

# Exercise and Type 2 Diabetes Mellitus: Implications for the Young

Nicole Mag, 2nd year Masters of Exercise Physiology

## DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterised by hyperglycaemia resulting from a deficiency in insulin secretion or action, or a combination of both. The consequent hyperglycaemia causes glycosylation of tissues and is associated with long-term damage to various organs including the eyes, kidneys and blood vessels. There are several pathogenic processes involved in the development of diabetes ranging from autoimmune destruction of beta-cells in the pancreas to insulin resistance at the tissue level. The majority of diabetes cases fall into two categories: type 1 diabetes, which is an absolute deficiency in insulin secretion, and type 2 diabetes, characterized by insulin resistance. Type 2 diabetes is a much more prevalent form (90% of all diabetes cases) and is caused by a combination of insulin resistance and inadequate compensatory insulin secretion.<sup>1</sup> Gestational diabetes, maturity onset diabetes of the young and malnutrition-related diabetes are other forms of the disease.<sup>2</sup>

## **Type 2 Diabetes**

Type 2 diabetes was previously referred to as non-insulin-dependent diabetes or adult-onset diabetes, and occurred almost exclusively in the adult population. Recently the number of adolescents and children with type 2 has begun to increase. Type 2 diabetes is comprised of insulin resistance, usually accompanied by a deficiency in insulin secretion. This is manifested by concurrent hyperglycaemia and hyperinsulinaemia. The characteristic feature of insulin resistance is the inability of normal insulin levels to produce an appropriate biological response. The primary deficiency in type 2 diabetes starts as an impaired tissue sensitivity to insulin, either in skeletal muscle or the liver. Both receptor and post-receptor defects are observed in adipocytes and skeletal muscle of people with type 2 diabetes. Thus, there is reduced effectiveness of insulin in clearing blood glucose. Persistent hyperinsulinaemia is thought to induce a desensitisation of the target tissues for insulin, challenging the pancreas to secrete more insulin. However, in type 2 diabetes the insulin secretion is insufficient to compensate for the insulin resistance.<sup>3</sup> Hyperinsulinaemia is thought to predict the conversion to type 2 diabetes in people who are insulin resistant.<sup>4</sup> Hyperglycaemia experienced by type 2 diabetic patients develops

gradually over time. Often people diagnosed with type 2 diabetes do not require exogenous insulin.

There are many different causes of this form of diabetes; however obesity seems to be the most prominent. Type 2 diabetes is strongly correlated with obesity, physical inactivity and a family history of the disease. Its prevalence varies among different racial/ethnic groups. It is often associated with a strong genetic component. Eighty percent of the people diagnosed with this form of diabetes are obese.<sup>1</sup> Obesity itself has been proven to cause some degree of insulin resistance. Type 2 diabetes frequently goes undiagnosed for many years until the patient presents with a diabetic complication.

## **Prevalence of Obesity and Type 2 Diabetes**

The United States has seen a rise in obesity and type 2 diabetes rates over the last two decades. In a study conducted by Mokdad *et al.* (1999) it was found that between the years of 1991 and 1998, obesity increased in every U.S. state regardless of sex, race, educational level, smoking status and age. Obesity rates increased from 12.0% in 1991 to 17.9% in 1998. This rapid increase in obesity, in all segments of the population and regions of the country, implies that "there have been sweeping changes in US society that are contributing to weight gain".<sup>5</sup> These changes cannot be due to motivation, biological or genetic factors alone because they are too widespread.<sup>5</sup> The rise in obesity rates is of great concern to anyone concerned with public health because of its associations with chronic diseases such as cardiovascular disease and diabetes.

The same group conducted a follow-up study in 2000 and noted that the self-reported incidence of diabetes increased from 4.9% in 1990 to 7.3% in 2000.<sup>6</sup> Across all U.S. states, an increase was seen in the prevalence of obesity and diabetes. Approximately 15 million adults in 2000 had diabetes. Mokdad *et al.* (2001) stated that "during the 1990s, epidemics of obesity and diabetes developed", with most U.S. adults being overweight (>56%), one fifth being obese, and 7.3% having diabetes. Weight gain proved to be a major risk factor for the development of diabetes. For every 1 kg increase in measured weight, the risk of diabetes increased by 9%.<sup>6</sup>

While more Americans seem to be gaining weight, fewer seem to be exercising. In 2000, 28.2% of the U.S. population were not regularly active and 27% of adults did not engage

in physical activity during their leisure time.<sup>6</sup>

### **Type 2 Diabetes and Adolescents**

The rapid emergence of type 2 diabetes in children recently being reported in America is alarming. Evidence suggests that type 2 diabetes may account for nearly half of all newly reported diabetes cases in paediatric populations between the ages of 10 and 19.<sup>7</sup> Fewer than 4% of the new diabetic cases were reported to be type 2 before the 1990's. Up to 45% have been reported in recent studies.<sup>8</sup> This represents a tenfold increase in the number of cases of type 2 diabetes during the past decade. Type 2 diabetes is considered a major health problem in the U.S. and worldwide.

Type 2 diabetes is strongly linked to lifestyle. In children, as in adults, type 2 diabetes is more highly associated with obesity than with any other clinical condition. Fagot-Campagna *et al.* (2000) reported that mean body mass index (BMI) for children with type 2 diabetes is above the 95th percentile for age.<sup>9</sup> In 2000, the American Diabetes Association (ADA) stated that "obesity is a hallmark of type 2 diabetes with up to 85% of affected children being either overweight or obese".<sup>8</sup> In general, American children are becoming more overweight than they were in past decades. Depending on the definition used, at least 11% and possibly as many as 25% of U.S. children and adolescents are overweight.<sup>10</sup> The disturbing increase in the prevalence of obesity seen over the past few decades must reflect major changes in non-genetic factors. Obesity is a reflection of a problem in a society which more and more favours inactivity. Mirroring the rapid increase in obesity is a decrease in physical activity. Hill & Trowbridge (1998) reported that only 36% of young people are physically active in school on a daily basis.<sup>10</sup>

In addition to obesity, other important risk factors for type 2 diabetes include ethnicity, age, gender, sedentary lifestyle, family history and prenatal influences. Children presenting with type 2 diabetes usually have a family history of the disease with 45-80% of patients having at least one parent with diabetes.<sup>8</sup> Worldwide the overall rate of new type 2 diabetes cases is increasing; however the rate of children presenting with the disease is increasing at a much faster speed.

Children who have symptoms of the disease are usually over the age of 10 and the peak age of diagnosis in adolescents is during the usual pubertal age period of 12-16 years. During normal puberty, insulin resistance is increased and as a compensatory mechanism, insulin secretion increases, resulting in mild hyperinsulinaemia. The adverse effects of obesity can be seen in childhood as total adiposity accounts for 55% of

the difference in insulin sensitivity in healthy white children. The amount of visceral fat directly correlates with basal and glucose stimulated hyperinsulinaemia and inversely correlates with insulin sensitivity.<sup>8</sup> Obesity, puberty and sedentary lifestyle are thought to bring about type 2 diabetes by promoting insulin resistance. There is concern that as obesity rates continue to increase and affect younger children, type 2 diabetes may begin to present in children of younger ages.

Currently the greatest public health concern for the western world seems to be the obesity epidemic. It has been said that as countries become more "westernised" they are also having to deal with an increased frequency of obesity. The frequency of type 2 diabetes in children and adolescents is rising in countries other than America, such as Canada, Japan and Ireland. Paediatricians are seeing increasing rates of hypertension, dyslipidaemia and type 2 diabetes in obese children and adolescents. Early onset of type 2 diabetes may particularly increase the risk of microvascular complications, which are known to be directly related to glucose levels and duration of diabetes. There are also macrovascular complications that seem to come about before diabetes is even diagnosed. Children will have to face such complications at younger ages. If the rapid growth of newly diagnosed type 2 diabetes cases in children cannot be reversed, we will continue to face major health care challenges.

### **Type 2 Diabetes and Cardiovascular Disease**

A number of cardiovascular risk factors are elevated in people with type 2 diabetes. Obesity directly causes endothelial dysfunction and is in itself an independent risk factor for atherosclerosis. Both hyperinsulinaemia and hyperglycaemia in normal populations have been linked to an elevation in cardiovascular risk factors as well. Therefore, it is not necessarily type 2 diabetes *per se*, but the characteristics of this disease, that predispose this population to increased risk of cardiovascular disease. Although it has not yet been studied in detail, this pattern probably holds true for the children and adolescents diagnosed with type 2 diabetes.

Type 2 diabetes has been shown to be preceded by a long period, perhaps several decades, of hyperinsulinaemia. Many population studies have looked at cardiovascular risk factors and future complications of type 2 diabetes.<sup>4,11,12</sup> Vascular complications represent the primary cause of death among diabetics. While degrees of hyperglycaemia and duration of diabetes have been associated with the risk of microvascular complications, the same relationship has not been demonstrated with macrovascular complications.<sup>4</sup>

It is believed that the increased risk of macrovascular complications may start before the clinical diagnosis of type 2 diabetes due to early metabolic disturbances. Subjects that convert to type 2 diabetes are already at increased risk for coronary heart disease even before its clinical onset.

Mortality from coronary heart disease and incidence of non-fatal coronary heart disease events are two to four times higher in patients with type 2 diabetes.<sup>11</sup> Type 2 diabetes is known to be associated with adverse patterns of cardiovascular risk factors including hypertension, central obesity, and dyslipidaemia. This dyslipidaemia is characterised mainly by increased serum triglycerides, and decreased high density lipoprotein (HDL).<sup>13</sup> In 2000, the ADA reported that children with type 2 diabetes were presenting with lipid disorders and hypertension.<sup>8</sup> Glowinska *et al.* (2001) noted that HDL cholesterol was significantly decreased in obese children with and without hypertension, and that triglyceride levels were significantly increased.<sup>14</sup> Elevated triglyceride levels may increase the concentrations of inflammatory cytokines and affect the permeability and inflammation of endothelial cells.<sup>15</sup>

The endothelium lines the internal lumen of all blood vessels and serves as an interface between circulating blood and vascular smooth muscle cells.<sup>16</sup> Activation of the endothelium by factors such as bacteria, viruses, cigarette smoking, hypertension or diabetes promotes an inflammatory reaction. Endothelial cells produce substances involved in the regulation of thrombosis and fibrinolysis. The soluble forms of substances such as ICAM-1, VCAM-1, PAI-1, hsCRP and e-selectin have been proposed as markers of endothelial damage. These markers are increased in patients with type 2 diabetes, especially those with microvascular complications.<sup>17</sup> During endothelial cell activation, an increase in leukocyte adhesion molecules can be seen.<sup>2</sup> This promotes thrombus formation, infiltration of the vascular wall by leukocytes and smooth muscle cell migration and proliferation.<sup>14</sup> A study of obese children, found that they had elevated levels of sICAMS-1 and sVCAMS-1 compared to "normal weight" controls.<sup>14</sup> Abnormal endothelial function is also directly associated with degree of hyperglycaemia.<sup>15</sup> Hyperglycaemia can increase oxidative shear stress and may contribute to initial disturbances in endothelial function. In addition, insulin acts both directly and indirectly on endothelial function. In insulin resistant states, such as obesity, insulin's vascular action may be blunted. Improvement of endothelial function is

seen with control of blood glucose levels and is dependent on initial levels of hyperglycaemia. Reduction of risk factors that lead to reduced endothelial inflammation may reverse previous damage and prevent future cardiovascular mortality.

## EXERCISE AND TYPE 2 DIABETES

There are many health benefits associated with regular physical activity of moderate intensity. Exercise training can decrease the risk of coronary heart disease through a number of physiological and metabolic mechanisms. Many studies have reported that regular physical activity can decrease the risk of chronic diseases such as coronary heart disease, hypertension and type 2 diabetes.<sup>18,19,20,21</sup> The health benefits of physical activity appear to accumulate in proportion to the total amount of activity performed. This is measured by either caloric expenditure or time.<sup>17</sup> There seems to be a dose-response relationship between the amount and intensity of exercise and improvements in the risk parameters of cardiovascular health.<sup>22</sup>

Currently in America, only about 22% of people are actively performing light to moderate intensity physical activity for at least 30 minutes a day, 54% of the population is "somewhat active" but would not meet this criteria and another 24% are considered "completely sedentary".<sup>23</sup> In a 2003 study, which assessed the physical activity level of Irish children from rural, suburban and inner-city schools, it was reported that 75% of girls and 81% of boys aged 10 to 17 years met the criteria set by the AMA regarding physical activity.<sup>24</sup> It was also shown that the level of physical activity decreased with age in both girls and boys suggesting that the tendency toward a more sedentary lifestyle may not be an American problem alone but a trend observed in the western world.

## **Exercise in the Prevention of Type 2 Diabetes in At-Risk Populations**

Type 2 diabetes can be prevented or delayed in persons at high risk for the disease by lifestyle intervention. One intervention study examined 3234 participants who were at risk for developing type 2 diabetes. Participants were randomly assigned to three groups, lifestyle intervention, metformin or placebo. The lifestyle intervention consisted of at least 150 minutes of physical activity a week and at least a 7% loss in body weight. The incidence of diabetes was decreased by 58% through lifestyle intervention alone, and by 31% in a metformin treated group of pre-diabetic subjects. These results were similar in both men and women and in all racial and ethnic groups. Intensive lifestyle changes were as

effective in older individuals as in the young. The group who participated in the lifestyle intervention program showed greater decreases in glycosylated haemoglobin and an increased rate of normal post-load glucose disposal at follow-up compared to those in the metformin treated group. The lifestyle intervention program prevented one person in seven from developing type 2 diabetes during the three year treatment period. It also delayed the development of complications from the disease.

### **Exercise and Insulin Resistance**

Exercise can have both short and long-term effects on insulin sensitivity. A single exercise session improves and partially normalises both insulin responsiveness and sensitivity for glucose utilisation. Exercise often results in decreased plasma glucose levels which can persist for several hours. Repeated bouts of physical activity of sufficient duration and intensity can lead to prevention, or a correction, of physiological and biochemical changes in the body which have been associated with a sedentary lifestyle. Exercise that depletes the muscle glycogen stores seems to lead to increased insulin sensitivity as the body "super compensates" for the lost glycogen stores in the muscle.<sup>18</sup> Individuals with type 2 diabetes who participate in regular exercise can potentially improve their metabolic control.

Both acute and chronic physical activity lead to enhancement of insulin-mediated glucose metabolism in healthy individuals.<sup>25</sup> Metabolic control can be improved with chronic exercise regardless of weight reduction as has been demonstrated in a group of patients with type 2 diabetes.<sup>20</sup> The improvement in metabolic control observed may be a reflection of a lower degree of peripheral insulin resistance or an increase in insulin sensitivity following each exercise bout.<sup>26</sup> A preservation of lean body tissues, muscle mass, and a decrease in fat mass can significantly contribute to an increase in insulin sensitivity.

Regular physical training results in a lower basal and glucose stimulated insulin concentration in the blood. Insulin response to a glucose challenge is markedly decreased and glucose tolerance is normal or improved. There are marked increases in insulin-stimulated glucose disposal rates and insulin sensitivity following physical training.<sup>26</sup>

### **Exercise and Dyslipidaemia**

It has been documented that endurance type activities are associated with the most striking effects on glucose control, heart and lung function and blood lipid profiles. The effects of training on metabolic control appear to correlate

with age, whereas blood lipid profile seems to be dependent on body weight.<sup>26</sup>

Blood lipid profile appears to improve with exercise. Thompson *et al.* (2001) reported a reduction in triglycerides 18-24 hours after exercise.<sup>27</sup> This is consistent with the introduction of metabolic changes and can persist for up to 72 hours. The reduction in triglycerides post exercise is most significant in those people who had the most elevated triglycerides at baseline. They also reported that exercise acutely increases HDL cholesterol. The HDL increase generally parallels the decrease in triglycerides, suggesting mediation by similar metabolic mechanisms. Prolonged exercise usually produces small decreases in total cholesterol and low density lipoprotein (LDL) cholesterol as well. Reports have shown acute decreases in LDL cholesterol by 5-8% in hypercholesterolaemic men after exercise. These effects appear to increase with energy expenditure and do not seem to require a minimum threshold.

### **Exercise and Endothelial Dysfunction**

Exercise has been proven to decrease cardiovascular risk markers in people with endothelial dysfunction. Rigla *et al.* (2001) looked at changes in markers of endothelial dysfunction in type 1 and type 2 diabetic patients after exercise.<sup>17</sup> They showed that in addition to improving other metabolic abnormalities, physical training improved markers of endothelial dysfunction including thrombomodulin, vWF and PAI-1. Another study reported decreased level of vWF and increased PAI-1 at baseline in people with type 2 diabetes compared with a control group. After their subjects performed exercise the two groups were similar.<sup>22</sup> The decrease shown in endothelial dysfunction markers reinforces the idea of a possible protective effect of exercise on the endothelium.

### **IMPLICATIONS FOR THE YOUNG**

While many studies have looked at cardiovascular disease in patients with type 2 diabetes, no study to date has looked at the implications of cardiovascular disease in young type 2 diabetic patients. This group displays the same diabetic characteristics as older type 2 diabetic patients: hyperinsulinaemia, hyperglycaemia, and insulin resistance. The same risk factors for cardiovascular disease have also been seen in young people with type 2 diabetes including obesity, hypertension, and dyslipidaemia. The concern lies in the development of microvascular and macrovascular complications at a younger age.

Exercise and diet are recommended as the first-line treatment for children with type 2

diabetes.<sup>8</sup> Physical exercise has been proven to help control the blood glucose levels of both type 1 and type 2 diabetic patients and prevent the development of type 2 diabetes in at-risk populations. Consistent exercise acts by increasing energy expenditure and basal metabolic rate, and is an important component to weight management. The increased caloric expenditure is known to improve glucose tolerance, insulin sensitivity and blood lipid profile.

With the increasing rates of obesity in many westernised populations one has to take a closer look at activity levels. Many societies are becoming more sedentary. It is important to encourage children and adolescents to be physically active to prevent the obesity rates from continuing to rise. Exercise may also prevent the chronic conditions associated with obesity. Having a more active lifestyle can reverse many of the health problems facing the youth of today.

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