University of Alberta

Effects of Resistance Exercise Training on Women with Gestational Diabetes

by

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the
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ABSTRACT

Thirty-two patients with gestational diabetes were randomized either to a group treated with diet alone or to a group treated with diet plus resistance exercise. Patients in the diet plus resistance exercise group exercised three times per week for 30 minutes each session. Patients in the diet alone group were asked to maintain their normal activity level. The number of women requiring insulin treatment was the same, regardless of treatment. However, a sub-group analysis examining only overweight women (prepregnant BMI > 25 kg/m^2) showed a lower incidence of insulin use in the diet plus exercise group ($p<0.05$). Women in the diet plus exercise group required less insulin ($p<0.05$) and showed a longer delay from diagnosis to the initiation of insulin therapy ($p<0.05$) compared to the diet alone group. In conclusion, resistance exercise training may be a useful treatment to avoid insulin treatment for overweight women with gestational diabetes.

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CHAPTER 1

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy (Metzger and Coustan, 1998). Glucose tolerance deteriorates in all pregnancies (Kuhl, 1998). However, in only 2-3% of pregnancies does the impairment become significant enough to fulfill the diagnosis of GDM (Gabbe, 1986). The criteria for a diagnosis of GDM are at least two abnormal values on an oral glucose tolerance test following an overnight fast and a 75-gram oral glucose load. Normal plasma glucose levels are defined as lower than 5.3 $mmol \bullet L^{-}$ fasting, 10.6 $mmol \bullet L^{-}$ after one hour, and 8.9 $mmol \bullet L^{-}$ after two hours. While some proposed mechanisms of this disorder include the autoimmune destruction of pancreatic beta-cells and increased insulin degradation, most experts agree that GDM is heterogeneous in nature and most likely involves insulin resistance over and above that seen in normal pregnancy as well as some degree of pancreatic beta-cell defect (Yamashita et al., 2000). Some evidence indicates that moderate exercise can reduce blood glucose levels in gestational diabetes. This chapter will review current theories of causation of GDM, current management, and will address the role of exercise in the treatment of GDM.

HORMONAL INFLUENCES ON CARBOHYDRATE TOLERANCE IN NORMAL PREGNANCY

Normal pregnancy is characterized by a marked reduction in insulin sensitivity which increases with advancing gestation in both obese and lean pregnant women (Ryan et al., 1985; Buchanan et al., 1990; Catalano et al., 1991; Sivan et al., 1997; Catalano et al., 1999). Patterns of normal hormonal changes during pregnancy may help to explain this increase in insulin resistance. The diabetogenic hormones of pregnancy include estrogens, progestins, prolactin, human placental lactogen (hPL), and cortisol. Levels of these hormones increase with increasing gestation and tend to induce peripheral insulin resistance as well as contribute to altered beta-cell function.

Table 1 summarizes the effects of the diabetogenic hormones on glucose homeostasis during normal pregnancy. The hormonal changes of pregnancy are intended to maintain a constant glucose supply to the fetus. As the metabolic requirements of the fetus increase with advancing gestation, these hormones also increase. This process of increasing glucose substrate is achieved by increasing peripheral insulin resistance as well as increasing glucose production by the liver.

Estrogen and progesterone both increase early in pregnancy and continue to increase for the remainder of gestation. Both hormones have been associated with an increase in insulin secretion in response to a glucose load (Kalkoff et al., 1970; Costrini and Kalkoff, 1971). Progesterone has also been shown to decrease glucose uptake in cultured rat adipocytes (Costrini and Kalkhoff, 1971; Ryan and Enns, 1988) and reduces

Table 1. Effects of gestational hormones on maternal glucose homeostasis during normal human pregnancy.

Hormone	Effect
Estrogen	↑ insulin binding to its receptor
Progesterone	↓ insulin binding to its receptor ↓ peripheral glucose uptake ↑ hepatic glucose production
Human Placental Lactogen	↓ peripheral glucose uptake
Prolactin	↓ peripheral glucose uptake
Cortisol	↓ insulin binding to its receptor ↓ peripheral glucose uptake ↑ hepatic glucose production

the ability of insulin to inhibit endogenous glucose production (Nelson et al., 1994). This implies that progesterone indirectly causes an increase in gluconeogenesis.

By late pregnancy, maternal concentrations of cortisol are approximately 2.5-fold higher than in the nonpregnant state (Gibson and Tulchinski, 1980). The excess free cortisol causes inhibition of peripheral glucose uptake as well as stimulation of hepatic glucose production (Rizza et al., 1982; Khani and Tayek, 2001).

Human placental lactogen (hPL) levels rise to a greater magnitude than any of the other gestational hormones (Beck and Daughday, 1967). HPL has been shown to inhibit peripheral glucose uptake and stimulate insulin secretion (Beck and Daughday, 1967; Ryan and Enns, 1988). Rat adipocytes cultured with hPL showed a reduction in maximum glucose transport (Ryan and Enns, 1988). In addition, a 12-hour infusion of

hPL results in impaired glucose tolerance as perceived by an increase in insulin and glucose concentrations in response to an oral glucose load compared to controls (Beck and Daughday, 1967; Brelje et al., 1993).

Plasma prolactin concentration increases 5-10-fold by late pregnancy (Tyson et al., 1972). In a similar manner to hPL, prolactin has been shown to inhibit peripheral glucose uptake and stimulate insulin secretion (Gaspard et al., 1975; Ryan and Enns, 1988). Nonpregnant women with the amenorrhea-galactorrhea syndrome and acquired hyperprolactinemia having prolactin levels similar to normal pregnant women demonstrate an increased basal insulin concentration and an increased insulin response to a glucose load (Gustafson et al., 1980). During oral glucose tolerance tests these women demonstrated similar plasma glucose levels to normal pregnant women and higher plasma glucose levels than nonpregnant controls (Gustafson et al., 1980). The addition of prolactin to pregnant rat adipocytes caused a decrease in maximal glucose uptake (Ryan and Enns, 1988).

While estrogen increases insulin binding to its receptor, it is balanced by the reduction of insulin binding caused by increased concentrations of progesterone and cortisol (Ryan and Enns, 1988). This results in no net effect on insulin binding to its receptor suggesting that the insulin resistance of pregnancy is caused by a postbinding defect in insulin action. While the diabetogenic hormones of pregnancy contribute to the insulin resistance of a normal pregnancy, they may not be responsible for the deterioration of glucose tolerance that is seen in GDM.

POTENTIAL CAUSATIVE FACTORS IN GESTATIONAL DIABETES

Mechanisms such as autoimmune disorders, defects in the pancreatic beta cell, and increased insulin resistance have been proposed to explain the development of GDM. Several studies have examined the presence of immunologic predictive markers of insulin dependent diabetes mellitus (IDDM), such as islet cell antibodies (ICAs), insulin autoantibodies (IAAs), and glutamic acid decarboxylase (GAD) autoantibodies in women with GDM. These markers are often present in subjects with Type I diabetes, and have also been shown to be present several years before disease onset.

The Role of Autoimmunity in GDM

In contrast to earlier evidence (Steel et al., 1980; Rubenstein et al., 1981; Freinkel et al., 1985), two recent studies using more specific and sensitive assays have shown that only 2.9% and 1.6% of women with GDM were ICA positive (Catalano et al., 1990; Damm et al., 1994). Furthermore, several studies have demonstrated that gestational diabetics have a very low prevalence of IAAs (Rubenstein et al., 1981; Ziegler et al., 1993; Damm et al., 1994; Mauricio et al., 1996; Dozio et al., 1997) and GAD autoantibodies (Tuomiletho et al., 1994; Petersen et al., 1996). These recent findings suggest that autoimmunity is an unlikely factor in the development of gestational diabetes.

Possible Beta-Cell Defect in Women with GDM

Though not secondary to an autoimmune mechanism, it has also been postulated that women with GDM have some defect in the pancreatic beta cells which secrete

insulin. Insulin secretion is considerably higher in both pregnant women with normal glucose tolerance and women with GDM compared with the nonpregnant state. Women with GDM have demonstrated fasting insulin levels which are comparable to or higher than those in pregnant women with normal glucose tolerance (Kuhl and Holst, 1976; Damm et al., 1993). However, insulin responses to oral or intravenous glucose are significantly lower in women with GDM than women with normal glucose tolerance (Kuhl, 1991; Catalano et al., 1993; Buchanan et al., 1990; Xiang et al., 1999; Homko et al., 2001). Further, the insulin response per unit glycemic stimulus is significantly lower in women with GDM compared with pregnant women with normal glucose tolerance (Kuhl and Holst, 1976; Festa et al., 1999).

Normal glucose-stimulated insulin secretion is biphasic and consists of a transient first phase response which is of greater magnitude than the sustained second phase response. Several studies have reported reduced first-phase insulin responses to intravenous or oral glucose in women with GDM compared with non-diabetic pregnant women (Buchanan et al., 1990; Catalano et al., 1993; Kautzky-Willer et al., 1997a). Second-phase insulin responses are of similar magnitude in women with normal glucose tolerance and those with GDM (Buchanan et al., 1990; Catalano et al., 1993). Peak plasma insulin during an oral glucose tolerance test occurs later in women with GDM than in women with normal glucose tolerance (Kuhl and Holst, 1976).

A reduction in the insulin response to a glucose load and delay in insulin peak in women with previous GDM (Dornhorst et al., 1991; Kuhl, 1991; Damm et al., 1995)

suggests that insulin secretion could be abnormal even before pregnancy. Women with previous GDM have a lower first-phase insulin response, despite normal fasting blood glucose and oral glucose tolerance, compared to women with no history of diabetes (Ryan et al., 1995). These data suggest that women with GDM have an underlying beta-cell defect that becomes unmasked under the stress of the high insulin resistance and hyperglycemia of pregnancy.

Simultaneously with insulin, the healthy beta cell secretes a small amount of the insulin precursor, proinsulin (See Figure 1). Proinsulin is cleaved first by prohormone convertase 1 and then by prohormone convertase 2 to produce mature insulin and C-peptide (Rhodes and Alarcon, 1994). Under stress conditions such as beta-cell hypersecretion, cleavage by prohormone convertase 2 appears to be rate limiting, leading to an accumulation of partially split proinsulin (Rhodes and Alarcon, 1994). An increased secretory demand to the beta-cell due to insulin resistance may lead to the secretion of inappropriately high amounts of intact as well as incompletely cleaved proinsulin which is an indication of beta-cell dysfunction (Mykkanen et al., 1997). Several studies have demonstrated significantly higher fasting and post-glycemic stimulus proinsulin levels in GDM compared to pregnant women with normal glucose tolerance (Dornhorst et al., 1991b; Swinn et al., 1995; Kautzgy-Willer et al., 1997a; 1997b). This indicates that impairment in beta-cell function is at least partially responsible for the onset of GDM. It has been proposed that increased proinsulin levels and an elevated proinsulin-to-insulin ratio that does not return to normal following delivery are specific to GDM and may serve as a predictor for the later development of Type II diabetes (Kautzky-Willer et al., 1997b).

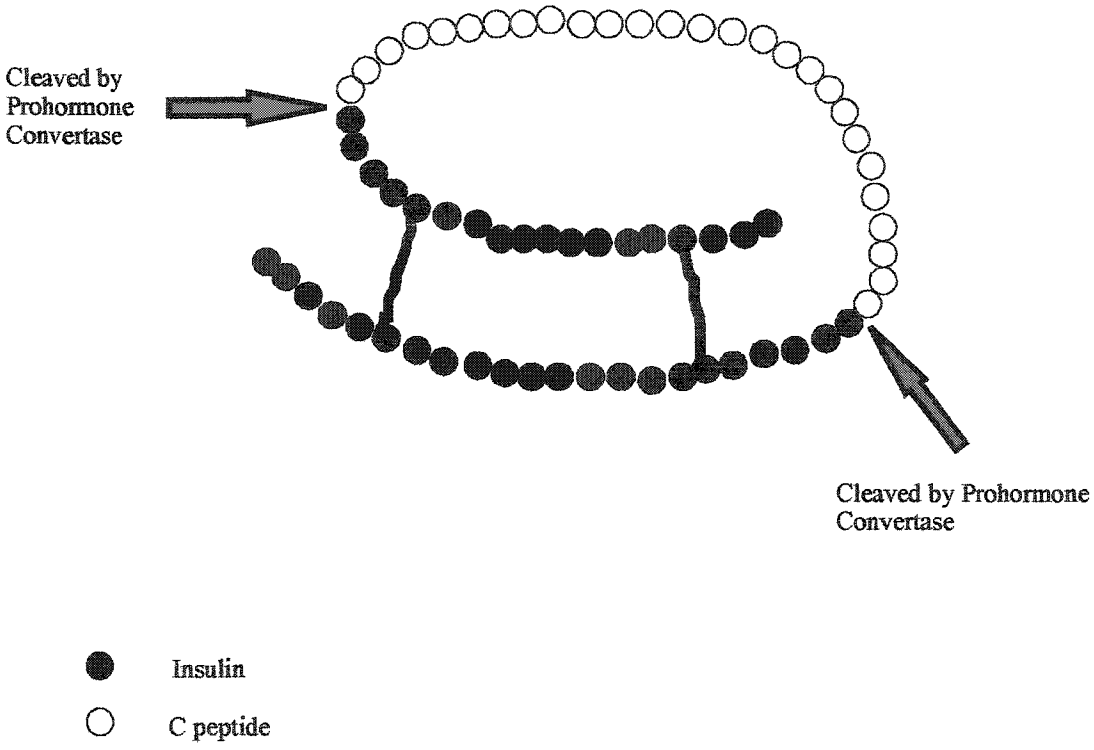

Figure 1. Proinsulin

Proinsulin is a continuous polypeptide chain with two disulfide bonds connecting the carboxy terminus to the amino terminus. Proinsulin is cleaved first by prohormone convertase 1 at the 32, 33 site and then by prohormone convertase 2 at the 64, 65 site to produce mature insulin and C-peptide.

Peripheral Insulin Resistance in the Development of GDM

Another possible mechanism for the increased carbohydrate intolerance in gestational diabetes is an increase in peripheral insulin resistance. Women with GDM consistently demonstrate increased insulin resistance in comparison with pregnant subjects who have normal glucose tolerance as well as nonpregnant controls (Ryan et al., 1985; Buchanan et al., 1990; Catalano et al., 1993; Kautzky-Willer et al., 1997a; Sivan et al., 1997; Catalano et al., 1999; Homko et al., 2001). Women with a previous history of GDM were found to be significantly more insulin resistant than matched control subjects with no history of diabetes (Byrne et al., 1995; Ryan et al., 1995; Kautzky-Willer et al., 1997a; Homko et al., 2001). Thus, women who are diagnosed with GDM may have a predisposition for carbohydrate intolerance prior to pregnancy.

While the cellular mechanisms of insulin resistance in GDM remain unclear, the literature indicates some defect in the insulin-signaling cascade. Cheatham and Kahn (1995) provide a thorough review of the insulin-signaling cascade. In healthy human tissue, insulin initiates its effect on glucose uptake by binding to the alpha-subunit of its receptor, which causes a conformational change activating the beta-subunit to undergo autophosphorylation on tyrosine residues (See Figure 2). This phosphorylation activates the insulin receptor tyrosine kinase. Tyrosine kinase activity catalyzes various cellular signaling proteins, including insulin receptor substrate-1 (IRS-1) to undergo tyrosine phosphorylation. Insulin stimulates the binding and activation of a lipid kinase enzyme, phosphatidylinositol-3 (PI 3)-kinase, to IRS-1. It is thought that the stimulation of PI 3-kinase activates the serine/threonine kinase Akt and deactivates glycogen synthase

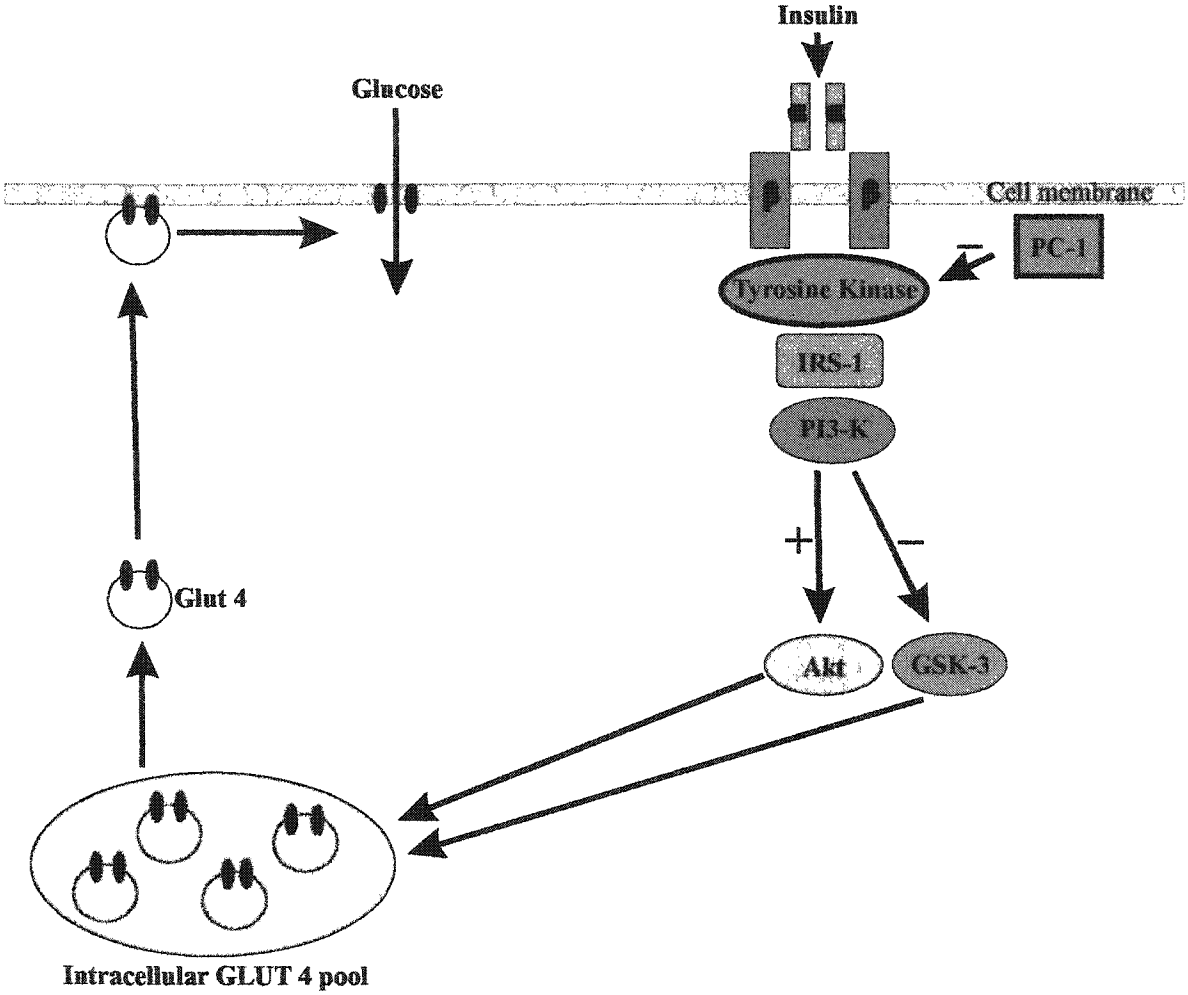

Figure 2. Insulin-stimulated glucose uptake in a muscle cell
Insulin binds to the alpha-unit of its receptor causing a conformational change which activates the beta subunitto undergo autophosphorylation. This activates tyrosine kinase activity which catalyzes insulin receptor substrate-1 (IRS-1)to undergo tyrosine phosphorylation. Phosphatidylinositol-3 (PI 3)-kinase activates Akt and deactivates glycogen synthase-3 (GSK-3) thereby stimulating the translocation of the GLUT 4 glucose transporter to the plasma membrane. GLUT 4 binds and fuses with the plasma membrane to allow influx of glucose into the cell. Adapted from Goodyear and Kahn, 1998.

Changes associated with GDM include an increase in plasma membrane glycoprotein-1 (PC-1) which inhibits tyrosine kinase activity, reduced IRS-1 protein content, and reduced GLUT 4 protein content.

kinase-3 (GSK-3) thereby increasing the translocation of vesicles containing the GLUT4 glucose transporter to the plasma membrane (Wojtaszewski et al., 2000). GLUT4 binds and fuses with the plasma membrane to allow the influx of glucose into the cell.

Most studies examining insulin receptor binding in normal and GDM pregnancies in blood cells suggest that there is no significant insulin receptor defect (Puavilai et al., 1982; Ryan et al., 1985; Anderson et al., 1986; 1987). Damm et al (1993) demonstrated that insulin binding to skeletal muscle insulin receptors was diminished to a similar extent in women with GDM and pregnant women with normal glucose tolerance compared to nonpregnant women. This indicates that insulin binding to its receptor is reduced in pregnancy regardless of carbohydrate tolerance and that this is not related to the pathogenesis of GDM.

Insulin receptor tyrosine kinase activity is one of the immediate postreceptor actions that regulate insulin signaling in peripheral tissue (Yamashita et al., 2000). A recent study demonstrated that insulin receptor tyrosine kinase activity in skeletal muscle from women with GDM was significantly lower than that in pregnant women with normal glucose tolerance (Shao et al., 2000a) resulting in reduced insulin-stimulated glucose uptake.

Plasma membrane glycoprotein-1 (PC-1) has been identified as an inhibitor of tyrosine kinase activity of the insulin receptor (Goldfine et al., 1998; Frittitta et al., 1997; Kumakura et al., 1998). Recent studies have demonstrated a negative correlation between

PC-1 and insulin action in subjects with and without Type II diabetes (Maddux et al., 1993; 1995; Frittitta et al., 1996; 1997; 1998; Goldfine et al., 1998). Skeletal muscle from women with GDM has demonstrated significantly higher levels of PC-1 protein compared to that of healthy pregnant women (Shao et al., 2000a). The inhibition of tyrosine kinase activity by PC-1 reduces peripheral glucose uptake by downregulating the entire insulin-signaling cascade. Elevated levels of this protein in these women likely contribute to the insulin resistance seen in GDM.

Insulin receptor substrate (IRS) proteins are the first signaling proteins that bind to the insulin receptor and translate the insulin signal to different substrates by linked signaling cascades (Yamashita et al., 2000). Levels of IRS-1 protein were reduced in skeletal muscle of women with GDM compared to pregnant women with normal glucose tolerance (Friedman et al., 1999). In addition, insulin stimulated IRS-1 tyrosine phosphorylation was significantly lower in women with GDM compared to normal pregnant women (Friedman et al., 1999; Shao et al., 2000a). A reduction in IRS-1 levels and tyrosine phosphorylation will act to downregulate the remainder of the insulin-signaling cascade thereby reducing insulin-stimulated glucose uptake. These reductions in women with GDM may be regulated by the reduction in insulin receptor tyrosine kinase activity as well as the increase in PC-1 protein seen in this population.

Studies have revealed that glucose transporter, GLUT-4 protein expression is reduced in adipose tissue from pregnant women and to a greater extent in GDM (Garvey et al., 1993; Okuno et al., 1995; Yamada et al., 1999). Of note is that insulin was able to

induce translocation of GLUT-4 to the plasma membrane in control subjects but not in GDM, suggesting a marked reduction in insulin-stimulated glucose transport rates in adipocytes of women with GDM. A recent study has shown that overexpression of human GLUT-4 in mice with GDM substantially improves insulin signaling in GDM, resulting in improved glycemic control (Ishizuka et al., 1999). It can be concluded therefore, that several of the proteins involved in the insulin-signaling cascade may have a significant role in the increased insulin resistance of GDM.

In summary, the literature suggests that the main mechanisms in the development of GDM include defects in insulin secretion by the pancreatic beta cell as well as increased insulin resistance. Defects in the pancreatic beta cell include higher fasting insulin secretion, lower insulin secretion in response to a glucose load, as well as higher amounts of proinsulin. The increased insulin resistance seen in GDM may be caused by reduced insulin receptor tyrosine kinase activity via increased levels of PC-1 protein, reduced levels of IRS-1 protein, and reduced expression of the GLUT 4 transporter protein.

EFFECTS OF GESTATIONAL DIABETES ON PREGNANCY

Regardless of etiology, the diagnosis of carbohydrate intolerance has implications for both the baby and mother. The established morbidity for the baby includes macrosomia, with the ensuing risk of fetal and maternal trauma during birth, and neonatal hypoglycemia. Women diagnosed with GDM have a 40-60% chance of recurrence in future pregnancies (Philipson and Super, 1989; Gaudier et al., 1992; Moses, 1996).

Furthermore, 50-60% of women with GDM will exhibit further deterioration of carbohydrate metabolism and develop Type II diabetes as they age (Cousins, 1983; Olds et al., 1988; O'Sullivan, 1989).

Several studies suggest that the risk of Type II diabetes can be reduced by lifestyle modifications such as diet, weight loss and physical activity (Eriksson and Lindgarde, 1991; Blair et al., 1995; Lynch et al., 1996; Pan et al., 1997; Tuomilehto et al., 2001). Regular moderate or vigorous exercise can reduce the risk of Type II diabetes by 30-50% (Manson and Spelsberg, 1994; Lynch et al., 1996). Recognition of those at risk could allow application of preventative strategies in pregnancy, such as changes in nutrition and physical activity, which may help minimize the progression to more significant disease.

THE USE OF INSULIN IN THE MANAGEMENT OF GESTATIONAL DIABETES

Current management of gestational diabetes includes blood glucose monitoring, dietary counseling, increased fetal surveillance, and insulin therapy as needed to achieve and maintain normoglycemia. While the underlying rationale for maternal use of exogenous insulin is that it will reduce the availability of substrate to the fetus, thereby reducing the risk of fetal macrosomia, there are several reasons to be somewhat skeptical about this treatment in gestational diabetics.

Controversy exists over whether insulin therapy actually reduces the risk of fetal macrosomia and operative deliveries in women with gestational diabetes. In a pilot study

to assess different levels of care in the management of GDM, Garner et al (1997) randomized women into a treatment group managed by strict glycemic control as well as tertiary level obstetric care or a control group receiving only routine obstetric care. Results indicated that treatment in a tertiary care setting with an obstetrician and an endocrinologist does not produce a significant reduction in fetal size as compared with no such intensive treatment (Garner et al., 1997). Likewise, randomized trials comparing women with gestational diabetes given no treatment, diet alone, or diet plus insulin have shown no difference in mean birth weight, macrosomia, or rate of operative deliveries between those in each of the three treatment groups (Persson et al., 1985; Li, et al., 1987).

Conversely, the Toronto Tri-Hospital Gestational Diabetes Project demonstrated that increasing levels of maternal carbohydrate intolerance in women without gestational diabetes correlates with an increase in such outcomes as macrosomia and cesarean sections (Sermer et al., 1995). Results from this project also showed that treatment of GDM does reduce birthweight however, no parallel reduction in cesarean sections was detected. Coustan and Imarah (1984) showed a reduction in macrosomia and rate of operative deliveries in women with gestational diabetes given prophylactic insulin compared with those who were treated with diet alone. However, this study was a nonrandomized retrospective chart review, therefore there may have been potential for bias. Langer et al (1994) demonstrated a significant improvement in the macrosomia rate and the cesarean section rate with more intensive monitoring as compared with conventional therapy in women with at least one abnormal value on a glucose tolerance

test. Women in both groups were given insulin upon failure of diet treatment and were treated with the same metabolic goal.

A potential disadvantage of insulin treatment is that doctors may have difficulty in monitoring patients and there is the chance of hypoglycemia while using these agents. An early report demonstrated that tight glycemic control resulted in an increase of small-for-gestational-age infants (Langer et al., 1989) which may reflect an increase in neonatal morbidity. Moreover, daily insulin injections can be stressful to pregnant women and high levels of stress have been associated with higher blood glucose levels (Zigrossi and Riga-Ziegler, 1986). Finally, administration of insulin is merely palliative in that it does not rectify peripheral insulin resistance which is one of the primary defects of GDM.

Treatment modalities such as exercise have been shown to overcome this peripheral resistance to insulin (Peterson et al., 1982). Exercise can provide several benefits to the gestational diabetic that insulin cannot. Exercise may serve as a more appropriate treatment modality in GDM for a stress-reducing effect in contrast to the stress-inducing effect of insulin therapy. In addition, one exercise session every other day may prove to be more acceptable to many women than daily insulin injections. Thus, the remainder of this paper will examine the evidence that exercise can be used as an alternative treatment to insulin in gestational diabetes.

EXERCISE AS AN ALTERNATIVE TREATMENT FOR GESTATIONAL DIABETES

Regular exercise is well known to improve glucose tolerance and diminish insulin requirements in subjects with diabetes mellitus (Krotkiewski et al., 1985; Koivisto et al., 1986; Rogers et al., 1988). Physical activity has both acute and long-term positive effects on insulin sensitivity, insulin secretion and glucose metabolism in both non-diabetic and diabetic individuals (Bogardus et al., 1984; Sato et al., 1984; Artal et al., 1985; Mikines et al., 1988). Although most of the current literature examines the effects of physical activity in Type II diabetes, Bung and Artal (1996) suggest that it is possible that regular exercise also may be useful to prevent or treat GDM.

Exercise can be broadly classified into two major types. *Aerobic* exercise uses large muscle groups rhythmically and continuously for a sustained period of 15 to 20 minutes or longer while maintaining 60-80% of the maximum heart rate. Common forms of aerobic exercise include walking, jogging/running, swimming, rowing, cycling, and cross-country skiing. In contrast, *resistance* exercise refers to overloading a muscle through a specific range of motion using some type of a resistance device. Modifiable variables associated with resistance exercise include intensity, volume, and duration. High-intensity, low-volume exercise involves lifting near maximal weights for few repetitions with long rest periods between sets. Conversely, moderate-intensity, high-volume (circuit-type) exercise incorporates the use of lighter resistive loads and more repetitions with shorter rest periods between sets.

In the past, the safety of exercise during pregnancy has been questioned due to the perceived risks to the developing fetus. Evidence is accumulating however, to support the safety of exercise in this group. While an increase in fetal heart rate with maternal heart rate during exercise is a normal physiological response (Brenner et al., 1999), a reduction of fetal heart rate is an indication of distress. Several recent studies have demonstrated no evidence of fetal bradycardia during or after either moderate (Bung et al., 1993; Clapp et al., 1993) or intense maternal exercise (Brenner et al., 1999; MacPhail et al., 2000).

Investigations of fetal outcome have demonstrated that women who perform regular aerobic and/or resistance exercise during pregnancy deliver babies with either similar (Bung et al., 1993; Avery et al., 1997; Avery et al., 1999) or more favourable (Hall and Kaufman, 1987) 1- and 5-minute Apgar scores. Hall and Kaufman (1987) found that women who exercised regularly during their pregnancy had a lower rate of operative deliveries than those who exercised irregularly or not at all. Furthermore, birth weights were similar between exercise and non-exercise groups. Thus, in the absence of medical and obstetrical complications of the mother, moderate exercise is safe and does not appear to have harmful effects on the fetus.

Recent evidence suggests that aerobic exercise may be instrumental in the prevention of GDM (Dyck et al., 1999). To determine whether exercise is effective in the prevention of GDM, 7 Aboriginal women with a history of this condition were placed on an exercise program early in a subsequent pregnancy. The program consisted of 45-minute sessions of low-impact aerobic exercise 3 times per week. While the recurrence

rate of GDM in indigenous women is reported to be as high as 90% (Peters et al., 1996), only two of the seven women in this study were diagnosed with recurrent GDM. Furthermore, only 1 of these 2 women required insulin therapy. Similarly, a retrospective analysis of the Central New York Regional Perinatal Data System demonstrated that a lack of exercise during pregnancy was significantly associated with the prevalence of GDM in obese women (Dye et al., 1997). Flaws in the methodology of these two studies render them insufficient to draw absolute conclusions. However, the findings suggest that aerobic exercise may improve glucose tolerance in pregnant women at risk for developing GDM.

This suggestion is reinforced by the finding that an acute bout of aerobic exercise has been shown to have a blood glucose-lowering effect in women with GDM. Blood glucose levels in women with GDM have been shown to be significantly lower after low and moderate intensity cycling compared with those at rest (Avery and Walker, 2001). In addition, 15 minutes of low-intensity aerobic exercise has been shown to lower blood glucose levels to a minor extent in pregnant women with Type II diabetes (Artal et al., 1985).

Exercise training refers to a series of exercise sessions which progressively increase in intensity or duration. Few studies have examined the effects of exercise training in women with gestational diabetes. Avery et al (1997) showed only non-significant reductions in blood glucose levels in women with GDM participating in 30-minute sessions of cycling 4 times per week compared with those on diet therapy.

However, several confounding variables could account for this. Subjects in the exercise group had a slightly higher pre-pregnant body mass index (BMI) than did those in the control group. Two of the women in the exercise group were smokers compared to none in the control group. The control group also showed a significant decline in carbohydrate intake compared to the exercise group. Finally, the sample size of 33 was small; therefore the statistical power (10-25%) was not high enough to detect a significant difference in blood glucose measurements. Furthermore, it is possible that a better endpoint for this type of study is the use of insulin as treatment for GDM. The comparison of blood glucose levels between groups is of minor relevance unless it can be put into the context of treatment. The use of insulin in the treatment of GDM has not yet been examined as an endpoint in women who exercise compared to those who do not.

Two studies have provided evidence that aerobic training will consistently lower blood glucose levels in GDM. Jovanovic-Peterson et al (1989) compared blood glucose levels among subjects with GDM randomized to diet therapy or a diet plus aerobic exercise program over a 6-week period. Women in the exercise group performed arm ergometry for 20 minutes three times per week. While both groups demonstrated a significant reduction in their fasting and 1-hour post-prandial blood glucose levels, as well as glycosylated hemoglobin, women in the exercise group had significantly lower fasting and post-prandial blood glucose values than those of the diet group. Bung et al. (1991) randomized women with GDM who failed diet therapy to either an insulin group or an aerobic exercise group who participated in three 45-minute sessions of stationary cycling per week. No significant differences were found in weekly blood glucose

determinations between the groups. This suggests that aerobic exercise is just as effective as insulin in the treatment of GDM. Results of these studies demonstrate that aerobic exercise with a frequency of as little as three times per week may eliminate the need for insulin therapy in women with GDM.

RESISTANCE EXERCISE IN THE TREATMENT OF DIABETES

Resistance exercise is an important component of training which is often overlooked. Participation in circuit-type resistance training has been shown to improve insulin sensitivity (Soukup and Kovaleski, 1993; Erikkson et al., 1998; Ishii et al., 1998), glucose disposal rate (Ishii et al., 1998), and glycemic control in Type II diabetics (Honkola et al., 1997; Dunstan et al., 1998; Erikkson et al., 1998). Furthermore, Smutok et al. (1994) demonstrated that strength training improves glucose tolerance to the same extent as aerobic training in men with abnormal glucose regulation. This indicates that resistance training is comparable to aerobic training in improving hyperglycemia.

Twenty-six untrained men with either impaired glucose tolerance or Type II diabetes volunteered to participate in 20 weeks of either a strength training program, an aerobic training program, or a non-exercising control group (Smutok et al., 1994). There were four men with impaired glucose tolerance in each exercise group, all of whom normalized their oral glucose tolerance test results following their respective training programs. In addition, subjects with Type II diabetes participating in both exercise programs improved their glucose tolerance.

Erikkson et al (1997) demonstrated a significant improvement in hemoglobin A1C (an indicator of long-term glycemic control) after three months of resistance training among male subjects with Type II diabetes. Home-monitored blood glucose concentrations also showed improvement. These findings indicate that the inclusion of resistance training in the treatment of Type II diabetes may be an effective way of improving glycemic control. Given the similarity in etiology between GDM and Type II diabetes (Bung et al., 1996), it is possible that the blood glucose lowering effect of resistance exercise may also be seen in women with GDM.

Other benefits associated with resistance training include improved blood lipid profiles (Durak et al., 1990a), improved coronary risk factors (Franklin et al., 1991), and reduced resting blood pressure (Keleman, 1989; Cononie et al., 1991). While these benefits are also seen with aerobic training, advantages specific to resistance training include improvements in muscle strength (Durak et al., 1990a) and muscle size (Miller et al., 1984) leading to an increase in glycogen storage capacity. These improvements result in enhanced metabolic activity through an increase in basal metabolic rate and improved fuel delivery and utilization.

During pregnancy, strengthening exercises may enable the body to compensate for a progressive anterior shift in the centre of gravity (Hall and Kaufman, 1987). Without compensation, this shift may produce biomechanical changes causing the physical discomfort that is so often associated with pregnancy. Women may find aerobic training to become increasingly uncomfortable as the pregnancy progresses. Exercises that use the

upper body or place little mechanical stress on the trunk produce no uterine activity (Durak et al., 1990b) and may be more comfortable in the late stages of pregnancy. Muscle conditioning exercises may be performed more easily than aerobic exercise during late pregnancy, as women can remain relatively stationary throughout the exercise. Moreover, having a greater number of exercise modality options may enhance exercise participation in this population.

MECHANISM OF IMPROVED CARBOHYDRATE TOLERANCE WITH EXERCISE

While having no effect on the insulin secretion defects of GDM, exercise improves insulin sensitivity by stimulating glucose uptake in the absence of insulin as well as increasing insulin-stimulated glucose uptake. Three lines of evidence support the hypothesis that muscle contractions stimulate muscle glucose uptake independent of insulin. First, *in vivo* and *in vitro* studies have demonstrated that the effect of insulin and contractions on glucose transport are additive (Ploug et al., 1987; Constable et al., 1988; Gao et al., 1994). Second, several investigators have used Wortmannin, a PI 3-kinase inhibitor, to demonstrate that PI 3-kinase activity is necessary for insulin- but not contraction-stimulated glucose transport (Lee et al., 1995; Yeh et al., 1995). Third, muscle from animals and humans with severe insulin resistance has demonstrated the ability to be stimulated to allow uptake of glucose by muscle contractions (Brozinick et al., 1992; Dolan et al., 1993).

The mechanism responsible for contraction-mediated glucose uptake is not completely understood but it does involve an increase in the translocation of GLUT-4 glucose transporters from intracellular storage sites to the cell membrane (See Figure 3) (Hansen et al., 1998). A rise in cytosolic calcium that occurs with muscle contractions may initiate the activation of intracellular signaling proteins that lead to the effects of exercise on muscle glucose uptake (Holloszy et al., 1986). Protein kinase C is a calcium-dependent signaling intermediary that is activated by muscle contraction and also may be involved in the regulation of contraction-stimulated glucose uptake (Cleland et al., 1989). Adenosine is secreted from the contracting muscle fibre and the adenosine receptor may also mediate this signaling mechanism (Vergauwen et al., 1994). In addition to the activation of intracellular signaling proteins, the glycogenolytic process may be an important factor in regulating contraction-mediated GLUT4 translocation. Contraction-stimulated hydrolysis of muscle glycogen may release GLUT4, leading to their translocation to the cell membrane (Goodyear and Kahn, 1998).

It has been hypothesized that intermediates in the insulin-signaling cascade are involved in the enhanced glucose uptake observed with a single bout of exercise. Recent evidence however, suggests that early steps in the insulin-signaling pathway such as tyrosine phosphorylation (Hansen et al., 1998; Treadway et al., 1989; Wojtaszewski et al., 1997) and PI3-kinase activitiy (Goodyear et al., 1995) are not activated to a greater extent by a given insulin concentration in exercised compared to control muscles. Furthermore, Wojtaszewski et al (2000) demonstrated that the increased insulin-stimulated glucose

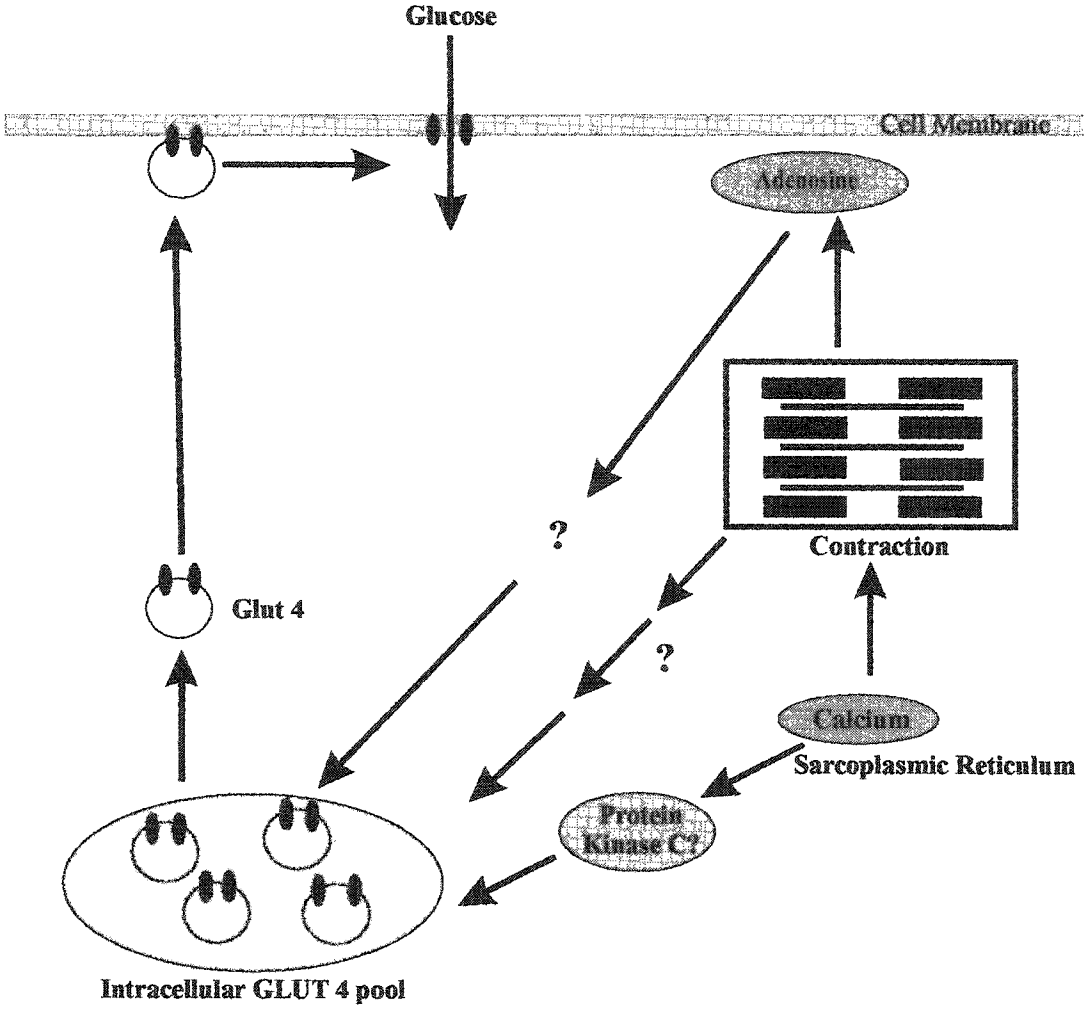

Figure 3. Contraction-stimulated glucose uptake in a muscle cell

Contraction stimulated glucose uptake is poorly understood apart from the increase of GLUT4 protein translocation from intracellular storage sites to the cell membrane. Muscle contractions cause a rise in cytosolic calcium which may initiate the activation of intracellular signaling proteins. Protein kinase C is a calcium-dependentprotein which may be involved in this process. Adenosine is secreted by the contracting muscle fiber and may also be involved in the translocation of GLUT 4 transport proteins to the cell membrane. Adapted from Goodyear and Kahn, 1998.

uptake in exercised muscle was not associated with an upregulation of the insulin receptor or later insulin signaling intermediates Akt or GSK-3. This implies that acute exercise increases insulin sensitivity at a point downstream from Akt and GSK-3.

The level of glycogen depletion in the exercised muscle may be a factor in the exercise-induced increase in insulin sensitivity and GLUT-4 translocation (Hansen et al., 1998; Derave et al., 1999). For example, in rats, there is an inverse relationship between muscle glycogen content and exercise- and insulin-stimulated GLUT-4 translocation, glucose transport, and glycogen synthase activity (Richter, 1996; Ivy and Kuo, 1998). In addition, exercise increases insulin stimulation of glycogen synthase activity facilitating glycogen resynthesis and suggesting an improvement in insulin sensitivity (Wojtaszewski et al., 2000).

While an acute bout of exercise can improve insulin sensitivity for approximately 48 hours, prolonged exercise training can have a positive impact on both fasting and post-prandial glucose levels (Trovati et al., 1984; Reitman et al., 1984; Holloszy et al., 1986; Jovanovic-Peterson et al., 1989). Evidence suggests that these adaptations are due to physical training rather than residual effects from the last exercise session. For example, several studies have found that insulin-stimulated glucose disposal is unaffected by 5-10 days of inactivity in trained individuals (King et al., 1988; Mikines et al., 1989a; Dela et al., 1995). Furthermore, studies using the hyperinsulinemic euglycemic clamp show that the improvement in glucose uptake with exercise training is still evident 3-4 days after the last exercise session (Hughes et al., 1993; Dela et al., 1995). These results indicate

that adaptations in glucose metabolism are evoked by regular physical exercise and not by a single exercise bout.

A key adaptation associated with exercise training is enhanced basal and exercise-induced skeletal muscle blood flow. A significant positive relationship has been demonstrated between basal limb blood flow and insulin-stimulated glucose uptake in athletes (Ebeling et al., 1993). Furthermore, insulin transport across the capillary seems to be a rate-limiting factor for insulin action (Yang et al., 1989). Indeed, Kirwan and colleagues (2000) demonstrated that trained subjects, with enhanced insulin action, had a 56% higher capillary to muscle fibre ratio than sedentary controls. The potentially greater ability to perfuse the muscle in trained subjects may contribute to a better delivery of insulin to the receptor site. Thus, the ability of exercise training to induce greater delivery of insulin and glucose to the muscle cell membrane may increase insulin-stimulated glucose uptake.

Exercise training also leads to an increased expression and function of several proteins involved in insulin signaling. Five days of exercise training led to a marked increase in insulin receptor protein expression, tyrosine phosphorylation, IRS-1 associated PI 3-kinase activity, and insulin-stimulated Akt phosphorylation in rat skeletal muscle (Chibalin et al., 2000). Similarly, insulin-stimulated IRS-1 associated PI 3-kinase activity has been shown to be higher in healthy, trained adults compared with sedentary controls (Houmard et al., 1999; Kirwan et al., 2000). Since Akt is located downstream from PI 3-kinase (see Fig. 1), the increase in phosphorylation of this protein is likely due

to the increased PI 3-kinase activity with training. Thus, improved insulin responsiveness on glucose transport may be related to enhanced signal transduction at the level of the IRS proteins and PI 3-kinase.

Animal studies have shown that increased skeletal muscle GLUT4 parallels the increase in insulin-stimulated muscle glucose uptake after exercise training (Ploug et al., 1990; Rodnick et al., 1990; Kawanaka et al., 1997; Chibalin et al., 2000; Reynolds et al., 2000). Furthermore, trained athletes with normal glucose tolerance show higher muscle GLUT4 levels than sedentary, age-matched controls (Houmard et al., 1991; Hardin et al., 1992). Evidence has shown that subjects with impaired glucose tolerance and those with normal glucose tolerance both exhibit an increase in muscle GLUT4 mRNA and protein with endurance training (Hughes et al., 1993; Dela et al., 1994; Daugaard et al., 2000). An increase in the intracellular pool of GLUT4 with exercise training may result in an increase in the amount of GLUT4 translocating to the cell surface and consequently an increase in glucose uptake.

The mechanism for the improvement of glucose tolerance with resistance training is not immediately apparent. Although resistance exercise stresses the muscle in different ways than does aerobic exercise, it has been established that muscle contraction in general evokes an insulin-like effect on glucose uptake (Holloszy et al., 1986). Therefore it can be inferred that resistance exercise will have similar mechanisms of action as aerobic exercise. Indeed, improvements in glycemic control using resistance exercise

have been seen even in those subjects who do not show a significant improvement in cardiovascular fitness (Miller et al., 1984; Eriksson et al., 1997).

Another possible mechanism is that the increase in muscle mass seen with resistance training is related to improved insulin binding and a corresponding increase in insulin clearance (Miller et al., 1984). This increase in muscle mass may increase the available glycogen storage area, thereby facilitating glucose clearance from circulation (Miller et al., 1984). Indeed, a strong correlation has been observed between thigh muscle size and glycemic control (Eriksson et al., 1997). The effects of regular exercise training on glucose tolerance are summarized in Figure 4.

CONCLUSION

In conclusion, the current management of GDM includes blood glucose monitoring, dietary counseling, and insulin therapy. Exogenous insulin is prescribed when changes in the diet fail to reduce blood glucose levels. While insulin therapy has been shown to be effective in reducing the rate of macrosomia in women with GDM, there are several reasons to remain cautious about this treatment. Aggressive use of insulin may result in small-for-gestational-age infants. Daily insulin injections are invasive and may be stressful to pregnant women. Finally, the use of insulin does not reduce the future risk of Type II diabetes in women with GDM.

Exercise may be a more attractive alternative to insulin for the maintenance of normoglycemia because it is less invasive and more easily incorporated into daily

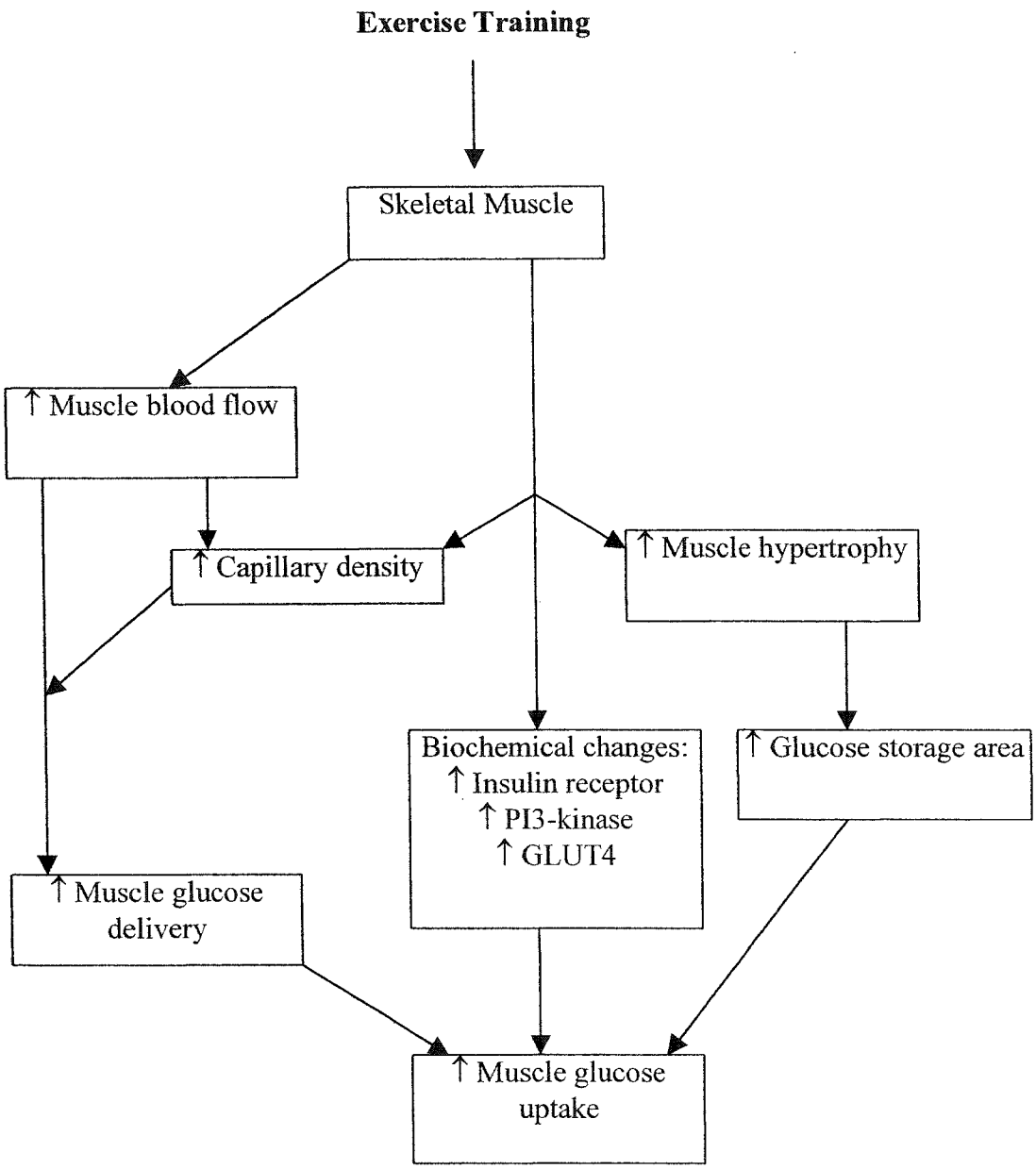

Figure 4. Effect of exercise on glucose tolerance. Adapted from Ivy et al., 1999

routines and living activities. Insulin therapy may not be the optimal treatment for gestational hyperglycemia because the hormonal changes of pregnancy reduce peripheral insulin sensitivity. Furthermore, incomplete compliance with medical regimens is common particularly with regard to insulin dose calculation and administration. Therefore exercise may result in better compliance with treatment regimens.

Exercise can improve carbohydrate tolerance by having an insulin-like effect in the muscle tissue during an exercise session. While the effect of a single exercise session may be very short-lived, exercise training over a period of time can lead to various adaptations that can have a positive effect on basal glucose uptake. These adaptations include increased skeletal muscle blood flow, increased muscle glycogen storage area, and increased expression and function of several of the proteins involved in insulin signaling.

There are numerous additional benefits of exercise during pregnancy. Exercise can help to control excessive weight gain, maintain aerobic and muscular fitness, alleviate back discomfort, improve posture, enhance self-image, reduce anxiety, and combat depression. Pregnancies complicated by diabetes have an additional benefit in its role in achieving and maintaining normoglycemia in women diagnosed with gestational diabetes. While aerobic exercise is advantageous in the prevention of GDM, recent evidence suggests that moderate aerobic activity may be used as an effective therapeutic approach as it seems to lower blood glucose levels and may eliminate the need for insulin

therapy. Thus, regular exercise, in conjunction with dietary intervention, could possibly serve as an alternative to diet and insulin in the treatment of GDM.

Although aerobic exercise has traditionally been accepted as the mode of exercise with which to treat high blood glucose levels in gestational diabetes, resistance exercise should also be considered. Resistance exercise has the potential to reduce the blood glucose levels and maintain normoglycemia in the gestational diabetic similarly to that in the Type II diabetic and may offer additional advantages over aerobic exercise. The benefits of resistance versus aerobic exercise may not involve the physiology of the effect but convenience and acceptance by the patient.

Research into the effect of resistance training in gestational diabetes is needed to determine whether it can be used as an alternative or adjunctive treatment. We have investigated the effects of circuit-type resistance training on the need for insulin in gestational diabetes. We anticipated that women with gestational diabetes would eliminate or significantly reduce the use of insulin as part of their treatment with the inclusion of resistance exercise training. In addition, maintaining an exercise program may prevent the return of gestational diabetes in future pregnancies as well as the potential onset of Type II diabetes with advancing age.

CHAPTER 2

THE EXPERIMENT

Objectives and Hypotheses

The primary objective was to compare the effect of resistance exercise plus diet versus diet therapy alone on the requirement for insulin in pregnancy affected by GDM. *Hypothesis:* Women who perform resistance training as well as follow appropriate diet advice will have a lower incidence of insulin use than women treated with diet alone.

The secondary objectives were to study the effect of resistance exercise plus diet versus diet therapy alone on:

1. The interval between the initial clinic visit and need for insulin. *Hypothesis:* Women participating in resistance exercise will have a longer interval between the onset of therapy and initiation of insulin treatment than women treated with diet alone.
2. The amount of insulin required. *Hypothesis:* The amount of insulin required will be lower in women performing resistance exercise than that in women treated with diet alone.

Methods

Subjects

Subjects were 32 otherwise healthy, nonsmoking pregnant women with a documented diagnosis of gestational diabetes between week 26 and 32 of gestation. Clearance to enter the study was provided by the physician monitoring each subject's pregnancy. All subjects provided written informed consent before entering the study.

Subjects were recruited from the Diabetic Outpatient Clinics at the Royal Alexandra and Grey Nuns Hospitals. Inclusion criteria for the study included maternal age between 20-40 years, gestational age between 26-32 weeks, body mass index below 40, and nonsmokers who were not involved in a regular exercise program. The study design, information form, and informed consent form were approved by the University of Alberta Health Research Ethics Board. Site approval was obtained from both the Caritas Health Group and the Royal Alexandra Hospital.

Subjects were approached upon their first visit to the Diabetes Outpatient Clinic. Interested individuals were given an information form and asked to complete a medical screening form as well as the informed consent form. Subjects were randomized using a random numbers table. Allocation was concealed in sequentially numbered opaque envelopes. Each new subject entering the study received the next envelope in sequence.

Inclusion Criteria

- Age 20-40 years
- Nonsmoker
- Physician diagnosis of GDM
- Between 26 and 32 weeks gestation
- Pre-pregnant body mass index (BMI) below 40
- No current regular exercise regimen

Exclusion Criteria

- Clinically significant valvular or ischemic heart disease
- Type I diabetes mellitus, peripheral vascular disease, thyroid disease or uncontrolled hypertension, other serious system disorder
- An incompetent cervix
- A history of two or more spontaneous abortions
- Bleeding or placenta previa
- Ruptured membranes, premature labour
- Toxemia or pre-eclampsia (current pregnancy)

- Evidence of fetal growth retardation (current pregnancy)
- Multiple pregnancy (i.e. twins)

The ability to determine the effects of exercise training on the various outcomes was limited by subjects' compliance to the diet advice as well as the exercise program. In addition, subjects were recruited from only 2 of the 3 Diabetic Outpatient Clinics in the Edmonton area.

Treatment Plan

Diet Alone

All subjects were managed with a standard diet that consisted of 40% carbohydrate, 20% protein, and 40% fat calculated at 24 to 30 kcal/kg/day divided into three meals and three snacks. A registered dietician administered each subject's diet plan. Meal plans were individualized to account for the ethnic background and food preferences of each subject. Subjects were monitored weekly to ensure appropriate weight gain.

Standard diet therapy consisted of the following:

- Determination of Body Mass Index (BMI) and Ideal Body Weight (IBW)
- Calculation of the required daily caloric intake (see table below)
- Allotted calories were distributed throughout the day (i.e. six small meals)
- Dietary mix were as follows: 40-50% carbohydrate; 20% protein; 30-40% fat

Table 2. Determination of Caloric Intake

Body Mass Before Pregnancy	Calculation of Caloric Intake
Ideal Body Weight (IBW)	30 kcal/kg/day
120-150% IBW	24 kcal/kg/day
> 150% IBW	12-18 kcal/kg/day
< 90% IBW	36-40 kcal/kg/day

Table 3. Distribution of Calories in a Diabetic Diet

Meal	Percentage of total calories per day
Breakfast	20%
Lunch	25%
Supper	25%
3 snacks after each meal	5%
1 snack before bed	15%

The women in the diet alone group were asked not to start a structured exercise program for the remainder of the pregnancy. Those choosing to exercise were asked to record the type and duration of exercise in a logbook.

Diet Plus Resistance Exercise

The exercise group followed the same standard diet while participating in a progressive physical conditioning program. An experienced instructor supervised three introductory sessions to ensure the safety of participants. Subjects in the exercise group were instructed to perform circuit-type resistance training 3 times per week. The progression of the exercise program was as follows:

Week 1 – 2 sets of 15 repetitions of each exercise
Week 2 – 2 sets of 15 repetitions
Week 3 – 3 sets of 15 repetitions
Week 4 to delivery – 3 sets of 20 repetitions

Eight exercises were performed in a continuous, circuit-type fashion with short rests (< 1 minute) between the stations. Exercises included pliés (i.e., squats with out-turned knees), military press, knee extension, hamstring curl, bench press, lateral pulldown, seated row, and tricep press. See Appendix 1 for a complete description of the exercises as they were described to each subject. All exercises were modified for the use of rubber tubing instead of weights. Subjects were instructed to exercise at a level that

felt "somewhat hard". As the exercises became easier to perform, subjects were instructed to perform the exercises farther away from the point at which the tubing was anchored. This was done to maintain the exercise intensity. Subjects were taught to monitor their own heart rate during exercise to ensure that it did not rise above 140 beats per minute. All exercise sessions were recorded in a logbook.

During the Study Protocol

Glucose monitoring included daily fasting and 1- or 2-hour postprandial measurements with portable glucometers. Nurse educators provided instruction on home glucose monitoring. Instruction in cleaning, calibration, and troubleshooting of the monitors was included in the subjects' education. Blood glucose values were recorded in a logbook, so that mean blood glucose values could be determined. A random glucose measurement was taken in a reference laboratory at least once during treatment to ensure the accuracy of the meter.

Insulin therapy was initiated if at any time during therapy two of the following three values were exceeded:

Mean fasting $\geq$ 5.3 mmol•L^{-} or
Mean 1-hour postprandial $\geq$ 7.8 mmol•L^{-} or 2-hour postprandial $\geq$ 6.7 mmol•L^{-}

Subjects were encouraged to continue the exercise protocol for the measurement of the secondary endpoints.

Goal of treatment

The goals for treatment were as follows:

$<$ 5.3 mmol•L^{-} fasting glucose

< 7.8 mmol•L^{-} 1 hour postprandial glucose
< 6.7 mmol•L^{-} 2 hour postprandial glucose
> 3.5 mmol•L^{-} = minimum glucose concentration

Table 4. Pre-Treatment Evaluation

Investigations	
Complete history and physical exam including:	• Maternal weight • Prepregnant Body Mass Index (kg/m^2) • Family history of diabetes • History of chronic hypertension • Past obstetric history • Blood pressure • Cervical exam • Parity • Previous gestational diabetes
Questionnaires	• Medical screening form • Informed consent form
Chemistry	• Fasting blood glucose • 2-hour GTT OR gestational diabetes screening test

Table 5. Evaluation During and After Protocol Treatment

Investigations During the Protocol		**During Treatment**
Physician Visits	• Body weight • Fasting and 2-hour post-prandial sugar	Weekly
Follow-up investigations		**Timing**
Assessment of fetal health	• Infant birthweight • neonatal hypoglycemia • mode of delivery • infant Apgar scores	Upon delivery – values were obtained from patient records.

Subjects were instructed to stop exercising and consult the physician if any of the following warning signs or symptoms occurred:

- Pain

- Bleeding
- Dizziness
- Shortness of breath
- Palpitations
- Faintness
- Tachycardia
- Back pain
- Pubic pain
- Difficulty walking

Statistical Considerations

Endpoints and Analysis

The primary endpoint of this study was the requirement for insulin in GDM. The number of women requiring administration of insulin was compared between the two groups. As this was intent to treat trial, subjects were analyzed according to the groups to which they were randomized.

Secondary endpoints included the length of time that insulin treatment was delayed and the amount of insulin administered.

A sub-group analysis was performed to determine the requirement for insulin between the treatment groups only in women with a body mass index above 25 kg/m^2.

The chi-square test was used to analyze the primary endpoint of requirement for insulin. The independent samples t-test was used to analyze the secondary endpoints. The power to detect a significant difference was calculated using the Pearson-Hartley chart. Variables that were not normally distributed were analyzed with the Mann-Whitney U-test.

Sample Size

Approximately 50% of women with GDM in the Edmonton area are prescribed insulin treatment. To calculate the sample size, it was estimated that the incidence of insulin use would need to be reduced to 25% to be considered statistically significant. For 0.8 power, alpha = 0.05 the sample size has been calculated at N=32 subjects equally randomized into each of the two groups.

CHAPTER 3

RESULTS

Subjects

The diet alone and diet plus exercise groups were similar in physical characteristics (Table 6). The diet alone group had a significantly higher prepregnant body mass as compared to the diet plus exercise group. However, there were no significant differences between the groups with regards to prepregnant body mass index (BMI).

Table 6: Demographic Characteristics

	Diet Alone (n=16)	Diet Plus Exercise (n=16)	P Value
Maternal Age	31.3 ± 5.0	30.5 ± 4.4	0.63
Height (cm)	165.1 ± 8.5	159.6 ± 7.1	0.06
Prepregnant Body Mass (kg)	*77.1 ± 19.2	65.9 ± 8.4	0.05
Prepregnant Body Mass Index (kg/m^2)	28.0 ± 5.7	25.9 ± 3.4	0.21
Gestational Age at First Visit (wk)	29.6 ± 2.1	29.0 ± 2.0	0.44
Weight Gain up to Diagnosis (kg)	9.5 ± 4.8	10.4 ± 3.5	0.56
Total Pregnancy Weight Gain (kg)	11.2 ± 5.7	11.3 ± 4.4	0.96
History of GDM (#)	3	3	1.0

Values are means ± standard deviations.
*Significant difference between diet alone and diet plus exercise groups.

Table 7 displays the diagnostic results for gestational diabetes for both groups. Nine women in each group were assessed using a non-fasting, random plasma glucose test (Gestational Diabetes Screen). No differences were found between the treatment groups on this variable. Nine women in the diet alone group as well as 7 women in the diet plus exercise group were diagnosed with a Glucose Tolerance Test. Fasting and 1-hour values were significantly higher in the diet alone group. However, there were no significant differences between groups with regards to the 2-hour measurement.

Table 7. Diagnostic Information

Diagnostic Test	Diet Alone	Diet Plus Exercise	P Value
Gestational Diabetes Screen ($mmol \cdot L^{-}$)	11.1 ± 1.4 (n=9)	11.1 ± 0.8 (n=9)	0.90
Glucose Tolerance Test Fasting ($mmol \cdot L^{-}$)	*5.5 ± 0.57 (n=9)	4.8 ± 0.57 (n=7)	0.03
Glucose Tolerance Test 1 Hour ($mmol \cdot L^{-}$)	*12.2 ± 0.83 (n=9)	11.3 ± 0.63 (n=7)	0.03
Glucose Tolerance Test 2 Hour ($mmol \cdot L^{-}$)	9.6 ± 1.4 (n=9)	9.9 ± 0.97 (n=7)	0.61

Values are means ± standard deviations.
*Significant difference between diet alone and diet plus exercise groups.

Insulin Treatment

The number of women requiring insulin treatment was not significantly different between the treatment groups. Nine of sixteen women in the group treated with diet alone required insulin as part of their treatment whereas seven of sixteen women in the diet plus exercise group required insulin therapy. This small difference was not significant ($p = 0.48$).

A sub-group analysis examining only women having a prepregnant BMI above 25 kg/m^2 showed a significantly lower incidence of insulin use in the diet plus exercise group. In this analysis, 8 of 10 women in the diet alone group required insulin while only 3 of 10 women in the diet plus exercise group were prescribed insulin therapy ($p<0.05$).

The amount of insulin prescribed was significantly lower in the diet plus exercise group (0.22 ± 0.2 units per kilogram) as compared to the diet alone group (0.48 ± 0.3 units per kilogram) (see Figure 5).

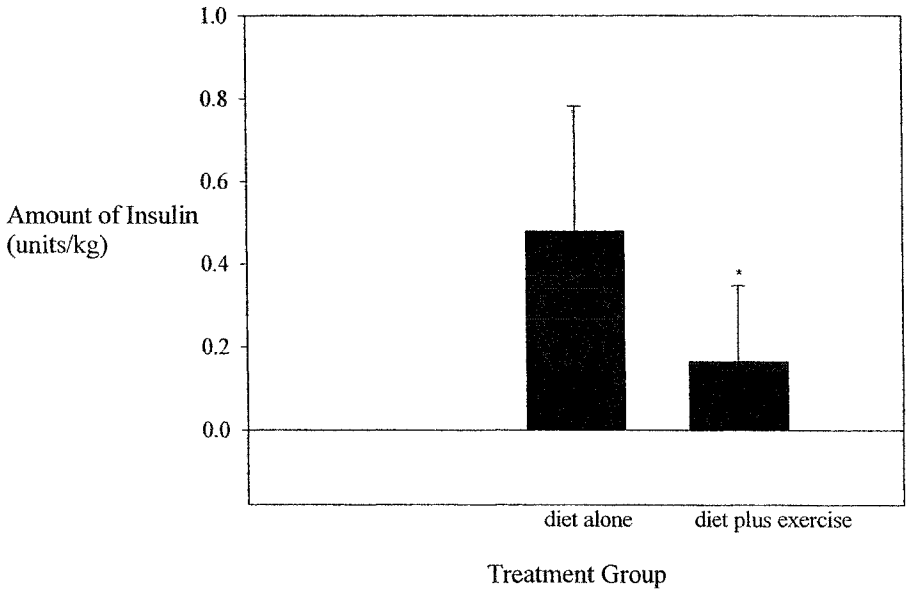

Figure 5. Amount of insulin prescribed
*$p<0.05$

The latency period between the first clinic visit and initiation of insulin therapy was significantly longer in the diet plus exercise group (3.71 ± 3.1 weeks) compared to the diet alone group (1.11 ± 0.8 weeks) (see Figure 6).

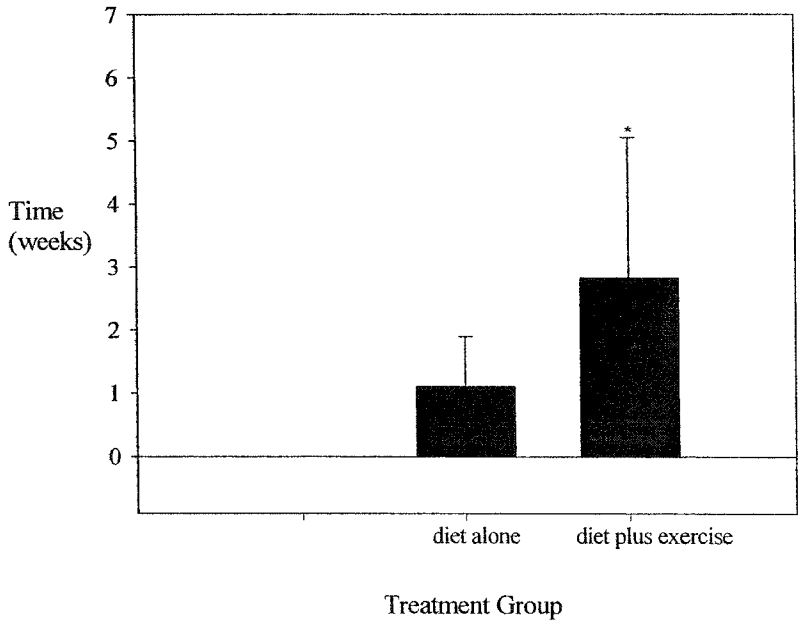

Figure 6. Delay in the initiation of insulin treatment
*p<0.05

Home Monitored Blood Glucose Levels

There were no differences between the treatment groups regarding home-monitored blood glucose measurements (see Table 8). However, when all post-meal values were pooled, the diet plus exercise group demonstrated lower blood glucose values (5.98 ± 0.29) as compared with the diet alone group (6.39 ± 0.81). Measurements

were taken before breakfast and 2 hours after every meal. Four women in each group failed to record their blood glucose measurements for the study.

Table 8. Home Monitored Blood Glucose Levels

Blood Glucose ($mmol \cdot L^{-}$)	Diet Alone (n=12)	Diet Plus Exercise (n=12)	P Value
Fasting	5.1 ± 0.65	4.7 ± 0.39	0.07
Breakfast	6.2 ± 1.1	5.7 ± 0.40	0.12
Lunch	6.2 ± 0.72	5.9 ± 0.43	0.12
Supper	6.7 ± 0.83	6.4 ± 0.52	0.34
Pooled post-meal	*6.4 ± 0.81	6.0 ± 0.29	0.02

Values are means ± standard deviations.
*Significant difference between diet alone and diet plus exercise groups.

Exercise Adherence

The diet plus exercise group participated in an average of 2.0 ± 0.9 sessions of resistance exercise per week of treatment. The diet alone group reported little activity other than light walking. Women who exercised 2-3 times per week had a lower incidence of insulin use than those who exercised 0-1.9 times per week did. Table 9 provides an overview of 4 levels of exercise compliance and the number of women requiring insulin in each subgroup.

Table 9. Exercise Adherence and Insulin Requirement

Exercise Sessions per Week (#)	Number of Women Requiring Insulin
3.0 (n=4)	1 (25%)
2.0-2.9 (n=6)	2 (30%)
1.0-1.9 (n=2)	2 (100%)
0.0-0.9 (n=4)	2 (50%)

Birth Outcomes

Birth outcomes are displayed in Table 10. There were no significant differences between the diet alone and diet plus exercise groups in gestational age at delivery, rate of caesarean sections, or birthweight. In addition, 1- and 5-minute Apgars were similar between the groups. Two subjects' delivery records were lost to follow-up.

Table 10. Birth Outcomes

Outcome	Diet Alone	Diet Plus Exercise	P Value
Gestational Age at Delivery (weeks)	39.0 ± 1.0	39.1 ± 1.5	0.86
Birthweight (grams)	3501.1 ± 410.1 (n=14)	3327.4 ± 326.9 (n=16)	0.21
1-minute Apgar	7.9 ± 1.8 (n=14)	7.8 ± 1.3 (n=16)	0.94
5-minute Apgar	8.6 ± 0.8 (n=14)	8.7 ± 0.6 (n=16)	0.79
**Rate of Cesarean Section	5 (31)	3 (19)	0.41

n=16 unless otherwise indicated
Values are means ± standard deviations.
**Values are *n* (%)

CHAPTER 4

DISCUSSION

The objective of this study was to determine the effect of resistance exercise training on the requirement for insulin therapy in gestational diabetes. The results demonstrate that resistance training did not significantly reduce the number of women requiring insulin to treat persistent hyperglycemia. The power to detect such a difference was approximately 55%. Fifty-six subjects would have been required to demonstrate that the effect was significant.

Women in the diet plus exercise group were prescribed significantly less insulin than those in the diet alone group. There was also a significantly longer latency to insulin requirement. This would suggest that resistance training has a positive influence on glycemic control.

A sub-group analysis showed that overweight women in the diet plus exercise group had a significantly lower incidence of insulin use than did overweight women in the diet alone group. This finding is consistent with the results of Dye and colleagues (1997). This large retrospective study demonstrated that lean women had similar rates of GDM whether they exercised during pregnancy or not. In contrast, obese women who exercised during their pregnancy had lower rates of GDM than their non-exercising counterparts. In addition, Avery and Walker (2001) suggested a greater effect of aerobic exercise for gestational diabetics who are overweight compared to those with normal

weight. This suggests that exercise is particularly useful in the prevention and treatment of GDM in obese compared to lean women.

These findings suggest that there is a difference in the mechanism of gestational diabetes in normal weight women versus overweight women. Women with gestational diabetes may represent a spectrum of abnormalities with some having an increase in insulin resistance, others having a beta-cell defect, and most having some degree of both. It is possible that gestational diabetes in lean women is due more to a beta-cell defect, which is not corrected with exercise, whereas overweight women may have a more pronounced peripheral insulin resistance as the mechanism.

Exercise training is likely to exert its effect on glycemia by improving peripheral insulin resistance. Improvement in insulin sensitivity results in an increase in insulin-stimulated glucose uptake. Evidence shows that the strongest protective effect of exercise in preventing Type II diabetes occurs among obese individuals (Helmrich et al., 1994; Manson et al., 1992). Since those who are overweight have a greater degree of insulin resistance than those of normal body weight, it is possible that exercise training may be more beneficial to obese women with GDM.

Exercise training appears to reduce hyperglycemia independent of changes in body composition. For example, one week of physical training has been shown to improve glucose tolerance in Type II diabetes (Rogers et al., 1988). The duration of the exercise program was considered too short to result in significant changes in body-fat

content. Furthermore, training of longer duration (> 2 months) has been shown to improve glycemic control in Type II diabetics despite no changes in body composition (Hughes et al., 1993; Dela et al., 1995). Taken together, these findings demonstrate that exercise training can reduce hyperglycemia independent of changes in adiposity.

Previous research using aerobic exercise as an alternative treatment modality for gestational diabetes has demonstrated positive results. Jovanovic-Peterson and colleagues (1989) demonstrated that a program of aerobic exercise training reduced blood glucose levels to a greater extent than diet alone. However, there was no reference to the relationship of the effect of exercise to maternal body composition. Furthermore, it has been shown that aerobic exercise may be used to replace insulin therapy in obese women with gestational diabetes (Bung et al., 1991). While both of these studies examined aerobic exercise, the current investigation focused on resistance exercise.

We believe this is the first study to examine the effects of resistance exercise training in gestational diabetes. There has been some investigation of this type of training in subjects with Type II diabetes. Ishii and colleagues (1998) demonstrated that circuit-type resistance training increased insulin-stimulated glucose disposal rate by 48% in previously untrained Type II diabetic men. These subjects participated in five training sessions per week for 4-6 weeks. Similarly, Type II diabetic men and women who participated in a 3-month circuit resistance training program demonstrated significant improvements in hemoglobin A1C as well as improvements in home-monitored blood glucose levels (Eriksson et al., 1997). Interestingly, the use of antidiabetic drugs was discontinued in one individual due to hypoglycemia. In addition, men with impaired

glucose tolerance participating in a 20-week resistance-training program normalized their glucose tolerance such that they were reclassified as normal (Smutok et al., 1994).

Given that resistance exercise training reduced the amount of insulin required in women with GDM, beginning an exercise program earlier in pregnancy may be more advantageous. Indeed, Jovanovic-Peterson and colleagues (1989) demonstrated that a program of aerobic exercise training reduced blood glucose levels in gestational diabetes but the difference was not seen until the fourth week of training. Correspondingly, in the present study, subjects in the diet plus exercise group were prescribed insulin an average of 3.7 weeks after the first clinic visit. Perhaps involving at-risk women in an exercise program early in pregnancy would either prevent GDM or at least prevent women from having to inject insulin as part of their treatment.

Adherence to the exercise program was satisfactory as women in this group exercised an average of 2.0 sessions per week. Compliance to aerobic exercise programs in previous studies involving women with GDM has been 90-100% for supervised programs (Bung et al., 1991; Jovanovic-Peterson et al., 1989) and 75-100% for home-based programs (Avery et al., 1997). The reduced amount of insulin required by the diet plus exercise group as well as the trend of reduced insulin requirement with increased exercise compliance in the current study indicates that an improvement in compliance has the potential to eliminate the use of insulin in more women. Women who exercised sporadically cannot be considered to have taken part in training per se. The objective of

this study was to determine the effects of a training program, not sporadic exercise, on the need for insulin.

Limitations of this study include compliance to both the diet advice and the exercise program. While the results of this study imply that exercise is more effective in the overweight population, it is possible that women in the diet plus exercise group made more of a change in their diet after diagnosis of gestational diabetes. As there was no analysis of dietary changes in the current investigation, it is impossible to estimate the effect that changes in the diet had on blood glucose. While adherence to the exercise program was satisfactory, several women failed to participate in the full complement of 3 sessions per week.

A further limitation of this study is that the diet alone group had significantly higher initial levels of hyperglycemia as indicated by the higher fasting and 1-hour values of the glucose tolerance test. However, no differences existed between the groups with regards to the gestational diabetes screening test or the 2-hour value of the glucose tolerance test. In addition, total post-prandial home-monitored blood glucose levels remained higher in the diet alone group despite being prescribed more insulin than the diet plus exercise group.

The outcome of this study has important implications not only for the management of GDM in overweight women but also the prevention of GDM. Future investigations should compare resistance training to insulin therapy in those who fail diet

therapy. In addition, a direct comparison should be made between aerobic and resistance training in women with GDM. Research is also needed to determine whether interventions with resistance exercise would help to prevent the onset of GDM.

CHAPTER 5

CONCLUSIONS

Based on the study findings and within the limitations of the study the following conclusions appear to be warranted:

- Resistance exercise training does not reduce the incidence of insulin use among women with gestational diabetes.
- Resistance exercise training reduces the incidence of insulin requirement among overweight women with gestational diabetes.
- The latency period between onset of treatment and initiation of insulin therapy is lengthened by resistance exercise training
- The use of resistance exercise training as an adjunct treatment reduces the amount insulin required by women with gestational diabetes

These conclusions fail to support the hypothesis of reduced incidence of insulin use with resistance exercise training in gestational diabetes. However, resistance exercise does reduce the incidence of insulin use in overweight women with GDM. In addition, this type of exercise does seem to have a physiological effect on blood glucose levels as demonstrated by the smaller amount of insulin required by the exercise group.

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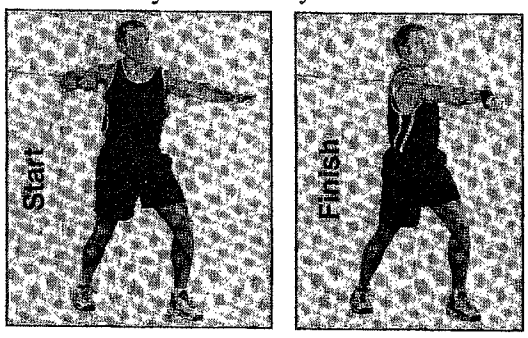
APPENDIX 1

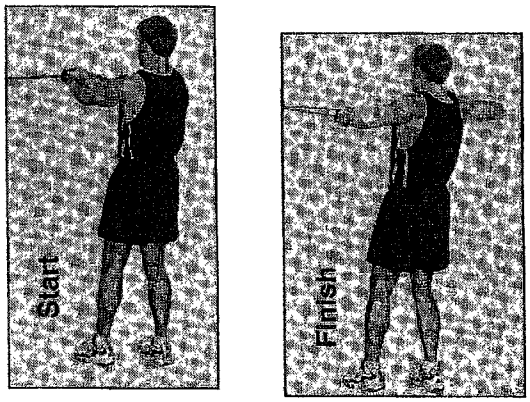
Resistance Exercises

1. Pliés – Place your feet apart and turn out the legs at the hips so that your toes are pointing outwards. Make sure your knees are in line with your feet. Bend your knees until they are over your toes then slowly straighten.

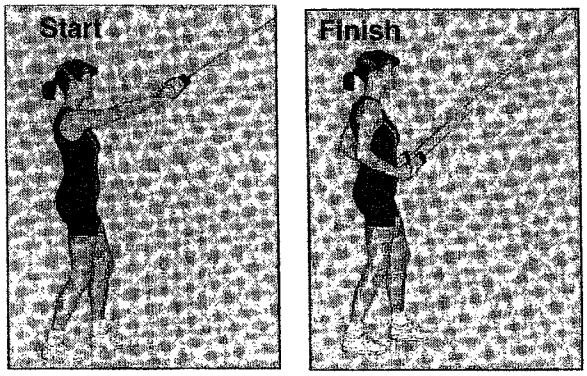
2. Chest Press – Place the door attachment at shoulder height in the door frame. Place your feet shoulder width apart with your knees slightly bent, facing away from the door. Grasp one handle in each hand and bring your elbows up, just below shoulder height. Make sure there is some resistance in the tube. Stabilize your torso by tightening your mid-section. Slowly push your arms forward until they are straight in front of you. Slowly return to the start position.



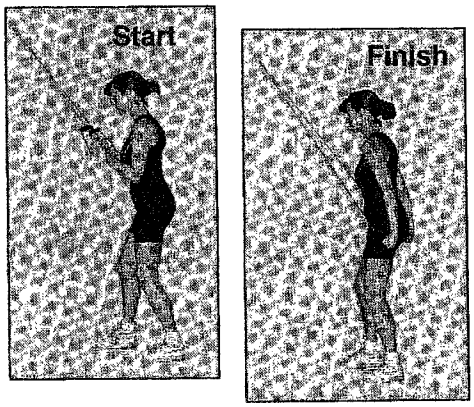
3. Standing Row – Place the door attachment at shoulder height in the doorframe. Place your feet shoulder width apart with your knees slightly bent, facing the door. Grip one handle in each hand with your arms straight out in front of you and in line with the tubing. Make sure there is some resistance in the tube. Stabilize your torso by tightening your mid-section. Slowly pull your arms backwards, bending at the elbow. Keep your elbows up at shoulder level as you pull backwards. Slowly return to the start position.



4. Standing High Pulldown – Place the door attachment at the top of the doorframe. Grip one handle in each hand. Position yourself so that you are facing the door, your arms straight out and slightly upward, in line with the tubing. Make sure the tubing is taught. Stabilize your torso by tightening your mid-section. Slowly, start pulling the handles back and down, bending at the elbows. Continue until your hands reach your mid-section. Slowly return to the start position.



5. Tricep Pulldown – Place the door attachment at the top of the doorframe. Place your feet shoulder width apart with one foot in front of the other. Grip one handle in each hand. Facing the door, place your elbows to your sides. Make sure the tubing is taught. Stabilize your torso by tightening your mid-section. Keeping your elbows at your side, straighten your arms downward. Do not let your elbows move away from your sides. Slowly return to the start position.



6. Forward Shoulder Press – Place the door attachment at hip height in the doorframe. With your back towards the door, grip the handles so they are on either side of your body. Make sure the tubing is taught. Stabilize your torso by tightening your mid-section. Begin this exercise with your hands in front, at shoulder height, and elbows tucked into your sides. Slowly push your arms up and out in front of you. Slowly return to the start position.

7. Knee extension – Tie your band in a knot close to the handles. Sit with your back against the back of a straight chair and place the tied band around your ankles. Leaving one foot on the ground, raise the other foot until your knee is almost straight. Lower slowly. Repeat 15-20 times and then do the same on the other leg. You may adjust the knot so that the resistance is appropriate.

8. Hamstring curl – Tie your band in a knot close to the handles. Stand beside a chair (or some other support) with one foot standing on the tied resistance band. Raise the opposite heel toward your butt. Slowly lower to the start position. Switch legs and repeat.

Photographs were reproduced from the following publications:

1. Jesperson M., Potvin A.N.,(2000) The Great Stretch Tubing Handbook Productive Fitness Products
2. Kochan-Vintinner A. (1999) Active Living During Pregnancy: physical activity guidelines for mother and baby. Larry Wolfe, Michelle Mottola (eds). Ottawa : Canadian Society for Exercise Physiology