguing relationships between adiponectin multimers and human pregnancy.

The perils of portliness - maternal overweight/obese is associated with decreased HMW adiponectin

The contribution of excess body weight to the concentration of adiponectin multimers and their relative distribution by comparing the concentrations of adiponectin species in normal weight and overweight/obese pregnant women is reported herein. Consistent with the non pregnant state [38,40,84,167,168], normal weight pregnant women had a higher median total, HMW and MMW adiponectin concentrations than overweight/obese patients. In contrast to normal weight pregnant women who had a higher HMW adiponectin than non-pregnant subjects, median concentration of HMW adiponectin was comparable between overweight/obese pregnant patients and non-pregnant women. The median HMW/Total adiponectin ratio was significantly higher in normal weight than in overweight/obese pregnant women. In addition, overweight/obese pregnant women had a distinct median concentration and relative distribution of adiponectin multimers with advancing gestation between 11–14, 19–22 and 31–34 weeks of gestation and at term. Specifically, a higher median concentration of HMW and MMW adiponectin was detected in normal weight than in overweight/obese pregnant women.

Lower concentrations of total adiponectin in overweight/obese pregnant women have been recently reported by our group [84]. The results of the current study are also in agreement with previous reports regarding decreased total adiponectin concentrations in overweight/obese and obese non-pregnant patients [38,40]. Contrary to other adipokines (e.g. leptin, TNF- α , and resistin), mRNA expression and serum concentrations of adiponectin are paradoxically lower in overweight/obese and obese than in normal weight individuals [38,40,120]; moreover, weight reduction is associated with an increase in circulating total [72,74,2264–267] and HMW adiponectin concentrations [135,149,264]. In addition to obesity, the inverse relationship between this hormone and body weight is upheld in extremely lean subjects with anorexia nervosa [158,26–270]. Taken together, these findings suggest that excess adipose tissue exerts a negative feedback on adiponectin production and/or secretion and regulates the relative distribution of its multimers. The current study extends the heretofore studies by analyzing both the absolute and the relative distribution of HMW, MMW and LMW adiponectin

concentrations in the setting of normal weight and overweight/obese pregnant women with advancing gestation and in labor.

In conclusion, the current report provides a comprehensive assessment of the ratio between the different adiponectin multimers concentrations in the maternal circulation during normal human pregnancy. Comparison of adiponectin species between non-pregnant and pregnant women, normal weight and overweight/obese patients revealed quantitative and qualitative changes suggesting that adiponectin multimers, especially its most active isoform, HMW adiponectin, play a role in the metabolic changes associated with pregnancy. Moreover, these findings, along with the nomograms presented herein, lay the groundwork for further studies addressing the complex and intriguing relationships between body weight, adiponectin and metabolic pathways in human pregnancy.

Acknowledgments

This research was supported in part by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

Reference List

1. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am J Obstet Gynecol* 1990;162:1008–1014. [PubMed: 2183610]
2. Burt RL. Peripheral utilization of glucose in pregnancy. III. Insulin tolerance. *Obstet Gynecol* 1956;7:658–664. [PubMed: 13322368]
3. Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. *Am J Clin Nutr* 2000;71:1256S–1261S. [PubMed: 10799399]
4. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol* 1991;165:1667–1672. [PubMed: 1750458]
5. Catalano PM, Roman-Drago NM, Amini SB, Sims EA. Longitudinal changes in body composition and energy balance in lean women with normal and abnormal glucose tolerance during pregnancy. *Am J Obstet Gynecol* 1998;179:156–165. [PubMed: 9704782]
6. Fisher PM, Sutherland HW, Bewsher PD. The insulin response to glucose infusion in normal human pregnancy. *Diabetologia* 1980;19:15–20. [PubMed: 6993263]
7. Kuhl C. Glucose metabolism during and after pregnancy in normal and gestational diabetic women. 1. Influence of normal pregnancy on serum glucose and insulin concentration during basal fasting conditions and after a challenge with glucose. *Acta Endocrinol(Copenh)* 1975;79:709–719. [PubMed: 1173969]
8. Langer O, Anyaegbunam A, Brustman L, Guidetti D, Mazze R. Gestational diabetes: insulin requirements in pregnancy. *Am J Obstet Gynecol* 1987;157:669–675. [PubMed: 3307425]
9. Lind T, Bell S, Gilmore E, Huisjes HJ, Schally AV. Insulin disappearance rate in pregnant and non-pregnant women, and in non-pregnant women given GHRH. *Eur J Clin Invest* 1977;7:47–52. [PubMed: 402276]
10. Phelps RL, Metzger BE, Freinkel N. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of serum glucose, insulin, free fatty acids, triglycerides, cholesterol, and individual amino acids in late normal pregnancy. *Am J Obstet Gynecol* 1981;140:730–736. [PubMed: 7020420]
11. Reece EA, Homko C, Wiznitzer A. Metabolic changes in diabetic and nondiabetic subjects during pregnancy. *Obstet Gynecol Surv* 1994;49:64–71. [PubMed: 8134054]
12. Ryan EA, O'Sullivan MJ, Skyler JS. Insulin action during pregnancy. Studies with the euglycemic clamp technique. *Diabetes* 1985;34:380–389. [PubMed: 3882502]
13. Spellacy WN, Goetz FC, Greenberg BZ, Ellis J. Serum Insulin in Normal “Early” Pregnancy. *Obstet Gynecol* 1965;25:862–865. [PubMed: 14287481]

14. Coustan DR, Carpenter MW. The diagnosis of gestational diabetes. *Diabetes Care* 1998;21 (Suppl 2):B5–B8. [PubMed: 9704220]
15. Buchanan TA, Xiang AH. Gestational diabetes mellitus. *J Clin Invest* 2005;115:485–491. [PubMed: 15765129]
16. Kuhl C. Aetiology of gestational diabetes. *Baillieres Clin Obstet Gynaecol* 1991;5:279–292. [PubMed: 1954714]
17. Ryan EA. Hormones and insulin resistance during pregnancy. *Lancet* 2003;362:1777–1778. [PubMed: 14654313]
18. Barbour LA, Shao J, Qiao L, Pulawa LK, Jensen DR, Bartke A, Garrity M, Draznin B, Friedman JE. Human placental growth hormone causes severe insulin resistance in transgenic mice. *Am J Obstet Gynecol* 2002;186:512–517. [PubMed: 11904616]
19. Beck P. Progestin enhancement of the serum insulin response to glucose in Rhesus monkeys. *Diabetes* 1969;18:146–152. [PubMed: 4974771]
20. Kalkhoff RK, Richardson BL, Beck P. Relative effects of pregnancy, human placental lactogen and prednisolone on carbohydrate tolerance in normal and subclinical diabetic subjects. *Diabetes* 1969;18:153–163. [PubMed: 5386597]
21. Kalkhoff RK, Jacobson M, Lemper D. Progesterone, pregnancy and the augmented serum insulin response. *J Clin Endocrinol Metab* 1970;31:24–28. [PubMed: 4316582]
22. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ. Induction of insulin resistance by androgens and estrogens. *J Clin Endocrinol Metab* 1994;79:265–271. [PubMed: 8027240]
23. Ryan EA, Enns L. Role of gestational hormones in the induction of insulin resistance. *J Clin Endocrinol Metab* 1988;67:341–347. [PubMed: 3292560]
24. Samaan N, Yen SC, Gonzalez D, Pearson OH. Metabolic effects of placental lactogen (HPL) in man. *J Clin Endocrinol Metab* 1968;28:485–491. [PubMed: 5643868]
25. Catalano PM, Hoegh M, Minium J, Huston-Presley L, Bernard S, Kalhan S, Hauguel-De Mouzon S. Adiponectin in human pregnancy: implications for regulation of glucose and lipid metabolism. *Diabetologia* 2006;49:1677–1685. [PubMed: 16752186]
26. Gimeno RE, Klamon LD. Adipose tissue as an active endocrine organ: recent advances. *Curr Opin Pharmacol* 2005;5:122–128. [PubMed: 15780819]
27. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science* 1993;259:87–91. [PubMed: 7678183]
28. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444:860–867. [PubMed: 17167474]
29. Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. *Am J Med Sci* 2005;330:280–289. [PubMed: 16355012]
30. Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest* 2000;106:473–481. [PubMed: 10953022]
31. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006;444:840–846. [PubMed: 17167471]
32. Matsuzawa Y, Funahashi T, Nakamura T. Molecular mechanism of metabolic syndrome X: contribution of adipocytokines adipocyte-derived bioactive substances. *Ann N Y Acad Sci* 1999;892:146–154. [PubMed: 10842660]
33. Montague CT, O’Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. *Diabetes* 2000;49:883–888. [PubMed: 10866038]
34. Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. *Cell* 2001;104:531–543. [PubMed: 11239410]
35. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;6:772–783. [PubMed: 16998510]
36. Trayhurn P. Endocrine and signalling role of adipose tissue: new perspectives on fat. *Acta Physiol Scand* 2005;184:285–293. [PubMed: 16026420]
37. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005;115:1111–1119. [PubMed: 15864338]

38. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999;257:79–83. [PubMed: 10092513]
39. Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. *Trends Endocrinol Metab* 2002;13:84–89. [PubMed: 11854024]
40. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem* 1996;271:10697–10703. [PubMed: 8631877]
41. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 2006;116:1784–1792. [PubMed: 16823476]
42. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). *Biochem Biophys Res Commun* 1996;221:286–289. [PubMed: 8619847]
43. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2004;24:29–33. [PubMed: 14551151]
44. Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human serum. *J Biochem(Tokyo)* 1996;120:803–812. [PubMed: 8947845]
45. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995;270:26746–26749. [PubMed: 7592907]
46. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res* 2005;96:939–949. [PubMed: 15890981]
47. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 1995;269:546–549. [PubMed: 7624778]
48. Farooqi IS, Keogh JM, Kamath S, Jones S, Gibson WT, Trussell R, Jebb SA, Lip GY, O’Rahilly S. Partial leptin deficiency and human adiposity. *Nature* 2001;414:34–35. [PubMed: 11689931]
49. Friedman JM. Obesity in the new millennium. *Nature* 2000;404:632–634. [PubMed: 10766249]
50. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the serum protein encoded by the obese gene. *Science* 1995;269:543–546. [PubMed: 7624777]
51. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* 1995;269:540–543. [PubMed: 7624776]
52. Argiles JM, Lopez-Soriano J, Busquets S, Lopez-Soriano FJ. Journey from cachexia to obesity by TNF. *FASEB J* 1997;11:743–751. [PubMed: 9271359]
53. Hotamisligil GS. The role of TNFalpha and TNF receptors in obesity and insulin resistance. *J Intern Med* 1999;245:621–625. [PubMed: 10395191]
54. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* 1997;389:610–614. [PubMed: 9335502]
55. Wang B, Jenkins JR, Trayhurn P. Expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture: integrated response to TNF-alpha. *Am J Physiol Endocrinol Metab* 2005;288:E731–E740. [PubMed: 15562246]
56. Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, Qi Y, Wang J, Rajala MW, Pocai A, Scherer PE, et al. Regulation of fasted blood glucose by resistin. *Science* 2004;303:1195–1198. [PubMed: 14976316]
57. Holcomb IN, Kabakoff RC, Chan B, Baker TW, Gurney A, Henzel W, Nelson C, Lowman HB, Wright BD, Skelton NJ, et al. FIZZ1, a novel cysteine-rich secreted protein associated with pulmonary inflammation, defines a new gene family. *EMBO J* 2000;19:4046–4055. [PubMed: 10921885]
58. Kim KH, Lee K, Moon YS, Sul HS. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. *J Biol Chem* 2001;276:11252–11256. [PubMed: 11278254]
59. Kusminski CM, McTernan PG, Kumar S. Role of resistin in obesity, insulin resistance and Type II diabetes. *Clin Sci(Lond)* 2005;109:243–256. [PubMed: 16104844]

60. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. *Nature* 2001;409:307–312. [PubMed: 11201732]
61. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006;444:881–887. [PubMed: 17167477]
62. Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. *Nature* 2006;444:847–853. [PubMed: 17167472]
63. Kirwan JP, Hauguel-De Mouzon S, Lepercq J, Challier JC, Huston-Presley L, Friedman JE, Kalhan SC, Catalano PM. TNF-alpha is a predictor of insulin resistance in human pregnancy. *Diabetes* 2002;51:2207–2213. [PubMed: 12086951]
64. Lopez-Bermejo A, Fernandez-Real JM, Garrido E, Rovira R, Brichs R, Genaro P, Bach C, Cabrero D, Kihara S, Funahashi T, et al. Maternal soluble tumour necrosis factor receptor type 2 (sTNFR2) and adiponectin are both related to blood pressure during gestation and infant's birthweight. *Clin Endocrinol(Oxf)* 2004;61:544–552. [PubMed: 15521955]
65. McLachlan KA, O'Neal D, Jenkins A, Alford FP. Do adiponectin, TNFalpha, leptin and CRP relate to insulin resistance in pregnancy? Studies in women with and without gestational diabetes, during and after pregnancy. *Diabetes Metab Res Rev* 2006;22:131–138. [PubMed: 16170833]
66. Retnakaran R, Hanley AJ, Raif N, Connelly PW, Sermer M, Zinman B. Reduced adiponectin concentration in women with gestational diabetes: a potential factor in progression to type 2 diabetes. *Diabetes Care* 2004;27:799–800. [PubMed: 14988306]
67. Silha JV, Krsek M, Skrha JV, Sucharda P, Nyomba BL, Murphy LJ. Serum resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. *Eur J Endocrinol* 2003;149:331–335. [PubMed: 14514348]
68. Steppan CM, Lazar MA. Resistin and obesity-associated insulin resistance. *Trends Endocrinol Metab* 2002;13:18–23. [PubMed: 11750858]
69. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005;365:1333–1346. [PubMed: 15823385]
70. Farvid MS, Ng TW, Chan DC, Barrett PH, Watts GF. Association of adiponectin and resistin with adipose tissue compartments, insulin resistance and dyslipidaemia. *Diabetes Obes Metab* 2005;7:406–413. [PubMed: 15955127]
71. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000;11:327–332. [PubMed: 10996528]
72. Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Giugliano D. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003;289:1799–1804. [PubMed: 12684358]
73. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev* 2007;8:21–34. [PubMed: 17212793]
74. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, Chuang LM. Weight reduction increases serum levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 2001;86:3815–3819. [PubMed: 11502817]
75. Frayn KN. Obesity and metabolic disease: is adipose tissue the culprit? *Proc. Nutr Soc* 2005;64:7–13.
76. Gable DR, Hurel SJ, Humphries SE. Adiponectin and its gene variants as risk factors for insulin resistance, the metabolic syndrome and cardiovascular disease. *Atherosclerosis* 2006;188:231–244. [PubMed: 16581078]
77. Okamoto Y, Arita Y, Nishida M, Muraguchi M, Ouchi N, Takahashi M, Igura T, Inui Y, Kihara S, Nakamura T, et al. An adipocyte-derived serum protein, adiponectin, adheres to injured vascular walls. *Horm Metab Res* 2000;32:47–50. [PubMed: 10741683]
78. Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, Ohashi K, Sakai N, Shimomura I, Kobayashi H, et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 2002;106:2767–2770. [PubMed: 12451000]
79. Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, Ishigami M, Kuriyama H, Kishida K, Nishizawa H, et al. Adipocyte-derived serum protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 2001;103:1057–1063. [PubMed: 11222466]

80. Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, Kumada M, Ohashi K, Okamoto Y, Nishizawa H, et al. Association of hypoadiponectinemia with impaired vasoreactivity. *Hypertension* 2003;42:231–234. [PubMed: 12860835]
81. Unger RH. Hyperleptinemia: protecting the heart from lipid overload. *Hypertension* 2005;45:1031–1034. [PubMed: 15897372]
82. Mazaki-Tovi S, Kanety H, Sivan E. Adiponectin and human pregnancy. *Curr Diab Rep* 2005;5:278–281. [PubMed: 16033679]
83. Mazaki-Tovi S, Kanety H, Pariente C, Hemi R, Wiser A, Schiff E, Sivan E. Maternal serum adiponectin levels during human pregnancy. *J Perinatol* 2007;27:77–81. [PubMed: 17262038]
84. Nien JK, Mazaki-Tovi S, Romero R, Erez O, Kusanovic JP, Gotsch F, Pineles BL, Gomez R, Edwin S, Mazor M, et al. Plasma adiponectin concentrations in non-pregnant, normal and overweight pregnant women. *J Perinat Med* 2007;35(6):522–31. [PubMed: 17919116]
85. Sivan E, Mazaki-Tovi S, Pariente C, Efraty Y, Schiff E, Hemi R, Kanety H. Adiponectin in human cord blood: relation to fetal birth weight and gender. *J Clin Endocrinol Metab* 2003;88:5656–5660. [PubMed: 14671149]
86. Nien JK, Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Gotsch F, Pineles BL, Friel LA, Espinoza J, Goncalves L, et al. Resistin: a hormone which induces insulin resistance is increased in normal pregnancy. *J Perinat Med* 2007;35(6):513–21. [PubMed: 17919114]
87. Fasshauer M, Kralisch S, Klier M, Lossner U, Bluher M, Klein J, Paschke R. Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* 2003;301:1045–1050. [PubMed: 12589818]
88. Malamitsi-Puchner A, Briana DD, Boutsikou M, Kouskouni E, Hassiakos D, Gourgiotis D. Perinatal circulating visfatin levels in intrauterine growth restriction. *Pediatrics* 2007;119:e1314–e1318. [PubMed: 17502346]
89. Sagawa N, Yura S, Itoh H, Mise H, Kakui K, Korita D, Takemura M, Nuamah MA, Ogawa Y, Masuzaki H, et al. Role of leptin in pregnancy--a review. *Placenta* 2002;23 (Suppl A):S80–S86. [PubMed: 11978063]
90. Ategbro JM, Grissa O, Yessoufou A, Hichami A, Dramane KL, Moutairou K, Miled A, Grissa A, Jerbi M, Tabka Z, et al. Modulation of adipokines and cytokines in gestational diabetes and macrosomia. *J Clin Endocrinol Metab* 2006;91:4137–4143. [PubMed: 16849405]
91. Kautzky-Willer A, Pacini G, Tura A, Biegelmayer C, Schneider B, Ludvik B, Prager R, Waldhausl W. Increased plasma leptin in gestational diabetes. *Diabetologia* 2001;44:164–172. [PubMed: 11270672]
92. Kinalski M, Telejko B, Kuzmicki M, Kretowski A, Kinalska I. Tumor necrosis factor alpha system and plasma adiponectin concentration in women with gestational diabetes. *Horm Metab Res* 2005;37:450–454. [PubMed: 16034719]
93. Ranheim T, Haugen F, Staff AC, Braekke K, Harsem NK, Drevon CA. Adiponectin is reduced in gestational diabetes mellitus in normal weight women. *Acta Obstet Gynecol Scand* 2004;83:341–347. [PubMed: 15005780]
94. Thyfault JP, Hedberg EM, Anchan RM, Thorne OP, Isler CM, Newton ER, Dohm GL, deVente JE. Gestational diabetes is associated with depressed adiponectin levels. *J Soc Gynecol Investig* 2005;12:41–45.
95. Williams MA, Qiu C, Muy-Rivera M, Vadachkoria S, Song T, Luthy DA. Serum adiponectin concentrations in early pregnancy and subsequent risk of gestational diabetes mellitus. *J Clin Endocrinol Metab* 2004;89:2306–2311. [PubMed: 15126557]
96. Worda C, Leipold H, Gruber C, Kautzky-Willer A, Knofler M, Bancher-Todesca D. Decreased serum adiponectin concentrations in women with gestational diabetes mellitus. *Am J Obstet Gynecol* 2004;191:2120–2124. [PubMed: 15592301]
97. Lewandowski KC, Stojanovic N, Press M, Tuck SM, Szosland K, Bienkiewicz M, Vatish M, Lewinski A, Prelevic GM, Randeva HS. Elevated serum levels of visfatin in gestational diabetes: a comparative study across various degrees of glucose tolerance. *Diabetologia* 2007;50:1033–1037. [PubMed: 17334748]

98. Chan TF, Chen YL, Lee CH, Chou FH, Wu LC, Jong SB, Tsai EM. Decreased serum visfatin concentrations in women with gestational diabetes mellitus. *J Soc Gynecol Investig* 2006;13:364–367.
99. Haider DG, Handisurya A, Storka A, Vojtassakova E, Luger A, Pacini G, Tura A, Wolzt M, Kautzky-Willer A. Visfatin response to glucose is reduced in women with gestational diabetes mellitus. *Diabetes Care* 2007;30:1889–1891. [PubMed: 17416788]
100. Krzyzanowska K, Krugluger W, Mittermayer F, Rahman R, Haider D, Shnawa N, Schernthaner G. Increased visfatin concentrations in women with gestational diabetes mellitus. *Clin Sci(Lond)* 2006;110:605–609. [PubMed: 16489932]
101. Nien JK, Mazaki-Tovi S, Romero R, Erez O, Kusanovic JP, Gotsch F, Pineles BL, Gomez R, Edwin S, Mazor M, et al. Adiponectin in severe preeclampsia. *J Perinat Med* 2007;36(6):503–12. [PubMed: 17919115]
102. Cortelazzi D, Corbetta S, Ronzoni S, Pelle F, Marconi A, Cozzi V, Cetin I, Cortelazzi R, Beck-Peccoz P, Spada A. Maternal and foetal resistin and adiponectin concentrations in normal and complicated pregnancies. *Clin Endocrinol(Oxf)* 2007;66:447–453. [PubMed: 17302882]
103. D'Anna R, Baviera G, Corrado F, Giordano D, De Vivo A, Nicocia G, Di Benedetto A. Adiponectin and insulin resistance in early- and late-onset pre-eclampsia. *BJOG* 2006;113:1264–1269. [PubMed: 17010118]
104. Haugen F, Ranheim T, Harsem NK, Lips E, Staff AC, Drevon CA. Increased plasma levels of adipokines in preeclampsia: relationship to placenta and adipose tissue gene expression. *Am J Physiol Endocrinol Metab* 2006;290:E326–E333. [PubMed: 16144822]
105. Hendler I, Blackwell SC, Mehta SH, Whitty JE, Russell E, Sorokin Y, Cotton DB. The levels of leptin, adiponectin, and resistin in normal weight, overweight and obese pregnant women with and without preeclampsia. *Am J Obstet Gynecol* 2005;193:979–983. [PubMed: 16157097]
106. Kajantie E, Kaaja R, Ylikorkala O, Andersson S, Laivuori H. Adiponectin concentrations in maternal serum: elevated in preeclampsia but unrelated to insulin sensitivity. *J Soc Gynecol Investig* 2005;12:433–439.
107. Lu D, Yang X, Wu Y, Wang H, Huang H, Dong M. Serum adiponectin, leptin and soluble leptin receptor in pre-eclampsia. *Int J Gynaecol Obstet* 2006;95(2):121–6. [PubMed: 16919629]
108. Naruse K, Yamasaki M, Umekage H, Sado T, Sakamoto Y, Morikawa H. Peripheral blood concentrations of adiponectin, an adipocyte-specific plasma protein, in normal pregnancy and preeclampsia. *J Reprod Immunol* 2005;65:65–75. [PubMed: 15694968]
109. Ramsay JE, Jamieson N, Greer IA, Sattar N. Paradoxical elevation in adiponectin concentrations in women with preeclampsia. *Hypertension* 2003;42:891–894. [PubMed: 14517227]
110. Tsuchida A, Yamauchi T, Ito Y, Hada Y, Maki T, Takekawa S, Kamon J, Kobayashi M, Suzuki R, Hara K, et al. Insulin/Foxo1 pathway regulates expression levels of adiponectin receptors and adiponectin sensitivity. *J Biol Chem* 2004;279:30817–30822. [PubMed: 15123605]
111. McCarthy JF, Misra DN, Roberts JM. Maternal plasma leptin is increased in preeclampsia and positively correlates with fetal cord concentration. *Am J Obstet Gynecol* 1999;180:731–736. [PubMed: 10076155]
112. Schiff E, Friedman SA, Baumann P, Sibai BM, Romero R. Tumor necrosis factor-alpha in pregnancies associated with preeclampsia or small-for-gestational-age newborns. *Am J Obstet Gynecol* 1994;170:1224–1229. [PubMed: 8178841]
113. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004;89:2548–2556. [PubMed: 15181022]
114. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood* 2000;96:1723–1732. [PubMed: 10961870]
115. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001;7:947–953. [PubMed: 11479628]
116. Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid

- oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci USA* 2001;98:2005–2010. [PubMed: 11172066]
117. Hara K, Boutin P, Mori Y, Tobe K, Dina C, Yasuda K, Yamauchi T, Otabe S, Okada T, Eto K, et al. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes* 2002;51:536–540. [PubMed: 11812766]
 118. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000;20:1595–1599. [PubMed: 10845877]
 119. Kissebah AH, Sonnenberg GE, Myklebust J, Goldstein M, Broman K, James RG, Marks JA, Krakower GR, Jacob HJ, Weber J, et al. Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. *Proc Natl Acad Sci USA* 2000;97:14478–14483. [PubMed: 11121050]
 120. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001;86:1930–1935. [PubMed: 11344187]
 121. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med* 2001;7:941–946. [PubMed: 11479627]
 122. Zacharova J, Chiasson JL, Laakso M. The common polymorphisms (single nucleotide polymorphism [SNP] +45 and SNP +276) of the adiponectin gene predict the conversion from impaired glucose tolerance to type 2 diabetes: the STOP-NIDDM trial. *Diabetes* 2005;54:893–899. [PubMed: 15734870]
 123. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived serum protein adiponectin. *Circulation* 1999;100:2473–2476. [PubMed: 10604883]
 124. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, et al. Adiponectin, an adipocyte-derived serum protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* 2000;102:1296–1301. [PubMed: 10982546]
 125. Kazumi T, Kawaguchi A, Sakai K, Hirano T, Yoshino G. Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure. *Diabetes Care* 2002;25:971–976. [PubMed: 12032101]
 126. Iwashima Y, Katsuya T, Ishikawa K, Ouchi N, Ohishi M, Sugimoto K, Fu Y, Motone M, Yamamoto K, Matsuo A, et al. Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension* 2004;43:1318–1323. [PubMed: 15123570]
 127. Matsushita K, Yatsuya H, Tamakoshi K, Wada K, Otsuka R, Takefuji S, Sugiura K, Kondo T, Murohara T, Toyoshima H. Comparison of circulating adiponectin and proinflammatory markers regarding their association with metabolic syndrome in Japanese men. *Arterioscler Thromb Vasc Biol* 2006;26:871–876. [PubMed: 16456090]
 128. Matsubara M, Maruoka S, Katayose S. Decreased plasma adiponectin concentrations in women with dyslipidemia. *J Clin Endocrinol Metab* 2002;87:2764–2769. [PubMed: 12050247]
 129. Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005;353:2121–2134. [PubMed: 16291982]
 130. Ouchi N, Kobayashi H, Kihara S, Kumada M, Sato K, Inoue T, Funahashi T, Walsh K. Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells. *J Biol Chem* 2004;279:1304–1309. [PubMed: 14557259]
 131. Shibata R, Ouchi N, Kihara S, Sato K, Funahashi T, Walsh K. Adiponectin stimulates angiogenesis in response to tissue ischemia through stimulation of amp-activated protein kinase signaling. *J Biol Chem* 2004;279:28670–28674. [PubMed: 15123726]
 132. Tsao TS, Murrey HE, Hug C, Lee DH, Lodish HF. Oligomerization state-dependent activation of NF-kappa B signaling pathway by adipocyte complement-related protein of 30 kDa (Acrp30). *J Biol Chem* 2002;277:29359–29362. [PubMed: 12087086]

133. Waki H, Yamauchi T, Kamon J, Ito Y, Uchida S, Kita S, Hara K, Hada Y, Vasseur F, Froguel P, et al. Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. *J Biol Chem* 2003;278:40352–40363. [PubMed: 12878598]
134. Aso Y, Yamamoto R, Wakabayashi S, Uchida T, Takayanagi K, Takebayashi K, Okuno T, Inoue T, Node K, Tobe T, et al. Comparison of serum high-molecular weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. *Diabetes* 2006;55:1954–1960. [PubMed: 16804063]
135. Bobbert T, Rochlitz H, Wegewitz U, Akpulat S, Mai K, Weickert MO, Mohlig M, Pfeiffer AF, Spranger J. Changes of adiponectin oligomer composition by moderate weight reduction. *Diabetes* 2005;54:2712–2719. [PubMed: 16123361]
136. Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, Engel J, Brownlee M, Scherer PE. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications for metabolic regulation and bioactivity. *J Biol Chem* 2003;278:9073–9085. [PubMed: 12496257]
137. Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, Wagner JA, Wu M, Knopps A, Xiang AH, et al. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. *J Biol Chem* 2004;279:12152–12162. [PubMed: 14699128]
138. Tsao TS, Tomas E, Murrey HE, Hug C, Lee DH, Ruderman NB, Heuser JE, Lodish HF. Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity. Different oligomers activate different signal transduction pathways. *J Biol Chem* 2003;278:50810–50817. [PubMed: 14522956]
139. Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, Funahashi T, Matsuzawa Y. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. *Circ Res* 2004;94:e27–e31. [PubMed: 14752031]
140. Tonelli J, Li W, Kishore P, Pajvani UB, Kwon E, Weaver C, Scherer PE, Hawkins M. Mechanisms of early insulin-sensitizing effects of thiazolidinediones in type 2 diabetes. *Diabetes* 2004;53:1621–1629. [PubMed: 15161771]
141. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 2003;423:762–769. [PubMed: 12802337]
142. Katsuki A, Suematsu M, Gabazza EC, Murashima S, Nakatani K, Togashi K, Yano Y, Sumida Y. Decreased high-molecular weight adiponectin-to-total adiponectin ratio in sera is associated with insulin resistance in Japanese metabolically obese, normal-weight men with normal glucose tolerance. *Diabetes Care* 2006;29:2327–2328. [PubMed: 17003319]
143. Abbasi F, Chang SA, Chu JW, Ciaraldi TP, Lamendola C, McLaughlin T, Reaven GM, Reaven PD. Improvements in insulin resistance with weight loss, in contrast to rosiglitazone, are not associated with changes in plasma adiponectin or adiponectin multimeric complexes. *Am J Physiol Regul Integr Comp Physiol* 2006;290:R139–R144. [PubMed: 16352858]
144. Basu R, Pajvani UB, Rizza RA, Scherer PE. Selective downregulation of the high molecular weight form of adiponectin in hyperinsulinemia and in type 2 diabetes: differential regulation from nondiabetic subjects. *Diabetes* 2007;56:2174–2177. [PubMed: 17513700]
145. Komaba H, Igaki N, Goto S, Yokota K, Doi H, Takemoto T, Kohno M, Hirose Y, Goto T. Increased serum high-molecular-weight complex of adiponectin in type 2 diabetic patients with impaired renal function. *Am J Nephrol* 2006;26:476–482. [PubMed: 17095862]
146. Nakashima R, Kamei N, Yamane K, Nakanishi S, Nakashima A, Kohno N. Decreased total and high molecular weight adiponectin are independent risk factors for the development of type 2 diabetes in Japanese-Americans. *J Clin Endocrinol Metab* 2006;91:3873–3877. [PubMed: 16882743]
147. Araki S, Dobashi K, Kubo K, Asayama K, Shirahata A. High molecular weight, rather than total, adiponectin levels better reflect metabolic abnormalities associated with childhood obesity. *J Clin Endocrinol Metab* 2006;91:5113–5116. [PubMed: 16984991]
148. Engl J, Bobbert T, Ciardi C, Laimer M, Tatarczyk T, Kaser S, Weiss H, Molnar C, Tilg H, Patsch JR, et al. Effects of pronounced weight loss on adiponectin oligomer composition and metabolic parameters. *Obesity (Silver Spring)* 2007;15:1172–1178. [PubMed: 17495193]

149. Salani B, Briatore L, Andraghetti G, Adami GF, Maggi D, Cordera R. High-molecular weight adiponectin isoforms increase after biliopancreatic diversion in obese subjects. *Obesity* (Silver Spring) 2006;14:1511–1514. [PubMed: 17030961]
150. Swarbrick MM, Austrheim-Smith IT, Stanhope KL, Van Loan MD, Ali MR, Wolfe BM, Havel PJ. Circulating concentrations of high-molecular-weight adiponectin are increased following Roux-en-Y gastric bypass surgery. *Diabetologia* 2006;49:2552–2558. [PubMed: 17019599]
151. Inoue T, Kotooka N, Morooka T, Komoda H, Uchida T, Aso Y, Inukai T, Okuno T, Node K. High molecular weight adiponectin as a predictor of long-term clinical outcome in patients with coronary artery disease. *Am J Cardiol* 2007;100:569–574. [PubMed: 17697807]
152. Oki K, Koide J, Nakanishi S, Nakashima R, Yamane K. Fenofibrate increases high molecular weight adiponectin in subjects with hypertriglyceridemia. *Endocr J* 2007;54:431–435. [PubMed: 17457016]
153. Aroda V, Ciaraldi TP, Chang SA, Dahan MH, Chang RJ, Henry RR. Circulating and cellular adiponectin in polycystic ovary syndrome: relationship to glucose tolerance and insulin action. *Fertil Steril* 2008;89(5):1200–8. [PubMed: 17706206]
154. Bluher M, Brennan AM, Kelesidis T, Kratzsch J, Fasshauer M, Kralisch S, Williams CJ, Mantzoros CS. Total and high-molecular weight adiponectin in relation to metabolic variables at baseline and in response to an exercise treatment program: comparative evaluation of three assays. *Diabetes Care* 2007;30:280–285. [PubMed: 17259495]
155. Fisher FF, Trujillo ME, Hanif W, Barnett AH, McTernan PG, Scherer PE, Kumar S. Serum high molecular weight complex of adiponectin correlates better with glucose tolerance than total serum adiponectin in Indo-Asian males. *Diabetologia* 2005;48:1084–1087. [PubMed: 15902402]
156. Glinborg D, Frystyk J, Hojlund K, Andersen KK, Henriksen JE, Hermann AP, Hagen C, Flyvbjerg A, Andersen M. Total and high molecular weight (HMW) adiponectin levels and measures of glucose and lipid metabolism following pioglitazone treatment in a randomized placebo-controlled study in polycystic ovary syndrome. *Clin Endocrinol(Oxf)* 2008;68(2):165–74. [PubMed: 17803698]
157. Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T. Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. *Diabetes Care* 2006;29:1357–1362. [PubMed: 16732021]
158. Modan-Moses D, Stein D, Pariente C, Yaroslavsky A, Ram A, Faigin M, Loewenthal R, Yissachar E, Hemi R, Kanety H. Modulation of adiponectin and leptin during refeeding of female anorexia nervosa patients. *J Clin Endocrinol Metab* 2007;92:1843–1847. [PubMed: 17327386]
159. O'Leary VB, Jorett AE, Marchetti CM, Gonzalez F, Phillips SA, Ciaraldi TP, Kirwan JP. Enhanced adiponectin multimer ratio and skeletal muscle adiponectin receptor expression following exercise training and diet in older insulin-resistant adults. *Am J Physiol Endocrinol Metab* 2007;293:E421–E427. [PubMed: 17488807]
160. Schober F, Neumeier M, Weigert J, Wurm S, Wanninger J, Schaffler A, Dada A, Liebisch G, Schmitz G, Aslanidis C, et al. Low molecular weight adiponectin negatively correlates with the waist circumference and monocyte IL-6 release. *Biochem Biophys Res Commun* 2007;361:968–973. [PubMed: 17678873]
161. Tsuchida A, Yamauchi T, Takekawa S, Hada Y, Ito Y, Maki T, Kadowaki T. Peroxisome proliferator-activated receptor (PPAR)alpha activation increases adiponectin receptors and reduces obesity-related inflammation in adipose tissue: comparison of activation of PPARalpha, PPARgamma, and their combination. *Diabetes* 2005;54:3358–3370. [PubMed: 16306350]
162. Ong GK, Hamilton JK, Sermer M, Connelly PW, Maguire G, Zinman B, Hanley AJ, Retnakaran R. Maternal serum adiponectin and infant birthweight: the role of adiponectin isoform distribution. *Clin Endocrinol(Oxf)* 2007;67:108–114. [PubMed: 17466005]
163. Retnakaran R, Hanley AJ, Connelly PW, Maguire G, Sermer M, Zinman B. Low serum levels of high-molecular weight adiponectin in Indo-Asian women during pregnancy: evidence of ethnic variation in adiponectin isoform distribution. *Diabetes Care* 2006;29:1377–1379. [PubMed: 16732024]

164. Takemura Y, Osuga Y, Koga K, Tajima T, Hirota Y, Hirata T, Morimoto C, Harada M, Yano T, Taketani Y. Selective increase in high molecular weight adiponectin concentration in serum of women with preeclampsia. *J Reprod Immunol* 2007;73:60–65. [PubMed: 16860876]
165. Retnakaran R, Connelly PW, Maguire G, Sermer M, Zinman B, Hanley AJ. Decreased high-molecular-weight adiponectin in gestational diabetes: implications for the pathophysiology of Type 2 diabetes. *Diabet Med* 2007;24:245–252. [PubMed: 17305786]
166. Diet, nutrition and the prevention of chronic diseases. *World Health Organ Tech Rep Ser* 2003;916:i-149.backcover
167. Abbasi F, Chu JW, Lamendola C, McLaughlin T, Hayden J, Reaven GM, Reaven PD. Discrimination between obesity and insulin resistance in the relationship with adiponectin. *Diabetes* 2004;53:585–590. [PubMed: 14988241]
168. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor- α expression. *Diabetes* 2003;52:1779–1785. [PubMed: 12829646]
169. Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J Clin Invest* 2001;108:1875–1881. [PubMed: 11748271]
170. Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M, Nawrocki AR, Rajala MW, Parlow AF, Cheeseboro L, et al. A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. *Endocrinology* 2004;145:367–383. [PubMed: 14576179]
171. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002;8:731–737. [PubMed: 12068289]
172. Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, Pang Z, Chen AS, Ruderman NB, Chen H, et al. Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. *J Biol Chem* 2006;281:2654–2660. [PubMed: 16326714]
173. Tomas E, Tsao TS, Saha AK, Murrey HE, Zhang CC, Itani SI, Lodish HF, Ruderman NB. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. *Proc Natl Acad Sci USA* 2002;99:16309–16313. [PubMed: 12456889]
174. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002;8:1288–1295. [PubMed: 12368907]
175. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003;278:45021–45026. [PubMed: 12944390]
176. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, Takahashi M, Arita Y, Kihara S, Matsuzawa Y. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. *Intern Med* 1999;38:202–206. [PubMed: 10225688]
177. Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, et al. Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem* 2002;277:25863–25866. [PubMed: 12032136]
178. Yamauchi T, Kamon J, Waki H, Imai Y, Shimozaawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J, et al. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biol Chem* 2003;278:2461–2468. [PubMed: 12431986]
179. Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? *Diabetes Care* 2003;26:2442–2450. [PubMed: 12882876]
180. Nawrocki AR, Scherer PE. The delicate balance between fat and muscle: adipokines in metabolic disease and musculoskeletal inflammation. *Curr Opin Pharmacol* 2004;4:281–289. [PubMed: 15140421]
181. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, Nagai M, Matsuzawa Y, Funahashi T. Adiponectin as a biomarker of the metabolic syndrome. *Circ J* 2004;68:975–981. [PubMed: 15502375]

182. Schulze MB, Rimm EB, Shai I, Rifai N, Hu FB. Relationship between adiponectin and glycemic control, blood lipids, and inflammatory markers in men with type 2 diabetes. *Diabetes Care* 2004;27:1680–1687. [PubMed: 15220246]
183. Shimabukuro M, Higa N, Asahi T, Oshiro Y, Takasu N, Tagawa T, Ueda S, Shimomura I, Funahashi T, Matsuzawa Y. Hypoadiponectinemia is closely linked to endothelial dysfunction in man. *J Clin Endocrinol Metab* 2003;88:3236–3240. [PubMed: 12843170]
184. Yamamoto Y, Hirose H, Saito I, Nishikai K, Saruta T. Adiponectin, an adipocyte-derived protein, predicts future insulin resistance: two-year follow-up study in Japanese population. *J Clin Endocrinol Metab* 2004;89:87–90. [PubMed: 14715832]
185. Yatagai T, Nishida Y, Nagasaka S, Nakamura T, Tokuyama K, Shindo M, Tanaka H, Ishibashi S. Relationship between exercise training-induced increase in insulin sensitivity and adiponectinemia in healthy men. *Endocr J* 2003;50:233–238. [PubMed: 12803245]
186. Combs TP, Wagner JA, Berger J, Doeber T, Wang WJ, Zhang BB, Tanen M, Berg AH, O'Rahilly S, Savage DB, et al. Induction of adipocyte complement-related protein of 30 kilodaltons by PPARgamma agonists: a potential mechanism of insulin sensitization. *Endocrinology* 2002;143:998–1007. [PubMed: 11861525]
187. Steffes MW, Gross MD, Schreiner PJ, Yu X, Hilner JE, Gingerich R, Jacobs DR Jr. Serum adiponectin in young adults--interactions with central adiposity, circulating levels of glucose, and insulin resistance: the CARDIA study. *Ann Epidemiol* 2004;14:492–498. [PubMed: 15301786]
188. Mantzoros CS, Li T, Manson JE, Meigs JB, Hu FB. Circulating adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in women with type 2 diabetes. *J Clin Endocrinol Metab* 2005;90:4542–4548. [PubMed: 15914524]
189. Shetty GK, Economides PA, Horton ES, Mantzoros CS, Veves A. Circulating adiponectin and resistin levels in relation to metabolic factors, inflammatory markers, and vascular reactivity in diabetic patients and subjects at risk for diabetes. *Diabetes Care* 2004;27:2450–2457. [PubMed: 15451915]
190. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004;291:1730–1737. [PubMed: 15082700]
191. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, et al. Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 2003;23:85–89. [PubMed: 12524229]
192. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia* 2003;46:459–469. [PubMed: 12687327]
193. Kantartzis K, Rittig K, Balletshofer B, Machann J, Schick F, Porubska K, Fritsche A, Haring HU, Stefan N. The relationships of plasma adiponectin with a favorable lipid profile, decreased inflammation, and less ectopic fat accumulation depend on adiposity. *Clin Chem* 2006;52:1934–1942. [PubMed: 16916991]
194. Okada T, Saito E, Kuromori Y, Miyashita M, Iwata F, Hara M, Harada K. Relationship between serum adiponectin level and lipid composition in each lipoprotein fraction in adolescent children. *Atherosclerosis* 2006;188:179–183. [PubMed: 16307747]
195. von Eynatten M, Schneider JG, Humpert PM, Kreuzer J, Kuecherer H, Katus HA, Nawroth PP, Dugi KA. Serum adiponectin levels are an independent predictor of the extent of coronary artery disease in men. *J Am Coll Cardiol* 2006;47:2124–2126. [PubMed: 16697337]
196. von Eynatten M, Hamann A, Twardella D, Nawroth PP, Brenner H, Rothenbacher D. Relationship of adiponectin with markers of systemic inflammation, atherogenic dyslipidemia, and heart failure in patients with coronary heart disease. *Clin Chem* 2006;52:853–859. [PubMed: 16556684]
197. Nakamura T, Kodama Y, Takano H, Umetani K, Fujioka D, Saito Y, Kawabata K, Obata JE, Kitta Y, Kobayashi T, et al. Increase in circulating levels of adiponectin after treatment with statin and fibrate in patients with coronary artery disease and hyperlipidemia. *Atherosclerosis* 2007;193:449–451. [PubMed: 16997309]
198. Westphal S, Borucki K, Taneva E, Makarova R, Luley C. Adipokines and treatment with niacin. *Metabolism* 2006;55:1283–1285. [PubMed: 16979396]

199. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, Kumada M, Hotta K, Nishida M, Takahashi M, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. *Circulation* 2002;105:2893–2898. [PubMed: 12070119]
200. Matsuzawa Y, Shimomura I, Kihara S, Funahashi T. Importance of adipocytokines in obesity-related diseases. *Horm Res* 2003;60 (Suppl 3):56–59. [PubMed: 14671398]
201. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005;26:439–451. [PubMed: 15897298]
202. Koerner A, Kratzsch J, Kiess W. Adipocytokines: leptin--the classical, resistin--the controversial, adiponectin--the promising, and more to come. *Best Pract Res Clin Endocrinol Metab* 2005;19:525–546. [PubMed: 16311215]
203. Ouchi N, Shibata R, Walsh K. Cardioprotection by adiponectin. *Trends Cardiovasc Med* 2006;16:141–146. [PubMed: 16781946]
204. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes* 2006;55:1537–1545. [PubMed: 16731815]
205. Bora PS, Kaliappan S, Lyzogubov VV, Tytarenko RG, Thotakura S, Viswanathan T, Bora NS. Expression of adiponectin in choroidal tissue and inhibition of laser induced choroidal neovascularization by adiponectin. *FEBS Lett* 2007;581:1977–1982. [PubMed: 17466298]
206. Brakenhielm E, Veitonmaki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, Funahashi T, Cao Y. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. *Proc Natl Acad Sci USA* 2004;101:2476–2481. [PubMed: 14983034]
207. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. *Obes Rev* 2007;8:395–408. [PubMed: 17716297]
208. Butte NF, Wong WW, Treuth MS, Ellis KJ, O'Brian SE. Energy requirements during pregnancy based on total energy expenditure and energy deposition. *Am J Clin Nutr* 2004;79:1078–1087. [PubMed: 15159239]
209. Catalano PM. Management of obesity in pregnancy. *Obstet Gynecol* 2007;109:419–433. [PubMed: 17267845]
210. Ehrenberg HM, Huston-Presley L, Catalano PM. The influence of obesity and gestational diabetes mellitus on accretion and the distribution of adipose tissue in pregnancy. *Am J Obstet Gynecol* 2003;189:944–948. [PubMed: 14586331]
211. Hytten, FE.; Chamberlin, G. *Clinical Physiology in Obstetrics*. Oxford, United Kindom: Blackwell Scientific Publications; 1991. p. 152-173.
212. Kinoshita T, Itoh M. Longitudinal variance of fat mass deposition during pregnancy evaluated by ultrasonography: the ratio of visceral fat to subcutaneous fat in the abdomen. *Gynecol Obstet Invest* 2006;61:115–118. [PubMed: 16272815]
213. Pipe NG, Smith T, Halliday D, Edmonds CJ, Williams C, Coltart TM. Changes in fat, fat-free mass and body water in human normal pregnancy. *Br J Obstet Gynaecol* 1979;86:929–940. [PubMed: 118770]
214. Aberg A, Rydhstroem H, Frid A. Impaired glucose tolerance associated with adverse pregnancy outcome: a population-based study in southern Sweden. *Am J Obstet Gynecol* 2001;184:77–83. [PubMed: 11174484]
215. Al-Shawaf T, Moghraby S, Akiel A. Does impaired glucose tolerance imply a risk in pregnancy? *Bf J Obstet Gynaecol* 1988;95:1036–1041.
216. Dixon JB, Dixon ME, O'Brien PE. Birth outcomes in obese women after laparoscopic adjustable gastric banding. *Obstet Gynecol* 2005;106:965–972. [PubMed: 16260513]
217. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, Saade G, Eddleman K, Carter SM, Craigo SD, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. *Am J Obstet Gynecol* 2004;190:1091–1097. [PubMed: 15118648]
218. Eskenazi B, Fenster L, Sidney S. A multivariate analysis of risk factors for preeclampsia. *JAMA* 1991;266:237–241. [PubMed: 2056625]
219. Joffe GM, Esterlitz JR, Levine RJ, Clemens JD, Ewell MG, Sibai BM, Catalano PM. The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous

- women. Calcium for Preeclampsia Prevention (CPEP) Study Group. *Am J Obstet Gynecol* 1998;179:1032–1037. [PubMed: 9790393]
220. Sibai BM, Gordon T, Thom E, Caritis SN, Klebanoff M, McNellis D, Paul RH. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 1995;172:642–648. [PubMed: 7856699]
 221. Solomon CG, Seely EW. Brief review: hypertension in pregnancy: a manifestation of the insulin resistance syndrome? *Hypertension* 2001;37:232–239. [PubMed: 11230277]
 222. Wolf M, Sandler L, Munoz K, Hsu K, Ecker JL, Thadhani R. First trimester insulin resistance and subsequent preeclampsia: a prospective study. *J Clin Endocrinol Metab* 2002;87:1563–1568. [PubMed: 11932283]
 223. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477–2486. [PubMed: 15951574]
 224. Yogev Y, Xenakis EM, Langer O. The association between preeclampsia and the severity of gestational diabetes: the impact of glycemic control. *Am J Obstet Gynecol* 2004;191:1655–1660. [PubMed: 15547538]
 225. D'Anna R, Baviera G, Corrado F, Giordano D, Di Benedetto A, Jasonni VM. Plasma adiponectin concentration in early pregnancy and subsequent risk of hypertensive disorders. *Obstet Gynecol* 2005;106:340–344. [PubMed: 16055585]
 226. Suwaki N, Masuyama H, Nakatsukasa H, Masumoto A, Sumida Y, Takamoto N, Hiramatsu Y. Hypoadiponectinemia and circulating angiogenic factors in overweight patients complicated with pre-eclampsia. *Am J Obstet Gynecol* 2006;195(6):1687–92. [PubMed: 16769024]
 227. Crouch E, Persson A, Chang D, Heuser J. Molecular structure of pulmonary surfactant protein D (SP-D). *J Biol Chem* 1994;269:17311–17319. [PubMed: 8006040]
 228. McCormack FX, Pattanajitvilai S, Stewart J, Possmayer F, Inchley K, Voelker DR. The Cys6 intermolecular disulfide bond and the collagen-like region of rat SP-A play critical roles in interactions with alveolar type II cells and surfactant lipids. *J Biol Chem* 1997;272:27971–27979. [PubMed: 9346948]
 229. Wong GW, Wang J, Hug C, Tsao TS, Lodish HF. A family of Acrp30/adiponectin structural and functional paralogs. *Proc Natl Acad Sci USA* 2004;101:10302–10307. [PubMed: 15231994]
 230. Wang Y, Xu A, Knight C, Xu LY, Cooper GJ. Hydroxylation and glycosylation of the four conserved lysine residues in the collagenous domain of adiponectin. Potential role in the modulation of its insulin-sensitizing activity. *J Biol Chem* 2002;277:19521–19529. [PubMed: 11912203]
 231. Wang Y, Lam KS, Chan L, Chan KW, Lam JB, Lam MC, Hoo RC, Mak WW, Cooper GJ, Xu A. Post-translational modifications of the four conserved lysine residues within the collagenous domain of adiponectin are required for the formation of its high molecular weight oligomeric complex. *J Biol Chem* 2006;281:16391–16400. [PubMed: 16621799]
 232. Phillips SA, Ciaraldi TP, Kong AP, Bandukwala R, Aroda V, Carter L, Baxi S, Mudaliar SR, Henry RR. Modulation of circulating and adipose tissue adiponectin levels by antidiabetic therapy. *Diabetes* 2003;52:667–674. [PubMed: 12606507]
 233. Abke S, Neumeier M, Weigert J, Wehrwein G, Eggenhofer E, Schaffler A, Maier K, Aslanidis C, Scholmerich J, Buechler C. Adiponectin-induced secretion of interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1, CCL2) and interleukin-8 (IL-8, CXCL8) is impaired in monocytes from patients with type I diabetes. *Cardiovasc Diabetol* 2006;5:17. [PubMed: 16939660]
 234. Rovin BH, Song H. Chemokine induction by the adipocyte-derived cytokine adiponectin. *Clin Immunol* 2006;120:99–105. [PubMed: 16503200]
 235. Haugen F, Drevon CA. Activation of nuclear factor-kappaB by high molecular weight and globular adiponectin. *Endocrinology* 2007;148:5478–5486. [PubMed: 17702846]
 236. Neumeier M, Weigert J, Schaffler A, Wehrwein G, Muller-Ladner U, Scholmerich J, Wrede C, Buechler C. Different effects of adiponectin isoforms in human monocytic cells. *J Leukoc Biol* 2006;79:803–808. [PubMed: 16434692]

237. Tasanen K, Eble JA, Aumailley M, Schumann H, Baetge J, Tu H, Bruckner P, Bruckner-Tuderman L. Collagen XVII is destabilized by a glycine substitution mutation in the cell adhesion domain Col15. *J Biol Chem* 2000;275:3093–3099. [PubMed: 10652291]
238. Lara-Castro C, Luo N, Wallace P, Klein RL, Garvey WT. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. *Diabetes* 2006;55:249–259. [PubMed: 16380500]
239. Wang AY, Hickman JJ, Richards AA, Whitehead JP, Prins JB, Macdonald GA. High molecular weight adiponectin correlates with insulin sensitivity in patients with hepatitis C genotype 3, but not genotype 1 infection. *Am J Gastroenterol* 2005;100:2717–2723. [PubMed: 16393225]
240. Iwahashi H, Funahashi T, Kurokawa N, Sayama K, Fukuda E, Okita K, Imagawa A, Yamagata K, Shimomura I, Miyagawa JJ, et al. Plasma adiponectin levels in women with anorexia nervosa. *Horm Metab Res* 2003;35:537–540. [PubMed: 14517770]
241. Ebinuma H, Miyazaki O, Yago H, Hara K, Yamauchi T, Kadowaki T. A novel ELISA system for selective measurement of human adiponectin multimers by using proteases. *Clin Chim Acta* 2006;372:47–53. [PubMed: 16697359]
242. Ebinuma H, Miida T, Yamauchi T, Hada Y, Hara K, Kubota N, Kadowaki T. Improved ELISA for selective measurement of adiponectin multimers and identification of adiponectin in human cerebrospinal fluid. *Clin Chem* 2007;53:1541–1544. [PubMed: 17599956]
243. Nakano Y, Tajima S, Yoshimi A, Akiyama H, Tsushima M, Tanioka T, Negoro T, Tomita M, Tobé T. A novel enzyme-linked immunosorbent assay specific for high-molecular-weight adiponectin. *J Lipid Res* 2006;47:1572–1582. [PubMed: 16603722]
244. Hammarstedt A, Sopasakis VR, Gogg S, Jansson PA, Smith U. Improved insulin sensitivity and adipose tissue dysregulation after short-term treatment with pioglitazone in non-diabetic, insulin-resistant subjects. *Diabetologia* 2005;48:96–104. [PubMed: 15624096]
245. Fuglsang J, Skjaerbaek C, Frystyk J, Flyvbjerg A, Ovesen P. A longitudinal study of serum adiponectin during normal pregnancy. *BJOG* 2006;113:110–113. [PubMed: 16398779]
246. Catalano PM, Nizielski SE, Shao J, Preston L, Qiao L, Friedman JE. Downregulated IRS-1 and PPARgamma in obese women with gestational diabetes: relationship to FFA during pregnancy. *Am J Physiol Endocrinol Metab* 2002;282:E522–E533. [PubMed: 11832353]
247. Desoye G, Schweditsch MO, Pfeiffer KP, Zechner R, Kostner GM. Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum. *J Clin Endocrinol Metab* 1987;64:704–712. [PubMed: 3546352]
248. Paradisi G, Biaggi A, Ferrazzani S, De Cavolis S, Caruso A. Abnormal carbohydrate metabolism during pregnancy: association with endothelial dysfunction. *Diabetes Care* 2002;25:560–564. [PubMed: 11874947]
249. Sivan E, Homko CJ, Chen X, Reece EA, Boden G. Effect of insulin on fat metabolism during and after normal pregnancy. *Diabetes* 1999;48:834–838. [PubMed: 10102701]
250. Faust IM, Johnson PR, Stern JS, Hirsch J. Diet-induced adipocyte number increase in adult rats: a new model of obesity. *Am J Physiol* 1978;235:E279–E286. [PubMed: 696822]
251. Garaulet M, Hernandez-Morante JJ, Lujan J, Tebar FJ, Zamora S. Relationship between fat cell size and number and fatty acid composition in adipose tissue from different fat depots in overweight/obese humans. *Int J Obes(Lond)* 2006;30:899–905. [PubMed: 16446749]
252. Hausman DB, DiGirolamo M, Bartness TJ, Hausman GJ, Martin RJ. The biology of white adipocyte proliferation. *Obes Rev* 2001;2:239–254. [PubMed: 12119995]
253. Hirsch J, Batchelor B. Adipose tissue cellularity in human obesity. *Clin Endocrinol Metab* 1976;5:299–311. [PubMed: 1085232]
254. Johnson PR, Stern JS, Greenwood MR, Hirsch J. Adipose tissue hyperplasia and hyperinsulinemia on Zucker obese female rats: a developmental study. *Metabolism* 1978;27:1941–1954. [PubMed: 723643]
255. Prins JB, O'Rahilly S. Regulation of adipose cell number in man. *Clin Sci(Lond)* 1997;92:3–11. [PubMed: 9038586]
256. Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell* 1994;79:1147–1156. [PubMed: 8001151]

257. Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, Olefsky JM. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes* 2002;51:2968–2974. [PubMed: 12351435]
258. He W, Barak Y, Hevener A, Olson P, Liao D, Le J, Nelson M, Ong E, Olefsky JM, Evans RM. Adipose-specific peroxisome proliferator-activated receptor gamma knockout causes insulin resistance in fat and liver but not in muscle. *Proc Natl Acad Sci USA* 2003;100:15712–15717. [PubMed: 14660788]
259. Iwaki M, Matsuda M, Maeda N, Funahashi T, Matsuzawa Y, Makishima M, Shimomura I. Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. *Diabetes* 2003;52:1655–1663. [PubMed: 12829629]
260. Yamauchi T, Kamon J, Waki H, Murakami K, Motojima K, Komeda K, Ide T, Kubota N, Terauchi Y, Tobe K, et al. The mechanisms by which both heterozygous peroxisome proliferator-activated receptor gamma (PPARgamma) deficiency and PPARgamma agonist improve insulin resistance. *J Biol Chem* 2001;276:41245–41254. [PubMed: 11533050]
261. Yang WS, Jeng CY, Wu TJ, Tanaka S, Funahashi T, Matsuzawa Y, Wang JP, Chen CL, Tai TY, Chuang LM. Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. *Diabetes Care* 2002;25:376–380. [PubMed: 11815513]
262. de Souza CJ, Eckhardt M, Gagen K, Dong M, Chen W, Laurent D, Burkey BF. Effects of pioglitazone on adipose tissue remodeling within the setting of obesity and insulin resistance. *Diabetes* 2001;50:1863–1871. [PubMed: 11473050]
263. De Vos P, Lefebvre AM, Miller SG, Guerre-Millo M, Wong K, Saladin R, Hamann LG, Staels B, Briggs MR, Auwerx J. Thiazolidinediones repress ob gene expression in rodents via activation of peroxisome proliferator-activated receptor gamma. *J Clin Invest* 1996;98:1004–1009. [PubMed: 8770873]
264. Hulver MW, Zheng D, Tanner CJ, Houmard JA, Kraus WE, Slentz CA, Sinha MK, Pories WJ, MacDonald KG, Dohm GL. Adiponectin is not altered with exercise training despite enhanced insulin action. *Am J Physiol Endocrinol Metab* 2002;283:E861–E865. [PubMed: 12217905]
265. Kopp HP, Krzyzanowska K, Mohlig M, Spranger J, Pfeiffer AF, Schernthaner G. Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. *Int J Obes(Lond)* 2005;29:766–771. [PubMed: 15917853]
266. Faraj M, Havel PJ, Phelis S, Blank D, Sniderman AD, Cianflone K. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab* 2003;88:1594–1602. [PubMed: 12679444]
267. Pender C, Goldfine ID, Tanner CJ, Pories WJ, MacDonald KG, Havel PJ, Houmard JA, Youngren JF. Muscle insulin receptor concentrations in obese patients post bariatric surgery: relationship to hyperinsulinemia. *Int J Obes Relat Metab Disord* 2004;28:363–369. [PubMed: 14724657]
268. Polak J, Kovacova Z, Jacek M, Klimcakova E, Kovacikova M, Vitkova M, Kuda O, Sebel M, Samcova E, Stich V. An increase in plasma adiponectin multimeric complexes follows hypocaloric diet-induced weight loss in obese and overweight pre-menopausal women. *Clin Sci(Lond)* 2007;112:557–565. [PubMed: 17201694]
269. Delporte ML, Brichard SM, Hermans MP, Beguin C, Lambert M. Hyperadiponectinaemia in anorexia nervosa. *Clin Endocrinol(Oxf)* 2003;58:22–29. [PubMed: 12519408]
270. Pannacciulli N, Vettor R, Milan G, Granzotto M, Catucci A, Federspil G, De GP, Giorgino R, De PG. Anorexia nervosa is characterized by increased adiponectin plasma levels and reduced nonoxidative glucose metabolism. *J Clin Endocrinol Metab* 2003;88:1748–1752. [PubMed: 12679468]

Figure 1. Comparison of the median serum total, HMW, MMW and LMW adiponectin concentrations between non-pregnant, normal weight and overweight/obese pregnant women
The median serum concentration of total, HMW and MMW adiponectin was significantly higher in normal weight than overweight/obese women. Among non-pregnant women, the median HMW adiponectin concentration was significantly higher than the median concentrations of MMW and LMW adiponectin. The median concentration of the latter was significantly higher than MMW adiponectin

Figure 2. Comparison of HMW/Total adiponectin MMW/Total adiponectin and LMW/Total adiponectin ratio between non-pregnant, normal weight and overweight/obese pregnant women
The median HMW to total adiponectin ratio was significantly higher in normal weight than overweight/obese pregnant women and in overweight/obese patients compared to non pregnant women. The median LMW to total adiponectin ratio was significantly higher in non-pregnant women than the median LMW/Total adiponectin ratio in normal weight and overweight/obese pregnant women. The median LMW to total adiponectin ratio was significantly higher in overweight/obese pregnant than in normal weight pregnant women.

Figure 3. Maternal serum total adiponectin (a), HMW adiponectin (b), MMW adiponectin (c) and LMW adiponectin (d) concentrations in normal weight and pregnant overweight/obese women according to gestational age groups

Among women between 11–14 weeks of gestation, normal weight women had a higher median concentration of total (a) and HMW (b) adiponectin than overweight/obese patients. Among women between 19–22 weeks of gestation, normal weight women had a higher median concentration of total (a), HMW (b) and MMW (c) adiponectin than overweight/obese patients. Among women between 31–34 weeks of gestation, normal weight women had a higher median concentration of total (a), HMW (b) and MMW (c) adiponectin than overweight/obese patients.

Among women at term, normal weight women had a higher median concentration of HMW (b) adiponectin than overweight/obese patients.

Figure 4. Comparison of median HMW/Total adiponectin MMW/Total adiponectin and LMW/Total adiponectin ratio between normal weight and overweight/obese pregnant women in 11–14 weeks (a) and 19–22 weeks (b) of gestation

The median HMW/Total adiponectin ratio was higher in normal weight than in overweight/obese pregnant women between 11–14 (a) and 19–22 (b) weeks of gestation.

Figure 5. Comparison of median serum total, HMW, MMW and LMW adiponectin concentrations between women at term in labor and not in labor

Women at term in labor had a higher median concentration of HMW adiponectin compared to women at term not in labor. Among pregnant women in labor and not in labor at term, the median serum concentration of HMW adiponectin was higher than the median concentrations of LMW and MMW adiponectin. The latter was higher than the median LMW adiponectin concentrations.

Table I

Clinical characteristics normal weight and overweight/obese pregnant women.

	Normal-weight (n=466)	Overweight (n=257)	p
Maternal age (years)	25 (21–30)	28 (23–33)	<0.01
Parity	1 (0–2)	1 (0–2)	NS
BMI at first trimester (kg/m²)	22.2 (20.6–23.4)	27.2 (25.8–29.5)	<0.01
BMI at delivery (kg/m²)	28.0 (26.2–29.6)	32.8 (30.7–34.9)	<0.01
Gestational age at sampling (weeks)	25.2 (18.7–33.4)	27.4(19.0–37.9)	NS
Gestational age at delivery (weeks)	39.8 (38.8–40.4)	39.7 (39.0–40.5)	NS

Values are expressed as median and interquartile range (IQR)

BMI-Body Mass Index; NS- not significant

Table II
Demographic and clinical characteristics of normal weight and overweight/obese pregnant women according to gestational age at sampling.

	11–14 weeks (n=53)	15–18 weeks (n=62)	19–22 weeks (n=62)	23–26 weeks (n=65)	27–30 weeks (n=61)	31–34 weeks (n=54)	Term in labor (n=58)	Term not in labor (n=51)
Normal weight								
Maternal age (years)	24 (21–30)	24 (21–29)	25 (21–31)	24 (20–30)	25 (21–30)	24 (21–31)	25 (21–30)	24 (20–29)
BMI at first trimester (kg/ m ²)	22.5 (20.1–23.6)	22.0 (20.5–23.6)	21.9 (20.3–23.0)	22.2 (20.9–23.4)	22.1 (20.7–22.9)	22.6 (20.8–23.7)	22.3 (20.9–23.7)	21.8 (20.4–23.2)
BMI at delivery (kg/m ²)	28.3 (26.6–30.0)	28.4 (26.4–30.0)	27.6 (25.9–29.2)	27.8 (26.0–29.6)	27.7 (26.2–28.7)	28.5 (27.0–30.2)	28.0 (25.7–29.4)	28.0 (25.2–29.6)
Gestational age at delivery (weeks)	40.0 (39.0–40.4)	39.7 (38.5–40.2)	39.8 (38.6–40.5)	39.7 (38.6–40.4)	39.8 (39.0–40.4)	40.0 (39.3–40.2)	39.7 (38.6–40.2)	39.7 (38.8–40.1)
Overweight/Obese								
	11–14 weeks (n=31)	15–18 weeks (n=31)	19–22 weeks (n=31)	23–26 weeks (n=29)	27–30 weeks (n=34)	31–34 weeks (n=32)	Term in labor (n=40)	Term not in labor (n=29)
Maternal age (years)	26 (23–32)	26 (21–32)	27 (24–34)	31 (26–36)	30 (25–34)	25 (22–30)	27 (24–32)	30 (23–34)
BMI at first trimester (kg/ m ²)	27.9 (25.8–29.4)	26.2 (25.4–28.4)	27.9 (25.9–29.9)	27.2 (25.8–30.2)	27.4 (25.9–31.4)	26.8 (25.7–28.8)	27.0 (25.6–29.7)	28.1 (26.2–31.2)
BMI at delivery (kg/m ²)	32.4 (31.4–35.5)	32.4 (30.1–34.0)	32.4 (31.5–35.0)	32.0 (30.0–35.1)	32.4 (30.1–35.6)	33.1 (30.4–34.7)	33.3 (30.9–34.5)	33.9 (31.4–37.4)
Gestational age at delivery (weeks)	39.2 (39.0–40.2)	40.0 (39.0–40.8)	39.7 (39.0–40.1)	39.8 (38.9–40.7)	40.0 (39.0–40.5)	39.3 (38.8–40.5)	39.4 (38.5–40.4)	40.0 (38.7–40.7)

Values are expressed as median and interquartile range (IQR)

Table III
Total HMW, MMW and LMW adiponectin serum concentrations (ng/mL) in normal weight pregnant women

	Gestational Age (weeks)	Percentiles				
		10	25	50	75	90
Total Adiponectin ng/mL	11–14 (n=53)	4604	5490	6578	9416	10897
	15–18 (n=62)	3593	5087	7338	8716	9745
	19–22 (n=62)	4190	4953	6697	8364	10580
	23–26 (n=65)	4215	4712	5780	8689	10142
	27–30 (n=61)	4081	5473	7008	9085	10847
	31–34 (n=54)	4236	5249	7304	8927	10963
	Term in labor (n=58)	4649	6012	7080	8823	11554
	Term not in labor (n=51)	3379	4658	6528	8707	10133
	11–14 (n=53)	2040	2998	3961	5636	7317
	15–18 (n=62)	1744	2815	4172	5391	6724
HMW Adiponectin ng/mL	19–22 (n=62)	2048	2837	3674	4872	7115
	23–26 (n=65)	1824	2768	3338	5126	6981
	27–30 (n=61)	1866	2496	4036	6005	6831
	31–34 (n=54)	1940	2587	4084	5472	6470
	Term in labor (n=58)	2434	3277	4405	5585	7771
	Term not in labor (n=51)	1802	2203	3916	5240	6061
	11–14 (n=53)	619	915	1456	2008	2701
	15–18 (n=62)	794	1055	1412	1813	2215
	19–22 (n=62)	645	1077	1467	2075	2565
	23–26 (n=65)	859	1044	1391	1790	2979
MMW Adiponectin ng/mL	27–30 (n=61)	683	1044	1507	1889	2425
	31–34 (n=54)	778	1180	1551	2048	2451
	Term in labor (n=58)	751	1253	1657	2090	2541
	Term not in labor (n=51)	545	884	1312	1916	2441
	11–14 (n=53)	360	916	1381	2099	2592
	15–18 (n=62)	385	785	1193	1897	2238
	19–22 (n=62)	438	817	1211	1580	2118
	23–26 (n=65)	355	759	1114	1595	2009
LMW Adiponectin ng/mL						

	Gestational Age (weeks)	Percentiles				
		10	25	50	75	90
	27-30 (n=61)	536	894	1188	1757	2519
	31-34 (n=54)	341	959	1345	1944	2706
	Term in labor (n=58)	532	782	1227	1800	2132
	Term not in labor (n=51)	478	723	1223	2056	2786

HMW – high molecular weight; MMW – medium molecular weight; LMW – low molecular weight.

Table IV
Total HMW, MMW and LMW adiponectin serum concentrations (ng/mL) in overweight/obese pregnant women

	Gestational Age (weeks)	Percentiles				
		10	25	50	75	90
Total Adiponectin ng/mL	11–14 (n=31)	3445	4270	5831	7208	10264
	15–18 (n=31)	3813	4534	5912	7744	10781
	19–22 (n=31)	3142	4348	5868	6162	7768
	23–26 (n=29)	3384	3905	5241	7826	10567
	27–30 (n=34)	3818	4770	6745	8715	11467
	31–34 (n=32)	3625	4291	5056	7183	8836
	Term in labor (n=40)	3869	4675	5983	8019	9534
	Term not in labor (n=29)	3751	4418	5238	6945	9096
	11–14 (n=31)	1235	1980	2723	3770	6033
	15–18 (n=31)	1961	2509	3123	4869	6960
HMW Adiponectin ng/mL	19–22 (n=31)	1587	2246	2795	3334	4537
	23–26 (n=29)	1411	1782	2913	4678	6305
	27–30 (n=34)	1937	2535	3711	5277	6946
	31–34 (n=32)	1704	2115	2672	3847	5869
	Term in labor (n=40)	1739	2255	3358	4792	6602
	Term not in labor (n=29)	1583	2110	2946	3783	4775
	11–14 (n=31)	724	1049	1402	1733	2349
	15–18 (n=31)	712	808	1233	1968	2286
	19–22 (n=31)	495	915	1171	1590	1933
	23–26 (n=29)	711	886	1212	1609	2111
MMW Adiponectin ng/mL	27–30 (n=34)	619	955	1418	2015	2479
	31–34 (n=32)	539	786	1204	1608	1829
	Term in labor (n=40)	676	907	1331	1715	2531
	Term not in labor (n=29)	701	1068	1468	1879	2343
	11–14 (n=31)	387	894	1550	1986	2579
	15–18 (n=31)	640	851	1123	1523	2443
	19–22 (n=31)	503	835	1203	1941	2383
	23–26 (n=29)	676	864	1260	1545	2859
	11–14 (n=31)	387	894	1550	1986	2579
	15–18 (n=31)	640	851	1123	1523	2443
LMW Adiponectin ng/mL	19–22 (n=31)	503	835	1203	1941	2383
	23–26 (n=29)	676	864	1260	1545	2859
	11–14 (n=31)	387	894	1550	1986	2579
	15–18 (n=31)	640	851	1123	1523	2443
	19–22 (n=31)	503	835	1203	1941	2383
	23–26 (n=29)	676	864	1260	1545	2859
	11–14 (n=31)	387	894	1550	1986	2579
	15–18 (n=31)	640	851	1123	1523	2443
	19–22 (n=31)	503	835	1203	1941	2383
	23–26 (n=29)	676	864	1260	1545	2859

	Gestational Age (weeks)	Percentiles				
		10	25	50	75	90
	27–30 (n=34)	530	967	1576	1861	2451
	31–34 (n=32)	498	802	1280	1719	2456
	Term in labor (n=40)	373	731	1101	1623	1832
	Term not in labor (n=29)	578	695	1104	1453	2548

HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.