Hindawi Publishing Corporation
Journal of Nutrition and Metabolism
Volume 2013, Article ID 285948, 16 pages
http://dx.doi.org/10.1155/2013/285948

Review Article

Potential Mechanisms of Exercise in Gestational Diabetes

Saeid Golbidi and Ismail Laher

Department of Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada V6T 1Z3

Correspondence should be addressed to Ismail Laher; ilaher@mail.ubc.ca

Received 25 September 2012; Revised 31 January 2013; Accepted 10 February 2013

Academic Editor: Peter M. Clifton

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first diagnosed during pregnancy. This condition shares same array of underlying abnormalities as occurs in diabetes outside of pregnancy, for example, genetic and environmental causes. However, the role of a sedentary lifestyle and/or excess energy intake is more prominent in GDM. Physically active women are less likely to develop GDM and other pregnancy-related diseases. Weight gain in pregnancy causes increased release of adipokines from adipose tissue; many adipokines increase oxidative stress and insulin resistance. Increased intramyocellular lipids also increase cellular oxidative stress with subsequent generation of reactive oxygen species. A well-planned program of exercise is an important component of a healthy lifestyle and, in spite of old myths, is also recommended during pregnancy. This paper briefly reviews the role of adipokines in gestational diabetes and attempts to shed some light on the mechanisms by which exercise can be beneficial as an adjuvant therapy in GDM. In this regard, we discuss the mechanisms by which exercise increases insulin sensitivity, changes adipokine profile levels, and boosts antioxidant mechanisms.

1. Introduction

Gestational diabetes mellitus (GDM) is the most prevalent metabolic disorder during pregnancy and is defined as glucose intolerance of variable severity that is first diagnosed during pregnancy and usually resolves not long after delivery [1, 2]. This definition includes any degree of glucose intolerance from just impaired to frankly diabetic [3]. Resolution of the condition is also important when differentiating between previously undiagnosed type 2 diabetes and GDM [4]. Insulin resistance, due to a series of hormonal changes, contributes to decreased blood glucose uptake by muscles [5]. This phenomenon seems to be important from an evolutionary point of view, as it ensures adequate glucose supply for fetal growth and development. In the third trimester a healthy pregnant woman has to increase her insulin secretion by 2–4 times to maintain glucose levels within normal limits. Pregnant women who develop GDM are unable to augment insulin production to compensate for their increased resistance to insulin [6].

There are several modifiable and unmodifiable risk factors for developing GDM. Obesity is a modifiable risk factor that is strongly associated with the development of gestational diabetes. In a survey of 97000 singleton births, obese women had a 3-fold increased risk of developing GDM than nonobese women [7]. Not only obese (body mass index (BMI) $> 30\,(\mathrm{kg/m^2})$) but also overweight women ($29 \geq \mathrm{BMI} \geq 25\,(\mathrm{kg/m^2})$) have a 1.8 to 6.5 times greater risk of developing GDM [8]. It is important to appreciate that there are parallel increases in both obesity and GDM, making it difficult to determine the contribution of obesity as an independent risk factor. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reveals a direct relationship between BMI and pregnancy complications (preeclampsia, caesarian section, higher neonatal birth weight) in pregnant women. This study also reported that maternal plasma glucose correlates with adverse pregnancy outcomes [9]. A study by Getahun et al. reports a significant increase in the prevalence of GDM from 1.2% to 4.2% in between 1989 and 2004 [10]. In the United States, GDM affects 14% of all pregnancies, causing approximately 200,000 cases annually [11]; however, its prevalence varies widely (1.7%–11.6%) between racial and ethnic groups [12]. Recently, the International Association of Diabetes and Pregnancy Study Groups recommended new screening criteria for GDM based on the HAPO study. Using these criteria, the total incidence of GDM reaches almost

18% percent [13]. In Canada GDM is diagnosed in 3.7% of nonaboriginal and 8%–18% of first-nations pregnancies [14]. Another meta-analysis study showed that the risk of developing GDM was 2.14-, 3.56-, and 8.56-fold higher in overweight, obese, and severely obese pregnant women [15]. The diagnosis of GDM is associated with increased body fatness as indexed by prepregnancy BMI; each unit increase in BMI raises the prevalence of GDM by 0.92% [16].

Until a few decades ago, physical activity was discouraged in pregnancy due to myths related to exercise-induced injury and/or adverse fetal and maternal outcomes [17]. However, findings from clinical and epidemiological studies show no adverse maternal and fetal effects on women engaged in mild and moderate physical activities. Indeed, pregnant women are now advised to engage in regular aerobic exercise in the absence of medical or obstetric complications [18]. The American College of Obstetricians and Gynecologists and the American Diabetes Association (ADA) recognize exercise as "a helpful adjunctive therapy" for GDM and suggest 30 minutes or more of moderated exercise a day on most, if not all, days of the week [19, 20]. This paper examines some of the most important pathophysiologic aspects of GDM and discusses how aerobic exercise can benefit some of the physiological adaptations of GDM.

2. Pathophysiology of GDM

Normal pregnancies are associated with increased insulin resistance, which begins in mid pregnancy and continues until delivery. This resistance is thought to be compensated by a nearly 200% to 250% increase in insulin secretion during pregnancy [21]. GDM can be considered as a transient form of type 2 diabetes, with the rapid onset triggered by the metabolic and hormonal changes of pregnancy. Indeed, the same set of underlying causes that induce diabetes, including autoimmune interactions with the pancreatic beta cells and monogenic causes of diabetes and insulin resistance of peripheral tissues, are also involved in the pathogenesis of GDM [22]. Some have even considered GDM "diabetes in evolution." It is likely that chronic insulin resistance has already developed in most (but not all) GDM patients before conception and that additional insulin resistance occurs during pregnancy [23]. In the long term, chronic insulin resistance and hypersecretion are likely to lead to beta cell dysfunction.

Autoimmune mechanisms may be principle underlying pathophysiologic pathway in a minority (≤10%) of GDM patients. Circulating antibodies against pancreatic beta cells or beta cell antigens (such as GAD) have been detected in GDM patients: insulin deficiency due to immunologic beta cell destruction is the initial step in this group of patients who have evolving type 1 diabetes [24]. The role of pregnancy as an inducer or accelerator of immunologic damage is yet to be determined.

A monogenic form of diabetes constitutes 1%-2% of all GDM patients, who either have an autosomal dominant mutation (sometimes referred to as maturity-onset diabetes of the young (MODY)) or a mutation in mitochondrial DNA (which is often associated with deafness). Such patients with preexisting disease are usually diagnosed during pregnancy screening tests. There is no direct correlation between BMI and the monogenic form of GDM, as patients tend not to be obese or have insulin resistance. The main underlying pathophysiology is dysregulation of beta cell mass or function which results in hyperglycemia. Several subtypes of MODY have been described in women with GDM, including MODY2 (mutation in glucokinase gene), MODY3 (mutation in hepatocyte nuclear factor 1α), and MODY4 (mutation in insulin promoter factor 1) [22].

The mechanisms of pregnancy-induced insulin resistance are not clear but variations in steroid and/or lactogenic hormone levels may have some role. In particular, human placental lactogen, human placental growth hormone, progesterone, cortisol, and prolactin are known to counteract the effects of insulin [25]. This is supported by some evidence such as (i) the chronology between raised insulin resistance and the growth of fetoplacental unit which is accompanied by increased production of these hormones, (ii) the similarity of metabolic changes after administration of these hormones to nonpregnant individuals having the metabolic dysregulation of GDM, and (iii) impaired glucose uptake after exposure of insulin-sensitive cells such as adipocytes caused by pregnancy hormones [25]. However, changes in hormone concentrations do not directly correlate with insulin resistance and do not imply a simple cause-and-effect relationship [26]. Recent data has focused on the roles of adipose tissue-derived mediators, such as adiponectin, leptin, resistin, tumor necrosis factor-alpha (TNF-α), visfatin, apelin, and chemerin in the pathogenesis of insulin resistance and inflammation (Figure 1) [27].

Adiponectin. Human adiponectin consists of 244 amino acids and has a distinct domain structure. It has a collagen-like and a globular C1q-like domain (similar to the complement component C1q). This adipokine circulates in the blood in at least three homomeric complexes: trimer (low-molecular weight form, LMW), hexamer (medium molecular weight form, MMW), and higher order multimers (high molecular weight form, HMW) [28, 29]. Plasma concentrations reveal a sexual dimorphism, with females having higher levels than males [30]. The HMW form may be the most biologically active form regulating glucose homeostasis [31, 32], but other studies show that even though the HMW form has a greater association with some cardiovascular diseases [33], it has a similar utility for the identification of insulin resistance and metabolic disturbances as does total adiponectin [34]. As opposed to other adipocytokines, plasma levels of adiponectin inversely correlate with body mass index (BMI), intra-abdominal fat, and indices of insulin resistance [35]. Plasma levels of adiponectin decrease with weight gain and are increased by weight loss [36, 37]. Many studies suggest that adiponectin is an important regulator of insulin sensitivity and glucose homeostasis, with several reports confirming an inverse relationship between insulin resistance and plasma adiponectin levels [38]. Hypoadiponectinemia is also associated with beta cell dysfunction [39, 40]. Other studies show that adiponectin has anti-inflammatory effects,

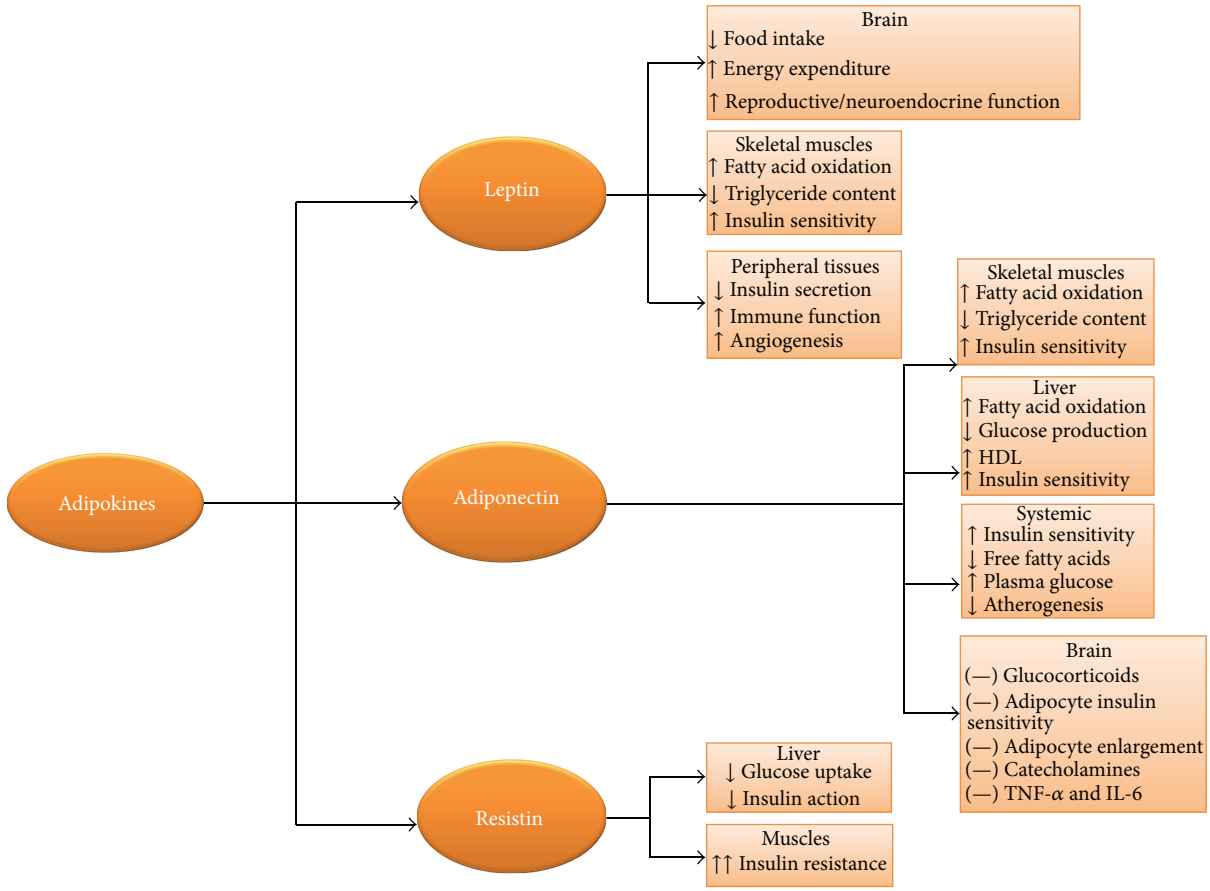

FIGURE 1: Selected physiologic roles of adipokines in relation to glucose metabolism and insulin sensitivity (↑increase, ↓decrease, (—) inhibit).

such as inhibition of endothelial nuclear factor kappa B (NF-κB) and suppression of phagocytic activity and TNF-α production in macrophages [38, 41, 42]. Adiponectin levels in early pregnancy seem to be unchanged or decreased [43–45] and are inversely related to maternal BMI and insulin sensitivity [46]. However, in GDM pregnancies, adiponectin levels decrease independently of changes in maternal BMI or insulin sensitivity [43, 47–49]. A study by Cseh et al. observed significantly decreased plasma adiponectin levels in 30 women with GDM, compared with 40 nondiabetic pregnant women; they reported that plasma adiponectin levels had a negative linear correlation with serum tumor necrosis factor-α (TNF-α), leptin, fasting C-peptide concentration, BMI, and fasting C-peptide/blood glucose ratio (which was used as an indirect parameter of insulin resistance) [50]. Furthermore, lower first trimester adiponectin levels were predictive of the development of GDM later in pregnancy. Women with adiponectin concentrations lower than 6.4 μg/mL experience a 4.6-fold increased risk of GDM, compared to those with higher concentrations [51]. A few studies have measured adiponectin levels after delivery at different time intervals (3 months and 1, and 1.5 years) in women with GDM and compared with those women having normal pregnancies. Hypoadiponectinemia persists even 1.57 years after delivery in GDM subjects, where it is associated with decreased insulin sensitivity and low HDL and and negatively correlated to other inflammatory markers such as CRP, plasminogen activator inhibitor-1 (PAI-1), and IL-6, even after adjustment for BMI [52–54]. Even though the basis for hypoadiponectinemia and GDM is unclear, suggested mechanisms for the insulin sensitizing effect of adiponectin include (a) promotion of insulin signaling at the receptor/postreceptor level, (b) reduction of gluconeogenesis, (c) improved lipid oxidation, and (d) inhibition of TNF-α signaling in adipose tissue [55]. Some experiments with globular adiponectin, whose *in vivo* importance is questionable, propose a role for AMPK [56] and PPARα [57] in its metabolic effects on skeletal muscles. Muscle binding of adiponectin translocates GLUT4 (resulting in increased glucose uptake) and increases nonoxidative glycolysis while also reducing intramyocellular triacylglycerol content to improve fatty acid oxidation [58, 59]. Adiponectin also sensitizes liver cells to the actions of insulin and suppresses the synthesis and function of enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase involved in gluconeogenesis [60]. Adiponectin also affects fatty acid metabolism in the liver with secondary influences on plasma triacylglycerol and circulating nonesterified fatty acids. Adiponectin also induces insulin secretion *in vitro* and *in vivo* [61]. While the information on the influence of adiponectin in normal insulin sensitivity is

unclear [62, 63], it does, however, appear to augment insulin secretion during insulin resistance [63]. Several studies report that adiponectin has antiapoptotic effects on beta cells, both in cell culture and islet preparations [64, 65].

Leptin. Leptin is a 16kDa protein hormone that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. It is one of the best known hormone markers of obesity, and in humans, the leptin gene is located on chromosome 7 [66]. So far, six types of receptors have been recognized for leptin (Ob-Ra-f). Ob-Re does not encode a transmembrane domain and is secreted and circulates in human plasma and represents the major leptin-binding activity [67]. Janus-activated kinase (JAK), signal transducers and activators of transcription (STAT), insulin receptor substrate, and the mitogen-activated protein kinase (MAPK) pathways are important leptin intracellular signaling mechanisms [68]. The binding of leptin to its receptor leads to the formation of the Ob-R/JAK2 complex and activation of STAT3, which is phosphorylated and migrates to the nucleus to presumably effect changes in gene expression [69]. Binding of leptin receptors to JAK2 also results in JAK2 autophosphorylation [70], which in turn phosphorylates insulin receptor substrate proteins, and involvement of phosphatidyl inositol 3-kinase to activate downstream signals [71].

During pregnancy leptin is produced by maternal and fetal adipose tissues, as well as by placental cells [72]. Plasma levels of leptin increase by 150% to 200% in the second and third trimesters over those occurring in the first trimester. Many physiological functions have been attributed to leptin, including regulation of food intake and energy balance through central hypothalamic pathways, signaling to the reproductive system (stimulating secretion of GnRH from hypothalamus, FSH and LH from pituitary gland), inhibition of insulin secretion from pancreatic beta cells, stimulation of glucose transport and utilization, glycogen synthesis, and fatty acid metabolism [73, 74]. Reduction of insulin secretion from pancreatic beta cells can result from the effect of leptin on the ATP-sensitive potassium channels. It has been proposed that leptin prevents beta cell stimulation by blocking cAMP signaling. Furthermore, leptin may hinder insulin secretion through cAMP-dependent protein kinase A (PKA) and protein kinase C (PKC). Leptin also regulates endocrine function, inflammation, immune response, and angiogenesis. Weight loss, fasting, and starvation reduce leptin concentrations, while weight gain and hyperinsulinemia have the opposite effects [75–79]. Plasma levels of leptin in pregnant women are 2- to 3-fold above nonpregnant levels and result from an upregulation of adipocyte synthesis in the presence of insulin resistance and hyperinsulinemia [79]. The origin of pregnancy-induced increases in leptin levels remains unclear [80]. Some evidence implies that the placenta, instead of adipose tissue, is the main site of leptin production; for instance, increased leptin levels precede increases in maternal weight [81]. The human placenta also has high leptin mRNA content [82]. Furthermore, maternal leptin levels drop after delivery. More than 90% of placental leptin is released to the maternal circulation [81]. Leptin also has many functional roles in the human fetus, including embryonic implantation, developmental growth, and organogenesis. For instance leptin plays critical roles in the development of the fetal skeletal and lung development.

Many studies document increased maternal leptin levels in GDM [83–86] and hyperleptinemia in early pregnancy, which may have predictive implications. In a study of 823 pregnant women in early pregnancy (13 weeks), Qiu et al. found a strong linear association between maternal plasma leptin concentration and the risk of GDM later in pregnancy. After adjusting for maternal prepregnancy adiposity and other confounders, those subjects with leptin concentration of 31.0 ng/mL had a 4.7-fold increased risk of GDM compared to those who had concentrations of 14.3 ng/mL or less [87]. Increases in leptin levels before the development of overt GDM have also been reported by others [88]. Moreover, increased leptin levels also occur in the amniotic fluid of pregnant women who subsequently progress to GDM. A 1 ng/mL increase in amniotic leptin levels raises the risk of GDM development by 4%. Amniotic fluid leptin levels and amniotic insulin concentration are directly correlated [89]. In spite of all this evidence, unchanged [90] and decreased levels [91] of leptin were reported in patients with GDM. Differences in disease severity or ethical variations may partially explain these discrepancies.

GDM is considered an aggravation of the inflammatory state that occurs in normal pregnancy and is associated with increased placenta expression of TNF-α and IL-6 [92]. These inflammatory cytokines increase the expression of placental leptin mRNA [93]. On the other hand, leptin increases production of TNF-α and IL-6 by monocytes. Thus, a vicious cycle develops which perpetuates the inflammatory state and intensifies insulin resistance.

Resistin. Resistin is a cysteine-rich peptide hormone that has been detected mostly in tissues involved in the inflammatory processes [94]. Cellular origins of resistin include adipocytes, monocytes, and macrophages [95]. The physiologic role of resistin in obesity and type 2 diabetes mellitus has been the subject of much controversy. Several studies have shown increased expression of resistin in abdominal adipose tissue of obese individuals [96–98] which correlates with the severity of obesity [99] and insulin resistance [100], while others failed to confirm any impact of obesity and insulin resistance on the concentrations of resistin [101, 102]. The detection of a high resistin expression in immune cells [103, 104] implies that it could possibly play a role in the establishment of insulin resistance through effects on inflammation.

Serum resistin levels in the first and second trimesters of normal pregnancy are similar to those found in nonpregnant women, but levels significantly increase in the third trimester [105]. Additionally, resistin gene expression in term placental tissue is significantly greater than that in chorionic villous tissue in the first trimester [106]. The increased third trimester resistin levels, along with other placental-derived hormones, might contribute to the insulin resistance and postprandial hyperglycemia in the second half of pregnancy. Physiologic concentrations of resistin (10 ng/mL) promote trophoblast

glucose uptake, while higher concentrations (50–100 ng/mL) significantly impair it [107].

The precise physiologic role of resistin in human pregnancy remains to be determined. Studies of resistin levels during pregnancy complicated with GDM have produced inconsistent results; elevated [43, 108, 109], lower [46, 110], or even unaltered values [45] have all been reported. Lappas et al. showed a biphasic effect of insulin on the release of resistin [111]. Low concentrations of insulin greatly enhance the release of resistin, while it returns to basal levels when the placenta is exposed to higher insulin concentrations, possibly by a downregulation of resistin expression in the presence of high insulin concentration. This biphasic effect of insulin may explain the low resistin levels reported in GDM [110].

TNF-α. Normal pregnancy is accompanied by a proinflammatory environment. TNF-α, which is correlated with insulin resistance in obesity, could also play similar roles in GDM and preeclampsia as well. The placenta is the main site of TNF-α (and interleukin-6, another inflammatory mediator) production during pregnancy and levels of TNF-α peak in late gestation. The vast majority of the TNF-α synthesized by the placenta is delivered to maternal circulation with only a small amount to the fetal compartment [26]. The rise in TNF-α levels may be related to pregnancy-associated increases insulin resistance [26, 112]. There is strong evidence linking TNF-α to downregulation of insulin receptor signaling in cultured adipocytes [113], hepatocytes [114], and skeletal muscles [115]. Importantly, increased TNF-α is associated with insulin resistance in obesity [116], aging [117], sepsis [118], and after muscle damage [119]. Studies made *in vitro* report that placental tissues from women with GDM release greater amounts of TNF-α in response to a glucose stimulus than those from women with normal glucose tolerance [120]. In this regard, TNF-α has been hypothesized to exert an inhibitory effect on insulin secretion and insulin-regulated glucose uptake in GDM, thus contributing to the sustained hyperglycemia [121]. Furthermore, TNF-α has been shown to be a significant independent predictor of insulin resistance in GDM [26].

Visfatin. Visfatin is another adipokine which is mainly expressed in visceral adipose tissue. It shows insulin-like effects on cultured cells and decreases plasma glucose levels in mice [122]. Its pathophysiological role, along with other adipokines, is largely unknown. Plasma level rises in visfatin increase during obesity, type 2 diabetes, and the metabolic syndrome [122–124] and fluctuate in normal weight pregnant women with peak levels between 19 and 26 weeks and a nadir between 27 and 34 weeks [109]. Some investigators have not observed a relationship between visfatin and visceral fat mass, BMI, or insulin sensitivity [123, 125]. Visfatin expression occurs in human fetal membranes and placenta [126], which is related to mRNA expression of TNF-α and IL-6 [127]. Visfatin is also secreted from the human amniotic epithelium and shows antiapoptotic effects on both amniotic epithelial cells and fibroblasts, where it protects them from apoptosis induced by chronic distension, labor, or infection [128]. Increased expression levels of visfatin mRNA in adipose tissue of both pregnant human [126] and animal [129] suggest its participation in energy homeostasis during pregnancy to meet the nutritional demands of fetal growth [130].

There are no consistent results on the plasma levels of visfatin in GDM, as both increased [131–133] and decreased [127, 134–136] concentrations have been reported. Mastorakos et al. reported that visfatin concentrations in the first trimester positively predict insulin sensitivity during the second trimester in nonobese, nondiabetic white women [137]. Furthermore, the immune-modulatory properties of visfatin can significantly affect insulin resistance. Treatment of human fetal membranes with recombinant human visfatin significantly increases levels of some inflammatory cytokines such as IL-1β, TNF-α, and IL-6, all of which influence insulin sensitivity [138].

Apelin. Apelin is another adipokine secreted from adipocytes [139] and several other tissues [140]. Even though its role in normal physiology has not been described precisely, several functions have been named for this bioactive peptide. Apelin participates in both normal and pathologic angiogeneses [141] which may help in the growth of adipose tissue [142]. Insulin increases apelin synthesis in adipocytes and plasma apelin level rises in obesity associated with insulin resistance [143]. Apelin also reduces blood pressure by enhancing endothelium dependent vasodilation [144].

Apelin expression has been demonstrated in human placental tissue [145] and is thought to be required for endothelial cell proliferation and growth of blood vessels [146]. A recent human study reported increased apelin levels in maternal serum of women with GDM [147]. However, further studies are needed to clarify the role of this novel adipokine in normal and complicated pregnancy.

Chemerin. Chemerin is another protein that is highly expressed in human adipose tissue, liver, and lung and has a role in adaptive and innate immunity [148]. Chemerin boosts inflammation by stimulating chemotaxis [149]. IL-β increases chemerin mRNA expression and secretion from 3T3-L1 derived adipocytes [150]. Since chemerin plays a role in adipocyte differentiation and glucose metabolism, it is also considered an adipokine [151]. Adenoviral small hairpin RNA targeted knockdown of chemerin (or its receptors) impairs differentiation of 3T3-L1 preadipocytes and decreases the expression of lipid and glucose metabolizing genes in adipose tissue [151]. Chemerin level in humans correlates with BMI, plasma lipids, and blood pressure [151]. Increased serum concentration of chemerin occurs in individuals with type 2 diabetes [152]. However, studies aimed at evaluating the role of chemerin in GDM did not demonstrate a clear association between metabolic dysregulation and chemerin levels during GDM [153, 154].

3. Role of Exercise in GDM Management

Even though some studies were inconclusive on the benefits of exercise in preventing GDM [155, 156], there is overwhelming evidence suggesting that women who exercise have a considerably lower chance of developing GDM [81, 82, 93, 157].

The Canadian Diabetes Association (CDA) recommends that "Physical activity should be encouraged, with the frequency, type, duration, and intensity tailored to individual obstetric risk" [1]. The American Diabetes Association also suggests "Women without medical or obstetrical contraindications are encouraged to start or continue a program of moderate exercise as part of treatment for GDM" [2]. Participating in any physical activity during the first 20 weeks of pregnancy leads to an approximately 50% risk reduction for GDM [158]. In a prospective cohort study among 21,765 women in the Nurses' Health Study II, Zhang et al. showed that physical activity before pregnancy is associated with a risk reduction in GDM. It is interesting to note that subjects not performing intense exercise but instead engage in brisk walking also enjoy a similar risk reduction [159]. Women who engage in intense physical activity before pregnancy have a 44% and 24% risk reduction for GDM and abnormal glucose tolerance, respectively [160]. In a case controlled study of physical activity in 155 pregnant women with GDM compared with 386 healthy pregnant controls, physical activity before and during pregnancy was associated with a reduced incidence of GDM [158].

In spite of these studies, there remain many long-standing myths on the harms of exercise during pregnancy. For instance, some believe that women who are unused to exercise before pregnancy should not start when pregnant, while others suggest that pregnancy means eating for two. In a study of pregnant women in Norway, 55% were recognized as nonexercisers (≤20 minutes of vigorous recreational physical activity at least once a week) in the third trimester and 66.5% reported walking ≤30 minutes per day [161]. Unfortunately, many women reduce their physical activity during pregnancy, resulting in gaining more weight than is recommended. Age, education, working status, health condition, and psychosocial factors such as social modeling and knowledge all determine likelihood of weight gain and a sedentary lifestyle during pregnancy [162].

Aerobic exercise is the recommended type of exercise to prevent excessive weight gain and maintain cardiovascular fitness. A recent study suggests that the amount of exercise for pregnant women should be equivalent to energy expenditure of 16 (ideally 28) metabolic equivalent tasks (METs) per week. This can be achieved by walking 5.1 kilometers every day or using a stationary bicycle for 45 min each day [163]. It is advised that activities such as contact sports be avoided and attention paid to adequate hydration and avoidance of exercising in uncomfortably hot and humid environments [164]. When starting an aerobic exercise program, careful consideration should be given to the intensity of exercise. Most experts suggest exercising to 60%–70% of maximal heart rate for those who were sedentary before pregnancy and 60%–90% of maximal heart rate for those who are well trained. Borg's rating of perceived exertion is another method to assure an ideal intensity of exercise when it is performed on a self-paced base. Scales from 6 to 11 are considered mild, 12 to 14 moderate (or somewhat hard), and 15 to 20 are hard exercises. "Talk test" or physical activity at relaxed strength that allows one to keep up conversation is another method to confirm that intensity of exercise is appropriate and women are not overexerting [82] (Table 1).

3.1. Suggested Exercise-Induced Benefits in GDM. There are a few studies of the mechanisms of exercise-induced benefits in GDM. However, because of the similarity between GDM and type 2 diabetes, most of the suggested mechanisms in diabetes can be extrapolated to GDM.

3.1.1. Increased Insulin Sensitivity. At least two distinct pathways are involved in glucose transport; one is stimulated by insulin or insulin mimetics and the other activated by contraction or hypoxia [165–167]. Phosphatidylinositol 3 kinase (PI3-kinase) is involved in the insulin activated (but not contraction activated) pathway [168], while 5'AMP-activated protein kinase (AMPK) participates in contraction activated reactions [169]. Insulin stimulated tyrosine phosphorylation of insulin receptor substrate (IRS), activity of PI3 kinase, and insulin stimulated Aκt kinase activity are all diminished in skeletal muscle of obese, diabetic, and GDM patients [92, 170]. Therefore, exercise can provide an alternative way to bypass the impaired insulin signal transduction in muscles of diabetic patients [171]. Regular physical activity improves insulin function and glucose tolerance in healthy individuals [172], patients with obesity [173], insulin resistance [174], and diabetics [175, 176]. Molecular mechanisms for improved glucose clearance and insulin sensitivity following exercise are related to the increased expression and activity of signaling proteins and enzymes that are involved in skeletal glucose and fat metabolism [177, 178]. The biogenesis of glucose transporter isoform 4 (GLUT4), a key enzyme in insulin stimulated glucose uptake by muscle, is increased by exercise training [179, 180]. Biopsies of the vastus lateralis muscle in pregnant women show increased GLUT4 expression in mildly exercise-trained women [181]. The transcriptional factor peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) stimulates GLUT4 expression in addition to stimulating mitochondrial biogenesis and promoting muscle remodeling to a fiber type composition that has greater oxidative capacity and less glycolytic metabolism in nature [182, 183].

However, exercise-induced improvement in insulin signaling is not exclusively restricted to increased GLUT4 protein expression, as its concentration is similar in sedentary diabetics and insulin-sensitive control subjects [184, 185]. While exercise increases GLUT4 protein and mRNA in diabetic patients [186], increased postreceptor insulin signaling, especially at the distal step of the insulin PI3-kinase cascade (which results in GLUT4 translocation and glucose uptake), is the main mechanism [178, 187, 188]. Atypical protein kinase C (aPKC) and Akt substrate of 160 kDa (AS160) are among newly characterized insulin signaling molecules [189, 190]. AS160 in the basal nonphosphorylated state acts as an inhibitor for GLUT4 translocation. Insulin stimulates AS160 phosphorylation by Akt on five of six phosphor-Akt substrate motifs, leading to increased GLUT4 membrane trafficking events [191]. The exact mechanisms of aPKC in controlling GLUT4 translocation are still not clear, but some reports

Table 1: Important facts about recommending exercise to pregnant women [82, 163, 164].

Key points
(i) Exercise is part of healthy lifestyle which should be continued during pregnancy.
(ii) The goal of aerobic exercise in pregnancy is to maintain or improve overall fitness (not training for athletic competitions).
(iii) Contact sports or activities with risks of falling or trauma (snow and water skiing, horseback riding, etc.) should be avoided.
(iv) Exercise does not increase adverse outcomes during pregnancy.
(v) Pregnant women previously unaccustomed to exercise should start gradually and not overexert themselves.
(vi) Women should have self-monitoring exertion. "Easy talk" can be helpful for detection of overexertion.
(vii) Exercise in uncomfortably hot and humid weather should be avoided.
(viii) Achieving 16 MET h/w is a reasonable goal of energy expenditure for those who were previously sedentary.

suggest that parallel to Akt, activation of aPKC is essential in both the process of translocation and docking/fusion of GLUT4 to the plasma membrane [192].

There are many changes in exogenous insulin requirement and glycemic control after a 4–8-week period of exercise in the last trimester of pregnancy [193–195]. For example, there are reduced levels of glycosylated hemoglobin, fasting, and 1-hour plasma glucose following a six-week arm ergometry in pregnant women with GDM [193]. This exercise protocol was significantly milder, in terms of duration and frequency, than those which have been suggested for diabetic or gravid subjects [196, 197]. In another study of GDM patients unresponsive to dietary therapy, 8 weeks of supervised exercise (50% of VO2max/3 times a week) maintained euglycemia without the need for insulin therapy [195]. It is important that exercise is performed on a chronic basis so as to have a sustained impact on glycemic control, since several studies report a decline in postprandial plasma glucose upon cessation of exercise [198, 199].

3.1.2. Adipokine Changes. Weight reduction in obese subjects, via exercise, results in a lower loss of muscle (compared to fat) than weight loss through diet [200]. Maintaining lean body mass is essential for better glucose transport and fat metabolism. A reduction in fat mass is helpful in increasing adiponectin levels and improving cytokine profiles. Controlling the release and activity of at least two cytokines, TNF-α and IL-6, could contribute to the natural protective effects of physical activity. Interleukin-6 (IL-6) is the first cytokine to be released into the circulation during exercise, and its levels increase in an exponential fashion in response to exercise [201]. IL-6 mRNA is upregulated in contracting skeletal muscle [202] and the transcriptional rate of the IL-6 gene is also markedly enhanced by exercise [203]. IL-6 acts as both a proinflammatory and anti-inflammatory cytokine: when secreted by T cells and macrophages, IL-6 stimulates the immune response and boosts inflammatory reactions, while muscle-produced IL-6 exerts anti-inflammatory effects through its inhibitory effects on TNF-α and IL-1β and activation of interleukin-1 receptor antagonist (IL-1ra) and IL-10 [204]. Exercise-induced increases in plasma IL-6 correlate with the muscle mass involved in exercise activity and also with the mode, duration, and especially the intensity of exercise [205]. Exercise also confers protection against TNF-induced insulin resistance [206]. IL-6 enhances lipid turnover and stimulates lipolysis as well as fat oxidation via activation of AMP-activated protein kinase [207]. The lipolytic effect of IL-6 on fat metabolism was confirmed in two clinical studies of healthy and diabetic subjects [207, 208]. During exercise, IL-6 also increases hepatic glucose production. Glucose ingestion during exercise reduces IL-6 production by muscles, suggesting that IL-6 is released due to the reduction in glycogen levels during endurance exercise and the consequences of adrenergic stimulation of IL-6 gene transcription via protein kinase A activation [209].

The study of Clapp III and Kiess is one the few experiments that evaluated the effects of exercise on metabolic markers during pregnancy [152]. They measured the concentrations of TNF-α and leptin in a control group of physically active women and compared this with groups of active and nonactive pregnant subjects. In this experiment, regular weight bearing exercise suppressed the pregnancy-associated changes normally seen in both TNF-α and leptin. The authors inferred that leptin reduction is a reflection of decreased fat accretion, and changes in TNF-α could be evidence of altered insulin resistance [152]. Even though exercise-induced TNF-α changes have been reported by other investigators in both pregnant and nonpregnant subjects [210, 211], there is no consistency in the case of exercise-induced leptin changes. For example, Hopkins et al. [212] reported an increase in maternal leptin from mid to late pregnancy following aerobic exercise. This discrepancy in leptin levels has been observed in nonpregnant individuals as well [213–215].

3.1.3. Oxidative Stress and Antioxidant Effect of Exercise on GDM. One characteristic of pregnancy is the early accumulation of fat depots, followed by increased adipose tissue lipolysis and increased levels of plasma free fatty acids (FFAs) which all enhance insulin resistance [216]. Intramyocellular accumulation of diacylglycerol and subsequent activation of protein kinase C are thought to mediate FFA-stimulated insulin resistance in skeletal muscles. Insulin resistance leads to reduction of tyrosine phosphorylation of the IRS-1 and inhibits activation of PI3 kinase [217]. Increased intramyocellular lipids increase cellular oxidative stress with subsequent generation of ROS, stimulating lipid membrane peroxidative injury of mitochondrial membranes. Oxidative stress inhibits expression of adipokines [218]. Increase in TNF-α and IL-6 during diabetes may be due to hyperglycemia related to oxidative stress and inflammation [83]. One of the cornerstone effects of exercise training is to augment the oxidative capacity of skeletal muscles, so that there is

an improvement in the rate of whole body fat oxidation [219]. This increase in fat oxidation capacity is partly due to increases in fatty acid transport proteins, leading to increased removal of plasma FFAs [220]. Plasma membrane-associated fatty acid binding proteins (FABPpm) and fatty acid translocase/CD36 (FAT/CD36) are among several key proteins that have been identified as fatty acid transporter proteins in human and animal muscles [221]. Exercise also activates AMPK, which stimulates fatty acid oxidation, glucose uptake, and mitochondrial biogenesis.

There are many studies which have evaluated the role and importance of oxidative stress in pathogenesis of type 2 diabetes; however, this role of oxidative stress in GDM has received much less attention. The term oxidative stress indicates a shift towards a prooxidant environment in the balance between oxidant species formation and antioxidant defenses. Chemical compounds capable of producing potential toxic reactive oxygen species (ROS) are known as prooxidants and antioxidants are compounds detoxifying ROS. Free radicals are reactive chemical species having a single unpaired electron in an outer orbit. This unstable configuration provides energy which is released through reactions with adjacent molecules such as proteins, lipids, carbohydrates, and nucleic acids. The majority of free radicals that damage biological systems are oxygen-free radicals [222].

An antioxidant stabilizes or deactivates free radicals before they attach to cells. Humans have evolved highly complex antioxidant systems (enzymatic and nonenzymatic) that work synergistically, and in combination with each other, to protect cells and organ systems against free radical induced damage. Antioxidants can be endogenously produced substances or can be obtained from exogenous sources, for example, as a part of a diet or as dietary supplements. Endogenous antioxidants play a crucial role in maintaining optimal cellular functions and thus systemic health and well-being. However under conditions which promote oxidative stress, endogenous antioxidants may not be sufficient and dietary antioxidants may be required to maintain optimal cellular functions. The most efficient enzymatic antioxidants involve glutathione peroxidase, catalase and superoxide dismutase. Nonenzymatic antioxidants include vitamins E and C, thiol antioxidants (glutathione, thioredoxin, and lipoic acid), melatonin, carotenoids, natural flavonoids, and other compounds [223].

There are limited data suggesting that oxidative stress may be involved in progression or pathophysiology of GDM. Coughlan et al. reported that the release of 8-isoprostane, along with superoxide dismutase activity and protein carbonyl from human placental explants, is significantly increased in GDM compared to normal placental tissues [224]. They also reported that placentae from women with GDM display a reduced capacity to respond to oxidative stress [225]. Markers of ROS, such as 8-isoprostane, are increased in placenta, subcutaneous adipose tissue, and skeletal muscle in women with GDM [226]. These data are consistent with the hypothesis that oxidative stress may be involved in the progression and/or pathogenesis of GDM. Other related studies suggest that oxidative stress in GDM is also related to an altered antioxidant capacity as well. In a comparison between healthy pregnant women with two groups with diabetes (GDM and type 1 diabetes), Peuchant et al. reported that plasma and erythrocyte free malondialdehyde (MDA) levels were significantly higher, while levels of plasma vitamin E, erythrocyte vitamin A, and glutathione peroxidase (GPX) were lower, in both diabetic (including GDM) subjects [227]. Evidence of lipid peroxidation and protein oxidative damage is also present in the erythrocytes of both mothers with GDM and their newborn infants [228]. In a longitudinal study, Toescu et al. showed evidence for higher serum lipid and lipid hydroperoxide levels and lower corrected antioxidant capacity throughout pregnancy in diabetic women (type 1, 2 and GDM) [229].

Exercise training leads to an upregulation of antioxidant defense mechanisms in various tissues, presumably due to increased levels of oxidative stress that occurs during exercise. Exercise-induced production of ROS provokes specific adaptations such as increased antioxidant/oxidative damage repairing enzyme activity, increased resistance to oxidative stress, and lower levels of oxidative damage. Physiological levels of shear stress increase the expression of Cu/Zn SOD in human aortic endothelial cells [230], while endurance training mainly induces Mn-SOD expression [231]. In our experiments with type 2 diabetic mice *(db/db)* we observed a specific downregulation of aortic Mn-SOD following diabetes. Low-intensity exercise increased Cu/Zn-SOD protein production, whereas moderate intensity exercise increased Mn-SOD [232]. Others have also reported such preferential effects of exercise on antioxidant enzyme regulation. For instance, Sankaralinqam et al. reported that arteries from pregnant women involved in low intensity exercise (stretching) had significantly greater expression of the vascular antioxidant enzyme SOD when compared with those who performed moderate intensity exercise (walking) [233]. The effect of exercise on raising the levels of glutathione peroxidase and catalase has also been reported in pregnant women [234].

4. Summary

Obesity is reaching epidemic proportions in modern society. Overweight women are at increased risk of several complications during pregnancy, including GDM. Complications of obesity further add to the metabolic changes that promote adipose tissue accretion in early gestation and later onset of insulin resistance. Recent investigations have focused on the role of adipokines or adipocytokines as mediators of insulin resistance. This paper focuses on their role in insulin resistance during pregnancy. Existing data supports the notion that exercise increases insulin sensitivity, possibly by changing the adipokines profile and by upregulating antioxidant defense mechanisms. It is likely that based on current knowledge, regular participation in physical activity could reduce risk profiles for GDM in pregnant women.

References

[1] "Canadian Diabetes Association Clinical Practice Guidelines Expert Committee: Canadian Diabetes Association clinical

practice guidelines for the prevention and management of diabetes in Canada," *Canadian Journal of Diabetes*, vol. 27, pp. S99–S105, 2003.

[2] American Diabetes Association, "Gestational diabetes mellitus," *Diabetes Care*, vol. 27, pp. S88–S90, 2004.

[3] K. G. Alberti and P. Z. Zimmet, "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation," *Diabetic Medicine*, vol. 15, no. 7, pp. 539–553, 1998.

[4] E. A. Reece, C. Homko, M. Miodovnik, and O. Langer, "A consensus report of the Diabetes in Pregnancy Study Group of North America conference: little Rock, Arkansas, May 2002," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 12, no. 6, pp. 362–364, 2002.

[5] R. Artal, "Exercise: the alternative therapeutic intervention for gestational diabetes," *Clinical Obstetrics and Gynecology*, vol. 46, no. 2, pp. 479–487, 2003.

[6] C. Kühl, "Etiology and pathogenesis of gestational diabetes," *Diabetes Care*, vol. 21, no. 2, pp. B19–B26, 1998.

[7] A. T. Blanco, S. W. Semilen, Y. Davis, S. Lopez, R. Lapinski, and C. J. Lockwood, "Pregnancy outcome and weight gain recommendations for the morbidly obese women," *Obstetrics and Gynecology*, vol. 91, no. 1, pp. 97–102, 1998.

[8] Y. Linné, "Effects of obesity on women's reproduction and complications during pregnancy," *Obesity Reviews*, vol. 5, no. 3, pp. 137–143, 2004.

[9] HAPO Study Cooperative Research Group, "Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index," *An International Journal of Obstetrics and Gynaecology*, vol. 117, no. 5, pp. 575–584, 2010.

[10] D. Getahun, C. Nath, C. V. Ananth, M. R. Chavez, and J. C. Smulian, "Gestational diabetes in the United States: temporal trends 1989 through 2004," *American Journal of Obstetrics and Gynecology*, vol. 198, no. 5, pp. 525.e1–525.e5, 2008.

[11] American Diabetes Association, "Standards of medical care in diabetes-2009," *Diabetes Care*, vol. 32, no. supplement 1, pp. S13–S61, 2009.

[12] S. Schneider, C. Bock, M. Wetzel, H. Maul, and A. Loerbroks, "The prevalence of gestational diabetes in advanced economies," *Journal of Perinatal Medicine*, vol. 40, no. 5, pp. 511–520, 2012.

[13] M. J. Paglia and D. R. Coustan, "Gestational diabetes: evolving diagnostic criteria," *Current Opinion in Obstetrics and Gynecology*, vol. 23, pp. 72–75, 2011.

[14] "Canadian Diabetes Association Clinical Practice Guidelines Expert Committee," *Canadian Diabetes Association*, vol. 32, pp. S1–S201, 2008.

[15] S. Y. Chu, W. M. Callaghan, S. Y. Kim et al., "Maternal obesity and risk of gestational diabetes mellitus," *Diabetes Care*, vol. 30, no. 8, pp. 2070–2076, 2007.

[16] M. R. Torloni, A. P. Betrán, B. L. Horta et al., "Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis: diagnostic in Obesity and Complications," *Obesity Reviews*, vol. 10, no. 2, pp. 194–203, 2009.

[17] M. M. Schlüssel, E. B. De Souza, M. E. Reichenheim, and G. Kac, "Physical activity during pregnancy and maternal-child health outcomes: a systematic literature review," *Cadernos de Saude Publica*, vol. 24, no. 4, pp. S531–S544, 2008.

[18] J. C. Dempsey, C. L. Butler, and M. A. Williams, "No need for a pregnant pause: physical activity may reduce the occurrence of gestational diabetes mellitus and preeclampsia," *Exercise and Sport Sciences Reviews*, vol. 33, no. 3, pp. 141–149, 2005.

[19] "ACOG Committee opinion. Number 267, January 2002: exercise during pregnancy and the postpartum period," *Obstetrics & Gynecology*, vol. 99, no. 1, pp. 171–173, 2002.

[20] American Diabetes Association, "Gestational diabetes mellitus," *Diabetes Care*, vol. 26, pp. S103–S105, 2003.

[21] B. E. Metzger, T. A. Buchanan, D. R. Coustan et al., "Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus," *Diabetes Care*, vol. 30, no. supplement 2, pp. s251–s260, 2007.

[22] T. A. Buchanan, A. Xiang, S. L. Kjos, and R. Watanabe, "What is gestational diabetes?" *Diabetes Care*, vol. 30, no. 2, pp. S105–S111, 2007.

[23] P. M. Catalano, E. D. Tzybir, R. R. Wolfe et al., "Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes," *American Journal of Physiology*, vol. 264, pp. E60–E67, 1993.

[24] T. A. Buchanan and A. H. Xiang, "Gestational diabetes mellitus," *Journal of Clinical Investigation*, vol. 115, no. 3, pp. 485–491, 2005.

[25] K. Y. Lain and P. M. Catalano, "Metabolic changes in pregnancy," *Clinical Obstetrics and Gynecology*, vol. 50, no. 4, pp. 938–948, 2007.

[26] J. P. Kirwan, S. Hauguel-De Mouzon, J. Lepercq et al., "TNF-α is a predictor of insulin resistance in human pregnancy," *Diabetes*, vol. 51, no. 7, pp. 2207–2213, 2002.

[27] I. Falcão-Pires, P. Castro-Chaves, D. Miranda-Silva, A. P. Lourenço, and A. F. Leite-Moreira, "Physiological, pathological and potential therapeutic roles of adipokines," *Drug Discovery Today*, vol. 17, pp. 880–889, 2012.

[28] T. S. Tsao, H. E. Murrey, C. Hug, D. H. Lee, and H. F. Lodish, "Oligomerization state-dependent activation of NF-κB signaling pathway by adipocyte complement-related protein of 30 kDa (Acrp30)," *Journal of Biological Chemistry*, vol. 277, no. 33, pp. 29359–29362, 2002.

[29] U. B. Pajvani, X. Du, T. P. Combs et al., "Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin: implications for metabolic regulation and bioactivity," *Journal of Biological Chemistry*, vol. 278, no. 11, pp. 9073–9085, 2003.

[30] S. Suzuki, E. M. Wilson-Kubalek, D. Wert, T. S. Tsao, and D. H. Lee, "The oligomeric structure of high molecular weight adiponectin," *FEBS Letters*, vol. 581, no. 5, pp. 809–814, 2007.

[31] U. B. Pajvani, M. Hawkins, T. P. Combs et al., "Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity," *Journal of Biological Chemistry*, vol. 279, no. 13, pp. 12152–12162, 2004.

[32] D. K. Oh, T. Ciaraldi, and R. R. Henry, "Adiponectin in health and disease," *Diabetes, Obesity and Metabolism*, vol. 9, no. 3, pp. 282–289, 2007.

[33] S. Rizza, F. Gigli, A. Galli et al., "Adiponectin isoforms in elderly patients with or without coronary artery disease," *Journal of the American Geriatrics Society*, vol. 58, no. 4, pp. 702–706, 2010.

[34] P. Almeda-Valdes, D. Cuevas-Ramos, R. Mehta et al., "Total and high molecular weight adiponectin have similar utility for the identification of insulin resistance," *Cardiovascular Diabetology*, vol. 9, article 26, 2010.

[35] S. Mazaki-Tovi, H. Kanety, and E. Sivan, "Adiponectin and human pregnancy," *Current Diabetes Reports*, vol. 5, no. 4, pp. 278–281, 2005.

[36] W. S. Yang, W. J. Lee, T. Funahashi et al., "Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 8, pp. 3815–3819, 2001.

[37] A. Mavri, P. Poredoš, D. Šuran, B. Gaborit, I. Juhan-Vague, and P. Poredoš, "Effect of diet-induced weight loss on endothelial dysfunction: early improvement after the first week of dieting," *Heart and Vessels*, vol. 26, no. 1, pp. 31–38, 2011.

[38] K. Ohashi, N. Ouchi, and Y. Matsuzawa, "Anti-inflammatory and anti-atherogenic properties of adiponectin," *Biochimie*, vol. 94, pp. 2137–2142, 2012.

[39] G. Musso, R. Gambino, G. Biroli et al., "Hypoadiponectinemia predicts the severity of hepatic fibrosis and pancreatic beta-cell dysfunction in nondiabetic nonobese patients with nonalcoholic steatohepatitis," *American Journal of Gastroenterology*, vol. 100, no. 11, pp. 2438–2446, 2005.

[40] R. Retnakaran, A. J. G. Hanley, N. Raif et al., "Adiponectin and beta cell dysfunction in gestational diabetes: pathophysiological implications," *Diabetologia*, vol. 48, no. 5, pp. 993–1001, 2005.

[41] N. Ouchi, S. Kihara, Y. Arita et al., "Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-κB signaling through a cAMP-dependent pathway," *Circulation*, vol. 102, no. 11, pp. 1296–1301, 2000.

[42] T. Yokota, K. Oritani, I. Takahashi 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*, vol. 96, no. 5, pp. 1723–1732, 2000.

[43] D. Cortelazzi, S. Corbetta, S. Ronzoni et al., "Maternal and foetal resistin and adiponectin concentrations in normal and complicated pregnancies," *Clinical Endocrinology*, vol. 66, no. 3, pp. 447–453, 2007.

[44] S. Mazaki-Tovi, H. Kanety, C. Pariente et al., "Maternal serum adiponectin levels during human pregnancy," *Journal of Perinatology*, vol. 27, no. 2, pp. 77–81, 2007.

[45] A. J. O'Sullivan, A. D. Kriketos, A. Martin, and M. A. Brown, "Serum adiponectin levels in normal and hypertensive pregnancy," *Hypertension in Pregnancy*, vol. 25, no. 3, pp. 193–203, 2006.

[46] T. F. Chan, S. S. F. Yuan, H. S. Chen et al., "Correlations between umbilical and maternal serum adiponectin levels and neonatal birthweights," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 83, no. 2, pp. 165–169, 2004.

[47] J. Chen, B. Tan, E. Karteris et al., "Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines," *Diabetologia*, vol. 49, no. 6, pp. 1292–1302, 2006.

[48] F. Haugen, T. Ranheim, N. K. Harsem, E. Lips, A. C. Staff, and C. A. Drevon, "Increased plasma levels of adipokines in preeclampsia: relationship to placenta and adipose tissue gene expression," *American Journal of Physiology*, vol. 290, no. 2, pp. E326–E333, 2006.

[49] C. Worda, H. Leipold, C. Gruber, A. Kautzky-Willer, M. Knöfler, and D. Bancher-Todesca, "Decreased plasma adiponectin concentrations in women with gestational diabetes mellitus," *American Journal of Obstetrics and Gynecology*, vol. 191, no. 6, pp. 2120–2124, 2004.

[50] K. Cseh, E. Baranyi, Z. Melczer, E. Kaszás, E. Palik, and G. Winkler, "Plasma adiponectin and pregnancy-induced insulin resistance," *Diabetes Care*, vol. 27, no. 1, pp. 274–275, 2004.

[51] M. A. Williams, C. Qiu, M. Muy-Rivera, S. Vadachkoria, T. Song, and D. A. Luthy, "Plasma adiponectin concentrations in early pregnancy and subsequent risk of gestational diabetes mellitus," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 5, pp. 2306–2311, 2004.

[52] C. Winzer, O. Wagner, A. Festa et al., "Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus," *Diabetes Care*, vol. 27, no. 7, pp. 1721–1727, 2004.

[53] S. M. Heitritter, C. G. Solomon, G. F. Mitchell, N. Skali-Ounis, and E. W. Seely, "Subclinical inflammation and vascular dysfunction in women with previous gestational diabetes mellitus," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 7, pp. 3983–3988, 2005.

[54] H. C. Sung, H. K. Soo, B. S. Youn et al., "High plasma retinol binding protein-4 and low plasma adiponectin concentrations are associated with severity of glucose intolerance in women with previous gestational diabetes mellitus," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 8, pp. 3142–3148, 2008.

[55] J. Bełtowski, "Adiponectin and resistin—new hormones of white adipose tissue," *Medical Science Monitor*, vol. 9, no. 2, pp. RA55–RA61, 2003.

[56] T. Yamauchi, J. Kamon, Y. Minokoshi et al., "Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase," *Nature Medicine*, vol. 8, pp. 1288–1295, 2002.

[57] T. Yamauchi, J. Kamon, H. Waki et al., "Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis," *Journal of Biological Chemistry*, vol. 278, no. 4, pp. 2461–2468, 2003.

[58] A. E. Civitarese, B. Ukropcova, S. Carling et al., "Role of adiponectin in human skeletal muscle bioenergetics," *Cell Metabolism*, vol. 4, no. 1, pp. 75–87, 2006.

[59] R. B. Ceddia, R. Somwar, A. Maida, X. Fang, G. Bikopoulos, and G. Sweeney, "Globular adiponectin increases GLUT4 translocation and glucose uptake but reduces glycogen synthesis in rat skeletal muscle cells," *Diabetologia*, vol. 48, no. 1, pp. 132–139, 2005.

[60] R. A. Miller, Q. Chu, J. Le Lay et al., "Adiponectin suppresses gluconeogenic gene expression in mouse hepatocytes independent of LKB1-AMPK signaling," *Journal of Clinical Investigation*, vol. 121, no. 6, pp. 2518–2528, 2011.

[61] M. Okamoto, M. Ohara-Imaizumi, N. Kubota et al., "Adiponectin induces insulin secretion in vitro and in vivo at a low glucose concentration," *Diabetologia*, vol. 51, no. 5, pp. 827–835, 2008.

[62] K. Staiger, N. Stefan, H. Staiger et al., "Adiponectin is functionally active in human islets but does not affect insulin secretory function or β-cell lipoapoptosis," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 12, pp. 6707–6713, 2005.

[63] M. S. Winzell, R. Nogueiras, C. Dieguez, and B. Ahrén, "Dual action of adiponectin on insulin secretion in insulin-resistant mice," *Biochemical and Biophysical Research Communications*, vol. 321, no. 1, pp. 154–160, 2004.

[64] N. Wijesekara, M. Krishnamurthy, A. Bhattacharjee, A. Suhail, G. Sweeney, and M. B. Wheeler, "Adiponectin-induced ERK and Akt phosphorylation protects against pancreatic beta cell apoptosis and increases insulin gene expression and secretion," *Journal of Biological Chemistry*, vol. 285, no. 44, pp. 33623–33631, 2010.

[65] A. T. Turer and P. E. Scherer, "Adiponectin: mechanistic insights and clinical implications," *Diabetologia*, vol. 55, no. 9, pp. 2319–2326, 2012.

[66] A. M. Brennan and C. S. Mantzoros, "Drug Insight: the role of leptin in human physiology and pathophysiology—emerging clinical applications," *Nature Clinical Practice Endocrinology and Metabolism*, vol. 2, no. 6, pp. 318–327, 2006.

[67] H. Ge, L. Huang, T. Pourbahrami, and C. Li, "Generation of soluble leptin receptor by ectodomain shedding of membrane-spanning receptors in vitro and in vivo," *Journal of Biological Chemistry*, vol. 277, no. 48, pp. 45898–45903, 2002.

[68] R. Yang and L. A. Barouch, "Leptin signaling and obesity: cardiovascular consequences," *Circulation Research*, vol. 101, no. 6, pp. 545–559, 2007.

[69] S. H. Bates and M. G. Myers, "The role of leptin—STAT3 signaling in neuroendocrine function: an integrative perspective," *Journal of Molecular Medicine*, vol. 82, no. 1, pp. 12–20, 2004.

[70] C. Kloek, A. K. Haq, S. L. Dunn, H. J. Lavery, A. S. Banks, and M. G. Myers Jr., "Regulation of Jak kinases by intracellular leptin receptor sequences," *Journal of Biological Chemistry*, vol. 277, no. 44, pp. 41547–41555, 2002.

[71] K. D. Niswender, B. Gallis, J. E. Blevins, M. A. Corson, M. W. Schwartz, and D. G. Baskin, "Immunocytochemical detection of phosphatidylinositol 3-kinase activation by insulin and leptin," *Journal of Histochemistry and Cytochemistry*, vol. 51, no. 3, pp. 275–283, 2003.

[72] H. Masuzaki, Y. Ogawa, N. Sagawa et al., "Nonadipose tissue production of leptin: leptin as a novel placenta- derived hormone in humans," *Nature Medicine*, vol. 3, no. 9, pp. 1029–1033, 1997.

[73] S. Hauguel-de Mouzon, J. Lepercq, and P. Catalano, "The known and unknown of leptin in pregnancy," *American Journal of Obstetrics and Gynecology*, vol. 194, no. 6, pp. 1537–1545, 2006.

[74] M. Wauters, R. V. Considine, and L. F. Van Gaal, "Human leptin: from an adipocyte hormone to an endocrine mediator," *European Journal of Endocrinology*, vol. 143, no. 3, pp. 293–311, 2000.

[75] C. Grunfeld, C. Zhao, J. Fuller et al., "Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters: a role for leptin in the anorexia of infection," *Journal of Clinical Investigation*, vol. 97, no. 9, pp. 2152–2157, 1996.

[76] P. J. Havel, S. Kasim-Karakas, W. Mueller, P. R. Johnson, R. L. Gingerich, and J. S. Stern, "Relationship of plasma leptin to plasma insulin and adiposity in normal weight and overweight women: effects of dietary fat content and sustained weight loss," *Journal of Clinical Endocrinology and Metabolism*, vol. 81, no. 12, pp. 4406–4413, 1996.

[77] E. Jequier, "Leptin signaling, adiposity and energy balance," *Annals of the New York Academy of Sciences*, vol. 967, pp. 379–388, 2002.

[78] C. Schubring, P. Englaro, T. Siebler et al., "Longitudinal analysis of maternal serum leptin levels during pregnancy, at birth and up to six weeks after birth: relation to body mass index, skinfolds, sex steroids and umbilical cord blood leptin levels," *Hormone Research*, vol. 50, no. 5, pp. 276–283, 1998.

[79] H. Laivuori, R. Kaaja, H. Koistinen et al., "Leptin during and after preeclamptic or normal pregnancy: its relation to serum insulin and insulin sensitivity," *Metabolism*, vol. 49, no. 2, pp. 259–263, 2000.

[80] D. D. Briana and A. Malamitsi-Puchner, "Reviews: adipocytokines in normal and complicated pregnancies," *Reproductive Sciences*, vol. 16, no. 10, pp. 921–937, 2009.

[81] E. Oteng-Ntim, R. Varma, H. Croker, L. Poston, and P. Doyle, "Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis," *BMC Medicine*, vol. 10, article 47, 2012.

[82] S. L. Nascimento, F. G. Surita, and J. G. Cecatti, "Physical exercise during pregnancy: a systematic review," *Current Opinion in Obstetrics and Gynecology*, vol. 24, no. 6, pp. 387–394, 2012.

[83] J. M. Atègbo, O. Grissa, A. Yessoufou et al., "Modulation of adipokines and cytokines in gestational diabetes and macrosomia," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 10, pp. 4137–4143, 2006.

[84] T. J. Highman, J. E. Friedman, L. P. Huston, W. W. Wong, and P. M. Catalano, "Longitudinal changes in maternal serum leptin concentrations, body composition, and resting metabolic rate in pregnancy," *American Journal of Obstetrics and Gynecology*, vol. 178, no. 5, pp. 1010–1015, 1998.

[85] M. C. Henson, K. F. Swan, and J. S. O'Neil, "Expression of placental leptin and leptin receptor transcripts in early pregnancy and at term," *Obstetrics and Gynecology*, vol. 92, no. 6, pp. 1020–1028, 1998.

[86] D. Chen, G. Xia, P. Xu, and M. Dong, "Peripartum serum leptin and soluble leptin receptor levels in women with gestational diabetes," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 89, no. 12, pp. 1595–1599, 2010.

[87] C. Qiu, M. A. Williams, S. Vadachkoria, I. O. Frederick, and D. A. Luthy, "Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus," *Obstetrics and Gynecology*, vol. 103, no. 3, pp. 519–525, 2004.

[88] X. L. Gao, H. X. Yang, and Y. Zhao, "Variations of tumor necrosis factor-α, leptin and adiponectin in mid-trimester of gestational diabetes mellitus," *Chinese Medical Journal*, vol. 121, no. 8, pp. 701–705, 2008.

[89] R. D'Anna, G. Baviera, M. L. Cannata, A. De Vivo, A. Di Benedetto, and F. Corrado, "Midtrimester amniotic fluid leptin and insulin levels and subsequent gestational diabetes," *Gynecologic and Obstetric Investigation*, vol. 64, no. 2, pp. 65–68, 2007.

[90] R. G. Lea, D. Howe, L. T. Hannah, O. Bonneau, L. Hunter, and N. Hoggard, "Placental leptin in normal, diabetic and fetal growth-retarded pregnancies," *Molecular Human Reproduction*, vol. 6, no. 8, pp. 763–769, 2000.

[91] M. A. Nuamah, S. Yura, N. Sagawa et al., "Significant increase in maternal plasma leptin concentration in induced delivery: a possible contribution of pro-inflammatory cytokines to placental leptin secretion," *Endocrine Journal*, vol. 51, no. 2, pp. 177–187, 2004.

[92] L. A. Barbour, C. E. McCurdy, T. L. Hernandez, J. P. Kirwan, P. M. Catalano, and J. E. Friedman, "Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes," *Diabetes Care*, vol. 30, no. 2, pp. S112–S119, 2007.

[93] J. A. Gavard and R. Artal, "Effect of exercise on pregnancy outcome," *Clinical Obstetrics and Gynecology*, vol. 51, pp. 467–480, 2008.

[94] R. R. Banerjee and M. A. Lazar, "Dimerization of resistin and resistin-like molecules is determined by a single cysteine," *Journal of Biological Chemistry*, vol. 276, no. 28, pp. 25970–25973, 2001.

[95] C. M. Steppan, S. T. Bailey, S. Bhat et al., "The hormone resistin links obesity to diabetes," *Nature*, vol. 409, no. 6818, pp. 307–312, 2001.

[96] P. G. McTernan, C. M. Kusminski, and S. Kumar, "Resistin," *Current Opinion in Lipidology*, vol. 17, no. 2, pp. 170–175, 2006.

[97] E. Adeghate, "An update on the biology and physiology of resistin," *Cellular and Molecular Life Sciences*, vol. 61, pp. 2485–2496, 2004.

[98] C. M. Steppan and M. A. Lazar, "The current biology of resistin," *Journal of Internal Medicine*, vol. 255, no. 4, pp. 439–447, 2004.

[99] K. Azuma, F. Katsukawa, S. Oguchi et al., "Correlation between serum resistin level and adiposity in obese individuals," *Obesity Research*, vol. 11, no. 8, pp. 997–1001, 2003.

[100] J. V. Silha, M. Krsek, J. V. Skrha, P. Sucharda, B. L. G. Nyomba, and L. J. Murphy, "Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistence," *European Journal of Endocrinology*, vol. 149, no. 4, pp. 331–335, 2003.

[101] K. M. Utzschneider, D. B. Carr, J. Tong et al., "Resistin is not associated with insulin sensitivity or the metabolic syndrome in humans," *Diabetologia*, vol. 48, no. 11, pp. 2330–2333, 2005.

[102] G. M. Dick, P. S. Katz, M. Farias III et al., "Resistin impairs endothelium-dependent dilation to bradykinin, but not acetylcholine, in the coronary circulation," *American Journal of Physiology*, vol. 291, no. 6, pp. H2997–H3002, 2006.

[103] D. B. Savage, C. P. Sewter, E. S. Klenk et al., "Resistin / Fizz3 expression in relation to obesity and peroxisome proliferator—activated receptor-γ action in humans," *Diabetes*, vol. 50, no. 10, pp. 2199–2202, 2001.

[104] L. Patel, A. C. Buckels, I. J. Kinghorn et al., "Resistin is expressed in human macrophages and directly regulated by PPARγ activators," *Biochemical and Biophysical Research Communications*, vol. 300, no. 2, pp. 472–476, 2003.

[105] D. Chen, M. Dong, Q. Fang, J. He, Z. Wang, and X. Yang, "Alterations of serum resistin in normal pregnancy and pre-eclampsia," *Clinical Science*, vol. 108, no. 1, pp. 81–84, 2005.

[106] S. Yura, N. Sagawa, H. Itoh et al., "Resistin is expressed in the human placenta," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 3, pp. 1394–1397, 2003.

[107] N. Di Simone, F. Di Nicuolo, D. Marzioni et al., "Resistin modulates glucose uptake and glucose transporter-1 (GLUT-1) expression in trophoblast cells," *Journal of Cellular and Molecular Medicine*, vol. 13, no. 2, pp. 388–397, 2009.

[108] E. Palik, E. Baranyi, Z. Melczer et al., "Elevated serum acylated (biologically active) ghrelin and resistin levels associate with pregnancy-induced weight gain and insulin resistance," *Diabetes Research and Clinical Practice*, vol. 76, no. 3, pp. 351–357, 2007.

[109] S. Mazaki-Tovi, R. Romero, J. P. Kusanovic et al., "Maternal visfatin concentration in normal pregnancy," *Journal of Perinatal Medicine*, vol. 37, no. 3, pp. 206–217, 2009.

[110] A. Megia, J. Vendrell, C. Gutierrez et al., "Insulin sensitivity and resistin levels in gestational diabetes mellitus and after parturition," *European Journal of Endocrinology*, vol. 158, no. 2, pp. 173–178, 2008.

[111] M. Lappas, K. Yee, M. Permezel, and G. E. Rice, "Release and regulation of leptin, resistin and adiponectin from human placenta, fetal membranes, and maternal adipose tissue and skeletal muscle from normal and gestational diabetes mellitus-complicated pregnancies," *Journal of Endocrinology*, vol. 186, no. 3, pp. 457–465, 2005.

[112] G. Winkler, K. Cseh, É. Baranyi et al., "Tumor necrosis factor system in insulin resistance in gestational diabetes," *Diabetes Research and Clinical Practice*, vol. 56, no. 2, pp. 93–99, 2002.

[113] G. S. Hotamisligil, D. L. Murray, L. N. Choy, and B. M. Spiegelman, "Tumor necrosis factor alpha inhibits signaling from the insulin receptor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, pp. 4854–4858, 1994.

[114] R. Feinstein, H. Kanety, M. Z. Papa, B. Lunenfeld, and A. Karasik, "Tumor necrosis factor-α suppresses insulin-induced tyrosine phosphorylation of insulin receptor and its substrates," *Journal of Biological Chemistry*, vol. 268, no. 35, pp. 26055–26058, 1993.

[115] L. F. del Aguila, K. P. Claffey, and J. P. Kirwan, "TNF-α impairs insulin signaling and insulin stimulation of glucose uptake in C2C12 muscle cells," *American Journal of Physiology*, vol. 276, no. 5, pp. E849–E855, 1999.

[116] G. S. Hotamisligil, P. Peraldi, A. Budavari, R. Ellis, M. F. White, and B. M. Spiegelman, "IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-α- and obesity-induced insulin resistance," *Science*, vol. 271, no. 5249, pp. 665–668, 1996.

[117] J. P. Kirwan, R. K. Krishnan, J. A. Weaver, L. F. del Aguila, and W. J. Evans, "Human aging is associated with altered TNF-α production during hyperglycemia and hyperinsulinemia," *American Journal of Physiology*, vol. 281, no. 6, pp. E1137–E1143, 2001.

[118] P. R. Ling, B. R. Bistrian, B. Mendez, and N. W. Istfan, "Effects of systemic infusions of endotoxin, tumor necrosis factor, and interleukin-1 on glucose metabolism in the rat: relationship to endogenous glucose production and peripheral tissue glucose uptake," *Metabolism*, vol. 43, no. 3, pp. 279–284, 1994.

[119] L. F. del Aguila, R. K. Krishnan, J. S. Ulbrecht et al., "Muscle damage impairs insulin stimulation of IRS-1, PI 3-kinase, and Akt-kinase in human skeletal muscle," *American Journal of Physiology*, vol. 279, no. 1, pp. E206–E212, 2000.

[120] M. T. Coughlan, K. Oliva, H. M. Georgiou, J. M. H. Permezel, and G. E. Rice, "Glucose-induced release of tumour necrosis factor-alpha from human placental and adipose tissues in gestational diabetes mellitus," *Diabetic Medicine*, vol. 18, no. 11, pp. 921–927, 2001.

[121] K. A. McLachlan, D. O'Neal, A. Jenkins, and F. P. Alford, "Do adiponectin, TNFα, leptin and CRP relate to insulin resistance in pregnancy? Studies in women with or without gestational diabetes, during and after pregnancy," *Diabetes/Metabolism Research and Reviews*, vol. 22, no. 2, pp. 131–138, 2006.

[122] A. Fukuhara, M. Matsuda, M. Nishizawa et al., "Visfatin: a protein secreted by visceral fat that Mimics the effects of insulin," *Science*, vol. 307, no. 5708, pp. 426–430, 2005.

[123] T. D. Filippatos, C. S. Derdemezis, I. F. Gazi et al., "Increased plasma visfatin levels in subjects with the metabolic syndrome," *European Journal of Clinical Investigation*, vol. 38, no. 1, pp. 71–72, 2008.

[124] M. P. Chen, F. M. Chung, D. M. Chang et al., "Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 1, pp. 295–299, 2006.

[125] J. Berndt, N. Klöting, S. Kralisch et al., "Plasma visfatin concentrations and fat depot-specific mRNA expression in humans," *Diabetes*, vol. 54, no. 10, pp. 2911–2916, 2005.

[126] S. A. Morgan, J. B. Bringolf, and E. R. Seidel, "Visfatin expression is elevated in normal human pregnancy," *Peptides*, vol. 29, no. 8, pp. 1382–1389, 2008.

[127] B. Telejko, M. Kuzmicki, A. Zonenberg et al., "Visfatin in gestational diabetes: serum level and mRNA expression in fat and placental tissue," *Diabetes Research and Clinical Practice*, vol. 84, no. 1, pp. 68–75, 2009.

[128] S. Ognjanovic, T. L. Ku, and G. D. Bryant-Greenwood, "Pre-B-cell colony-enhancing factor is a secreted cytokine-like protein from the human amniotic epithelium," *American Journal of Obstetrics and Gynecology*, vol. 193, no. 1, pp. 273–282, 2005.

[129] T. Josephs, H. Waugh, I. Kokay, D. Grattan, and M. Thompson, "Fasting-induced adipose factor identified as a key adipokine that is up-regulated in white adipose tissue during pregnancy and lactation in the rat," *Journal of Endocrinology*, vol. 194, no. 2, pp. 305–312, 2007.

[130] D. D. Briana, M. Boutsikou, D. Gourgiotis et al., "Role of visfatin, insulin-like growth factor-I and insulin in fetal growth," *Journal of Perinatal Medicine*, vol. 35, no. 4, pp. 326–329, 2007.

[131] K. C. Lewandowski, N. Stojanovic, M. Press et al., "Elevated serum levels of visfatin in gestational diabetes: a comparative study across various degrees of glucose tolerance," *Diabetologia*, vol. 50, no. 5, pp. 1033–1037, 2007.

[132] K. Krzyzanowska, W. Krugluger, F. Mittermayer et al., "Increased visfatin concentrations in women with gestational diabetes mellitus," *Clinical Science*, vol. 110, no. 5, pp. 605–609, 2006.

[133] S. Mazaki-Tovi, R. Romero, J. P. Kusanovic et al., "Visfatin in human pregnancy: maternal gestational diabetes vis-à-vis neonatal birthweight," *Journal of Perinatal Medicine*, vol. 37, no. 3, pp. 218–231, 2009.

[134] T. F. Chan, Y. L. Chen, C. H. Lee et al., "Decreased plasma visfatin concentrations in women with gestational diabetes mellitus," *Journal of the Society for Gynecologic Investigation*, vol. 13, no. 5, pp. 364–367, 2006.

[135] D. G. Haider, A. Handisurya, A. Storka et al., "Visfatin response to glucose is reduced in women with gestational diabetes mellitus," *Diabetes Care*, vol. 30, no. 7, pp. 1889–1891, 2007.

[136] M. Akturk, A. E. Altinova, I. Mert et al., "Visfatin concentration is decreased in women with gestational diabetes mellitus in the third trimester," *Journal of Endocrinological Investigation*, vol. 31, no. 7, pp. 610–613, 2008.

[137] G. Mastorakos, G. Valsamakis, D. C. Papatheodorou et al., "The role of adipocytokines in insulin resistance in normal pregnancy: visfatin concentrations in early pregnancy predict insulin sensitivity," *Clinical Chemistry*, vol. 53, no. 8, pp. 1477–1483, 2007.

[138] S. Ognjanovic, L. S. Tashima, and G. D. Bryant-Greenwood, "The effects of pre-B-cell colony-enhancing factor on the human fetal membranes by microarray analysis," *American Journal of Obstetrics and Gynecology*, vol. 189, no. 4, pp. 1187–1195, 2003.

[139] B. Masri, N. Morin, L. Pedebernade, B. Knibiehler, and Y. Audigier, "The apelin receptor is coupled to Gil or Gi2 protein and is differentially desensitized by apelin fragments," *Journal of Biological Chemistry*, vol. 281, no. 27, pp. 18317–18326, 2006.

[140] M. De Falco, L. De, N. Onori et al., "Apelin expression in normal human tissues," *In Vivo*, vol. 16, no. 5, pp. 333–336, 2002.

[141] S. Rayalam, M. A. Della-Fera, P. A. Krieg, C. M. Cox, A. Robins, and C. A. Baile, "A putative role for apelin in the etiology of obesity," *Biochemical and Biophysical Research Communications*, vol. 368, no. 3, pp. 815–819, 2008.

[142] O. Kunduzova, N. Alet, N. Delesque-Touchard et al., "Apelin/APJ signaling system: a potential link between adipose tissue and endothelial angiogenic processes," *The FASEB Journal*, vol. 22, no. 12, pp. 4146–4153, 2008.

[143] J. Bełtowski, "Apelin and visfatin: unique "beneficial" adipokines up regulated in obesity?" *Medical Science Monitor*, vol. 12, pp. RA112–RA119, 2006.

[144] K. Tatemoto, K. Takayama, M. X. Zou et al., "The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism," *Regulatory Peptides*, vol. 99, no. 2-3, pp. 87–92, 2001.

[145] L. Cobellis, M. De Falco, A. Mastrogiacomo et al., "Modulation of apelin and APJ receptor in normal and preeclampsia-complicated placentas," *Histology and Histopathology*, vol. 22, no. 1–3, pp. 1–8, 2007.

[146] C. M. Cox, S. L. D'Agostino, M. K. Miller, R. L. Heimark, and P. A. Krieg, "Apelin, the ligand for the endothelial G-protein-coupled receptor, APJ, is a potent angiogenic factor required for normal vascular development of the frog embryo," *Developmental Biology*, vol. 296, no. 1, pp. 177–189, 2006.

[147] M. Aslan, O. Celik, N. Celik et al., "Cord blood nesfatin-1 and apelin-36 levels in gestational diabetes mellitus," *Endocrine*, vol. 41, pp. 424–429, 2012.

[148] B. A. Zabel, A. M. Silverio, and E. C. Butcher, "Chemokine-like receptor 1 expression and chemerin-directed chemotaxis distinguish plasmacytoid from myeloid dendritic cells in human blood," *Journal of Immunology*, vol. 174, no. 1, pp. 244–251, 2005.

[149] V. Wittamer, J. D. Franssen, M. Vulcano et al., "Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids," *Journal of Experimental Medicine*, vol. 198, no. 7, pp. 977–985, 2003.

[150] S. Kralisch, S. Weise, G. Sommer et al., "Interleukin-1ß induces the novel adipokine chemerin in adipocytes in vitro," *Regulatory Peptides*, vol. 154, no. 1–3, pp. 102–106, 2009.

[151] K. Bozaoglu, K. Bolton, J. McMillan et al., "Chemerin is a novel adipokine associated with obesity and metabolic syndrome," *Endocrinology*, vol. 148, no. 10, pp. 4687–4694, 2007.

[152] J. F. Clapp III and W. Kiess, "Effects of pregnancy and exercise on concentrations of the metabolic markers tumor necrosis factor α and leptin," *American Journal of Obstetrics and Gynecology*, vol. 182, no. 2, pp. 300–306, 2000.

[153] D. Pfau, H. Stepan, J. Kratzsch et al., "Circulating levels of the adipokine chemerin in gestational diabetes mellitus," *Hormone Research in Paediatrics*, vol. 74, no. 1, pp. 56–61, 2010.

[154] G. Barker, R. Lim, G. E. Rice, and M. Lappas, "Increased chemerin concentrations in fetuses of obese mothers and correlation with maternal insulin sensitivity," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 25, pp. 2274–2280, 2012.

[155] G. Ceysens, D. Rouiller, and M. Boulvain, "Exercise for diabetic pregnant women," *Cochrane Database of Systematic Reviews*, vol. 3, p. CD004225, 2006.

[156] S. Han, P. Middleton, and C. A. Crowther, "Exercise for pregnant women for preventing gestational diabetes mellitus," *Cochrane Database of Systematic Reviews*, vol. 11, no. 7, Article ID CD009021, 2012.

[157] D. K. Tobias, C. Zhang, R. M. van Dam, K. Bowers, and F. B. Hu, "Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis," *Diabetes Care*, vol. 34, no. 1, pp. 223–229, 2011.

[158] J. C. Dempsey, C. L. Butler, T. K. Sorensen et al., "A case-control study of maternal recreational physical activity and risk of gestational diabetes mellitus," *Diabetes Research and Clinical Practice*, vol. 66, no. 2, pp. 203–215, 2004.

[159] C. Zhang, C. G. Solomon, J. E. Manson, and F. B. Hu, "A prospective study of pregravid physical activity and sedentary behaviors in relation to the risk for gestational diabetes mellitus," *Archives of Internal Medicine*, vol. 166, no. 5, pp. 543–548, 2006.

[160] E. Oken, Y. Ning, S. L. Rifas-Shiman, J. S. Radesky, J. W. Rich-Edwards, and M. W. Gillman, "Associations of physical activity and inactivity before and during pregnancy with glucose tolerance," *Obstetrics and Gynecology*, vol. 108, no. 5, pp. 1200–1207, 2006.

[161] L. A. H. Haakstad, N. Voldner, T. Henriksen, and K. Bø, "Physical activity level and weight gain in a cohort of pregnant Norwegian women," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 86, no. 5, pp. 559–564, 2007.

[162] L. A. H. Haakstad, N. Voldner, T. Henriksen, and K. Bø, "Why do pregnant women stop exercising in the third trimester?" *Acta Obstetricia et Gynecologica Scandinavica*, vol. 88, no. 11, pp. 1267–1275, 2009.

[163] G. S. Zavorsky and L. D. Longo, "Exercise guidelines in pregnancy: new perspectives," *Sports Medicine*, vol. 41, no. 5, pp. 345–360, 2011.

[164] Royal College of Obstetricians and Gynecologists. Exercise in Pregnancy. RCOG, Statement. No4. 2006, http://www.rcog.org.uk/womens-health/clinical-guidance/exercise-pregnancy.

[165] T. Hayashi, J. F. P. Wojtaszewski, and L. J. Goodyear, "Exercise regulation of glucose transport in skeletal muscle," *American Journal of Physiology*, vol. 273, no. 6, pp. E1039–E1051, 1997.

[166] S. Lund, G. D. Holman, O. Schmitz, and O. Pedersen, "Contraction stimulates translocation of glucose transporter GLUT4 in skeletal muscle through a mechanism distinct from that of insulin," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 92, no. 13, pp. 5817–5821, 1995.

[167] J. R. Zierath, T. S. Tsao, A. E. Stenbit, J. W. Ryder, D. Galuska, and M. J. Charron, "Restoration of hypoxia-stimulated glucose uptake in GLUT4-deficient muscles by muscle-specific GLUT4 transgenic complementation," *Journal of Biological Chemistry*, vol. 273, no. 33, pp. 20910–20915, 1998.

[168] B. Cheatham, C. J. Vlahos, L. Cheatham, L. Wang, J. Blenis, and C. R. Kahn, "Phosphatidylinositol 3-kinase activation is required for insulin stimulation of pp70 S6 kinase, DNA synthesis, and glucose transporter translocation," *Molecular and Cellular Biology*, vol. 14, no. 7, pp. 4902–4911, 1994.

[169] L. J. Goodyear, "AMP-activated protein kinase: a critical signaling intermediary for exercise-stimulated glucose transport?" *Exercise and Sport Sciences Reviews*, vol. 28, no. 3, pp. 113–116, 2000.

[170] A. Krook, M. Björnholm, D. Galuska et al., "Characterization of signal transduction and glucose transport in skeletal muscle from type 2 diabetic patients," *Diabetes*, vol. 49, no. 2, pp. 284–292, 2000.

[171] J. A. Houmard, C. D. Shaw, M. S. Hickey, and C. J. Tanner, "Effect of short-term exercise training on insulin-stimulated PI 3-kinase activity in human skeletal muscle," *American Journal of Physiology*, vol. 277, no. 6, pp. E1055–E1060, 1999.

[172] D. S. King, G. P. Dalsky, M. A. Staten, W. E. Clutter, D. R. Van Houten, and J. O. Holloszy, "Insulin action and secretion in endurance-trained and untrained humans," *Journal of Applied Physiology*, vol. 63, no. 6, pp. 2247–2252, 1987.

[173] B. H. Goodpaster, A. Katsiaras, and D. E. Kelley, "Enhanced fat oxidation through physical activity is associated with improvements in insulin sensitivity in obesity," *Diabetes*, vol. 52, no. 9, pp. 2191–2197, 2003.

[174] V. A. Hughes, M. A. Fiatarone, R. A. Fielding et al., "Exercise increases muscle GLUT-4 levels and insulin action in subjects with impaired glucose tolerance," *American Journal of Physiology*, vol. 264, no. 6, pp. E855–E862, 1993.

[175] C. R. Bruce, A. D. Kriketos, G. J. Cooney, and J. A. Hawley, "Disassociation of muscle triglyceride content and insulin sensitivity after exercise training in patients with Type 2 diabetes," *Diabetologia*, vol. 47, no. 1, pp. 23–30, 2004.

[176] P. Poirier, A. Tremblay, T. Broderick, C. Catellier, G. Tancrède, and A. Nadeau, "Impact of moderate aerobic exercise training on insulin sensitivity in type 2 diabetic men treated with oral hypoglycemic agents: is insulin sensitivity enhanced only in nonobese subjects?" *Medical Science Monitor*, vol. 8, no. 2, pp. CR59–CR65, 2002.

[177] G. L. Dohm, "Invited review: regulation of skeletal muscle GLUT-4 expression by exercise," *Journal of Applied Physiology*, vol. 93, no. 2, pp. 782–787, 2002.

[178] J. R. Zierath, "Invited review: exercise training-induced changes in insulin signaling in skeletal muscle," *Journal of Applied Physiology*, vol. 93, no. 2, pp. 773–781, 2002.

[179] P. S. MacLean, D. Zheng, and G. L. Dohm, "Muscle glucose transporter (GLUT 4) gene expression during exercise," *Exercise and Sport Sciences Reviews*, vol. 28, no. 4, pp. 148–152, 2000.

[180] I. Irrcher, P. J. Adhihetty, A. M. Joseph, V. Ljubicic, and D. A. Hood, "Regulation of mitochondrial biogenesis in muscle by endurance exercise," *Sports Medicine*, vol. 33, no. 11, pp. 783–793, 2003.

[181] M. F. Mottola, "The role of exercise in the prevention and treatment of gestational diabetes mellitus," *Current Diabetes Reports*, vol. 8, no. 4, pp. 299–304, 2008.

[182] J. J. Lehman, P. M. Barger, A. Kovacs, J. E. Saffitz, D. M. Medeiros, and D. P. Kelly, "Peroxisome proliferator-activated receptor γ coactivator-1 promotes cardiac mitochondrial biogenesis," *Journal of Clinical Investigation*, vol. 106, no. 7, pp. 847–856, 2000.

[183] H. Liang and W. F. Ward, "PGC-1α: a key regulator of energy metabolism," *American Journal of Physiology*, vol. 30, no. 4, pp. 145–151, 2006.

[184] W. T. Garvey, L. Maianu, J. A. Hancock, A. M. Golichowski, and A. Baron, "Gene expression of GLUT4 in skeletal muscle from insulin-resistant patients with obesity, IGT, GDM, and NIDDM," *Diabetes*, vol. 41, no. 4, pp. 465–475, 1992.

[185] O. Pedersen, J. F. Bak, P. H. Andersen et al., "Evidence against altered expression of GLUT1 or GLUT4 in skeletal muscle of patients with obesity for NIDDM," *Diabetes*, vol. 39, no. 7, pp. 865–870, 1990.

[186] F. Dela, T. Ploug, A. Handberg et al., "Physical training increases muscle GLUT4 protein and mRNA in patients with NIDDM," *Diabetes*, vol. 43, no. 7, pp. 862–865, 1994.

[187] J. R. Zierath and H. Wallberg-Henriksson, "From receptor to effector: insulin signal transduction in skeletal muscle from type II diabetic patients," *Annals of the New York Academy of Sciences*, vol. 967, pp. 120–134, 2002.

[188] J. P. Kirwan and M. Jing, "Modulation of insulin signaling in human skeletal muscle in response to exercise," *Exercise and Sport Sciences Reviews*, vol. 30, no. 2, pp. 85–90, 2002.

[189] M. Ishiki and A. Klip, "Minireview: recent developments in the regulation of glucose transporter-4 traffic: new signals, locations, and partners," *Endocrinology*, vol. 146, no. 12, pp. 5071–5078, 2005.

[190] R. V. Farese, M. P. Sajan, and M. L. Standaert, "Atypical protein kinase C in insulin action and insulin resistance," *Biochemical Society Transactions*, vol. 33, no. 2, pp. 350–353, 2005.

[191] C. Frøsig and E. A. Richter, "Improved insulin sensitivity after exercise: focus on insulin signaling," *Obesity*, vol. 17, no. 3, pp. S15–S20, 2009.

[192] C. B. Dugani and A. Klip, "Glucose transporter 4: cycling, compartments and controversies," *EMBO Reports*, vol. 6, no. 12, pp. 1137–1142, 2005.

[193] L. Jovanovic-Peterson, E. P. Durak, and C. M. Peterson, "Randomized trial of diet versus diet plus cardiovascular conditioning on glucose levels in gestational diabetes," *American Journal of Obstetrics and Gynecology*, vol. 161, no. 2, pp. 415–419, 1989.

[194] G. N. Brankston, B. F. Mitchell, E. A. Ryan, and N. B. Okun, "Resistance exercise decreases the need for insulin in overweight women with gestational diabetes mellitus," *American Journal of Obstetrics and Gynecology*, vol. 190, no. 1, pp. 188–193, 2004.

[195] P. Bung, R. Artal, N. Khodiguian, and S. Kjos, "Exercise in gestational diabetes: an optional therapeutic approach?" *Diabetes*, vol. 40, no. 2, pp. 182–185, 1991.

[196] American Diabetes Association, "Standards of medical care in diabetes—2008," *Diabetes Care*, supplement 1, pp. s12—s54, 2008.

[197] ACOG Committee Obstetric Practice, "ACOG Committee opinion. Number 267, January 2002: exercise during pregnancy and the postpartum period," *Obstetrics & Gynecology*, vol. 99, pp. 171–13, 2002.

[198] M. D. Avery, A. S. Leon, and R. A. Kopher, "Effects of a partially home-based exercise program for women with gestational diabetes," *Obstetrics and Gynecology*, vol. 89, no. 1, pp. 10–15, 1997.

[199] A. García-Patterson, E. Martín, J. Ubeda, M. A. María, A. de Leiva, and R. Corcoy, "Evaluation of light exercise in the treatment of gestational diabetes," *Diabetes Care*, vol. 24, no. 11, pp. 2006–2007, 2001.

[200] B. L. Marks, A. Ward, D. H. Morris, J. Castellani, and J. M. Rippe, "Fat-free mass is maintained in women following a moderate diet and exercise program," *Medicine and Science in Sports and Exercise*, vol. 27, no. 9, pp. 1243–1251, 1995.

[201] D. C. Nieman, J. M. Davis, D. A. Henson et al., "Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run," *Journal of Applied Physiology*, vol. 94, no. 5, pp. 1917–1925, 2003.

[202] N. Erdei, Z. Bagi, I. Édes, G. Kaley, and A. Koller, "H_2O_2 increases production of constrictor prostaglandins in smooth muscle leading to enhanced arteriolar tone in Type 2 diabetic mice," *American Journal of Physiology*, vol. 292, no. 1, pp. H649–H656, 2007.

[203] C. Keller, A. Steensberg, H. Pilegaard et al., "Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content," *The FASEB Journal*, vol. 15, no. 14, pp. 2748–2750, 2001.

[204] M. A. Febbraio and B. K. Pedersen, "Contraction-induced myokine production and release: is skeletal muscle an endocrine organ?" *Exercise and Sport Sciences Reviews*, vol. 33, no. 3, pp. 114–119, 2005.

[205] B. K. Pedersen and M. A. Febbraio, "Point: interleukin-6 does have a beneficial role in insulin sensitivity and glucose homeostasis," *Journal of Applied Physiology*, vol. 102, no. 2, pp. 814–819, 2007.

[206] A. Festa, R. D'Agostino, G. Howard, L. Mykkänen, R. P. Tracy, and S. M. Haffner, "Chronic subclinical inflammation as part of the insulin resistance syndrome: the insulin resistance atherosclerosis study (IRAS)," *Circulation*, vol. 102, no. 1, pp. 42–47, 2000.

[207] E. W. Petersen, A. L. Carey, M. Sacchetti et al., "Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro," *American Journal of Physiology*, vol. 288, no. 1, pp. E155–E162, 2005.

[208] G. van Hall, A. Steensberg, M. Sacchetti et al., "Interleukin-6 stimulates lipolysis and fat oxidation in humans," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 7, pp. 3005–3010, 2003.

[209] E. Hopps, B. Canino, and G. Caimi, "Effects of exercise on inflammation markers in type 2 diabetic subjects," *Acta Diabetologica*, vol. 48, pp. 183–189, 2011.

[210] L. Volpe, G. Di Cianni, C. Lencioni, I. Cuccuru, L. Benzi, and S. Del Prato, "Gestational diabetes, inflammation, and late vascular disease," *Journal of Endocrinological Investigation*, vol. 30, no. 10, pp. 873–879, 2007.

[211] H. Zhang and C. Zhang, "Vasoprotection by dietary supplements and exercise: role of TNFα signaling," *Experimental Diabetes Research*, vol. 2012, Article ID 972679, 6 pages, 2012.

[212] S. A. Hopkins, J. C. Baldi, W. S. Cutfield, L. McCowan, and P. L. Hofman, "Effects of exercise training on maternal hormonal changes in pregnancy," *Clinical Endocrinology*, vol. 74, no. 4, pp. 495–500, 2011.

[213] J. B. Ruige, J. M. Dekker, W. F. Blum et al., "Leptin and variables of body adiposity, energy balance, and insulin resistance in a population-based study: the Hoorn study," *Diabetes Care*, vol. 22, no. 7, pp. 1097–1104, 1999.

[214] P. W. Franks, I. S. Farooqi, J. Luan et al., "Does physical activity energy expenditure explain the between-individual variation in plasma leptin concentrations after adjusting for differences in body composition?" *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 7, pp. 3258–3263, 2003.

[215] J. A. Houmard, J. H. Cox, P. S. MacLean, and H. A. Barakat, "Effect of short-term exercise training on leptin and insulin action," *Metabolism*, vol. 49, no. 7, pp. 858–861, 2000.

[216] E. Herrera and H. Ortega-Senovilla, "Disturbances in lipid metabolism in diabetic pregnancy—are these the cause of the problem?" *Best Practice & Research*, vol. 24, no. 4, pp. 515–525, 2010.

[217] E. Sivan and G. Boden, "Free fatty acids, insulin resistance, and pregnancy," *Current Diabetes Reports*, vol. 3, no. 4, pp. 319–322, 2003.

[218] S. Furukawa, T. Fujita, M. Shimabukuro et al., "Increased oxidative stress in obesity and its impact on metabolic syndrome," *Journal of Clinical Investigation*, vol. 114, no. 12, pp. 1752–1761, 2004.

[219] L. P. Turcotte, E. A. Richter, and B. Kiens, "Increased plasma FFA uptake and oxidation during prolonged exercise in trained vs. Untrained humans," *American Journal of Physiology*, vol. 262, no. 6, pp. E791–E799, 1992.

[220] R. J. Tunstall, K. A. Mehan, G. D. Wadley et al., "Exercise training increases lipid metabolism gene expression in human skeletal muscle," *American Journal of Physiology*, vol. 283, no. 1, pp. E66–E72, 2002.

[221] H. A. Keizer, G. Schaart, N. N. Tandon, J. F. C. Glatz, and J. J. F. P. Luiken, "Subcellular immunolocalisation of fatty acid translocase (FAT)/CD36 in human type-1 and type-2 skeletal muscle fibres," *Histochemistry and Cell Biology*, vol. 121, no. 2, pp. 101–107, 2004.

[222] S. Golbidi, S. A. Ebadi, and I. Laher, "Antioxidants in the treatment of diabetes," *Current Diabetes Reviews*, vol. 7, pp. 106–125, 2011.

[223] S. Golbidi and I. Laher, "Antioxidant therapy in human endocrine disorders," *Medical Science Monitor*, vol. 16, no. 1, pp. RA9–RA24, 2010.

[224] M. T. Coughlan, P. P. Vervaart, M. Permezel, H. M. Georgiou, and G. E. Rice, "Altered placental oxidative stress status in gestational diabetes mellitus," *Placenta*, vol. 25, no. 1, pp. 78–84, 2004.

[225] M. T. Coughlan, M. Permezel, H. M. Georgiou, and G. E. Rice, "Repression of oxidant-induced nuclear factor-κB activity mediates placental cytokine responses in gestational diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 7, pp. 3585–3594, 2004.

[226] M. Lappas, M. Permezel, and G. E. Rice, "Release of proinflammatory cytokines and 8-isoprostane from placenta, adipose tissue, and skeletal muscle from normal pregnant women and women with gestational diabetes mellitus," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 11, pp. 5627–5633, 2004.

[227] E. Peuchant, J. L. Brun, V. Rigalleau et al., "Oxidative and antioxidative status in pregnant women with either gestational or type 1 diabetes," *Clinical Biochemistry*, vol. 37, no. 4, pp. 293–298, 2004.

[228] U. Kamath, G. Rao, C. Raghothama, L. Rai, and P. Rao, "Erythrocyte indicators of oxidative stress in gestational diabetes," *Acta Paediatrica*, vol. 87, no. 6, pp. 676–679, 1998.

[229] V. Toescu, S. L. Nuttall, U. Martin et al., "Changes in plasma lipids and markers of oxidative stress in normal pregnancy and pregnancies complicated by diabetes," *Clinical Science*, vol. 106, no. 1, pp. 93–98, 2004.

[230] N. Inoue, S. Ramasamy, T. Fukai, R. M. Nerem, and D. G. Harrison, "Shear stress modulates expression of Cu/Zn superoxide dismutase in human aortic endothelial cells," *Circulation Research*, vol. 79, no. 1, pp. 32–37, 1996.

[231] J. Hollander, R. Fiebig, M. Gore et al., "Superoxide dismutase gene expression in skeletal muscle: fiber-specific adaptation to endurance training," *American Journal of Physiology*, vol. 277, no. 3, pp. R856–R862, 1999.

[232] F. Moien-Afshari, S. Ghosh, M. Khazaei, T. J. Kieffer, R. W. Brownsey, and I. Laher, "Exercise restores endothelial function independently of weight loss or hyperglycaemic status in db/db mice," *Diabetologia*, vol. 51, no. 7, pp. 1327–1337, 2008.

[233] S. Sankaralingam, Y. Jiang, S. T. Davidge, and S. Yeo, "Effect of exercise on vascular superoxide dismutase expression in high-risk pregnancy," *American Journal of Perinatology*, vol. 28, no. 10, pp. 803–810, 2011.

[234] F. W. Wagey, "Pregnancy exercise increase enzymatic antioxidant in pregnant women," *Bali Medical Journal*, vol. 1, pp. 36–39, 2012.