Behavioral Risk Factors and Effects of Lifestyle Modification on Adults with Diabetes: A Brazilian Community-based Study

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Abstract

Lifestyle is directly related to the incidence of type 2 diabetes mellitus (DM-2), a risk dramatically elevated by obesity and inactivity. Several studies have verified that educational interventions can delay the onset of DM-2. Some of the interventions strategies utilized medication and diet, diet and/or physical exercise or the combination of diet and exercise, generally referred to a change in lifestyle. Despite the evidence that DM-2 can be preventive, there is still limited availability of effective prevention programs. DM-2 is considered an emerging public health problem as it is estimated that by the year of 2030 there will be about 366 million people with diabetes worldwide. DM2 remains a leading cause of cardiovascular disorders and many other complications. Our intent with this paper is to present researches and strategies (diet and physical activity interventions) that successfully improved plasma glucose control as a result of an effective lifestyle intervention program.

1 Epidemiology

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (ADA, 2012). The complications of DM due to chronic hyperglycemia lead to the end-stage renal disease, blindness, and non-traumatic lower-limb amputations (CDC, 2011). It is one of most common chronic diseases worldwide, and continues to increase in numbers and significance.

The prevalence of adults with DM in 2010 and 2030 were estimated in 80 countries around the world (Shan et al., 2010). The world prevalence of adult with DM in 2010 and 2030 were 6.4% and 7.7%, respectively. The highest regional prevalence for 2010 was for North America (10.2%), followed by the Eastern Mediterranean and Middle-East (9.3%) and South Asia (7.6%). The African region is expected to have the largest proportional increase in adult diabetes numbers by 2030 (98.1%), followed by the Eastern Mediterranean and Middle-East (93.9%), though North America will continue to have the world’s highest prevalence (12.1%). In Brazil, the prevalence of adult DM in 2010 was 6.6% and the estimation for 2030 is 7.8%. These estimates suggest that in 2030 there will be 438.7 million people worldwide with DM, with considerable disparity between populations and regions (Shan et al., 2010).

DM treatment represents an economic burden for the health care system and its complications account for a significant proportion of those costs (Dall et al., 2010). In 2007 the estimated total cost of DM in USA was US$ 174 billion, including US$ 116 billion of direct cost and US$58 billion of indirect cost (disability, work loss and premature mortality). Medical expenses for people with DM are considered to be 2 times or more than the cost for people without DM (CDC, 2011). In Brazil there are few data of the cost of DM. In 2003 a Latin America study estimated a total cost of DM more than 22 billion dollars in Brazil, which was considered the highest in Latin America countries (Barcelo et al., 2003).

2 Pathophysiology of T2DM and the Thrifty Genotype Concept for Hyperglycemia

The causes of T2DM are multifactorial and include both genetic and environmental elements that affect beta-cell
function and tissue (muscle, liver, adipose tissue, and pancreas) insulin sensitivity (Scheen, 2003). The genetic factors for insulin action include insulin receptor substrate-1 (IRS-1) gene polymorphisms, beta-3 adrenergic receptor gene and uncoupling protein (UCP) gene (Kaku, 2010).

A majority of individuals suffering from T2DM are obese, with central adiposity. Factors that cause increase in visceral adipose tissue (VAT) includes: a) the stores regulated factors involving overeating especially excessive intake of high dense sugar-rich food, smoking, increased alcohol intake, and disorders of endocrine system (increase in cortisol and abnormality in sex hormone secretion); b) lowered energy expenditure due lack of exercise; c) genetic factors and; d) aging (Kaku, 2010).

The mechanisms impairing the biological effects of insulin could involve either serine/threonine kinase activation (Kroder et al, 1996) or an interaction between suppressor of cytokine signaling (SOCS) proteins and the insulin receptor (Mooney et al., 2001; Lagathu et al., 2003; Rieusset et al., 2004). This could prevent its interaction with the insulin receptor beta subunit and the insulin signalizing pathway (Bastard et al., 2006).

In obesity the serine/threonine inhibitory phosphorylation by the fatty acids, pro-inflammatory cytokines and reactive oxygen species are mediated through specific intracellular signaling pathways involving C-Jun NH2 Terminal Kinase (JNK), Activating Protein-1 (AP-1), nuclear factor kappa beta (NF-kB) and IκB kinase (IKK) signaling molecules (Hirosumi et al., 2002; Hiraba-ra et al., 2012; Bastard et al., 2006).

The predominant paradigm used to explain the link between T2DM and central adiposity is the portal/visceral hypothesis (Scheen, 2003). This hypothesis proposes that increased adiposity, particularly in the visceral adipose tissue, leads to increased free fatty acids flux and inhibition of insulin action via Randle’s effect in insulin-sensitive tissues (Ravussin et al., 2002).

Alternatively to this hypothesis there are lines of evidence favoring the ectopic fat storage syndrome (Ravussin et al., 2002) The first line is that the failure to develop adequate adipose tissue mass (also known as lipodystrophy) results in severe insulin resistance and T2DM. Second, most obese patients shunt lipid into the skeletal muscle, liver and pancreatic insulin-secreting cell with the degree of lipid infiltration correlating highly with insulin resistance. Third, increased fat cell size may represent the failure of the adipose tissue mass to expand and thus to accommodate an increased energy influx. Taken together, these three observations support the acquired lipodystrophy hypothesis as a link between adiposity and insulin resistance (Ravussin et al., 2002).

Paralleling to the ectopic fat storage syndrome there is the endocrine paradigm where adipose tissue plays a critical role as an endocrine gland secreting factors (leptin, interleikine-6 (IL-6), tumor necrosis factor alfa (TNF-α), Angiotensin II, Adipo Q and Resistin) with potent effects on the metabolism of distant tissues (Ravussin et al., 2002; Scheen, 2003).

The role of fat cells in metabolic dysfunctions has long been considered; however, recently several findings have converged to indicate that adipocytes share with immune cells certain properties such as complement activation and cytokine production. Fat cell precursors also share features with macrophages and preadipocytes have the capacity for phagocytizing in response to several stimuli. Moreover, a relative recent and striking discovery is that obesity is associated with a low grade inflammation in adipose tissue and it is now well established that obesity is an independent risk factor of T2DM. VAT accumulation is an important predictive factor of glucose impairment while location of adipose tissue in the lower part of the body is not associated with increased metabolic alterations (Bastard et al., 2006).

The increase in macrophage infiltration could represent the major cause and/or consequence of the low-grade infiltration state associated with obesity (Wellen et al., 2003; Wellen et al., 2005). Locally present macrophages are responsible for the major part of the production of the locally produced cytokines (Weisberg et al., 2003). Hence it is now considered that both overproduction of pro-inflammatory cytokines by tissue from obese humans, and the deficiency in anti-inflammatory adipokines could be involved in the pathophysiology of insulin resistance (Bastard et al., 2006). Adipokine is generally any protein that can be synthesized and secreted by adipocytes. The main adipokines related to T2DM are leptin, TNF-α, IL-6, adiponectin and resistin (Bastard et al., 2006).

The concept of diabetic thrifty genotype is exceptionally efficient in the intake or utilization of food with basic difference of a quick insulin trigger in response to hyperglycemia. The survival benefit of this phenotype
was to minimize urinary glucose loss when fasting was replaced by feasting, leading to the more efficient utilization of food and storage of energy. A quick insulin trigger that helped primitive man survive famine by storing energy more efficiently, now leads to obesity, and eventually to T2DM. Besides this theory (Neel, 1962) focusing on energy storage thus allowing primitive man to survive a fast longer, there is another theory (Cahill & Wen, 1967) focusing on maintaining muscle mass. According to the latter the more efficient one in conserving muscle protein the better chances to withstand prolonged periods of deprivation, to be able to hunt successfully and to escape it preyed upon (Reaven, 1998).

The quick insulin trigger and ensuring hyperinsulinemia, when fasting, decreases urinary loss of glucose, and leads to enhanced energy storage. The consequences for a modern man, faced with a longer life-span, high-dense food intake and decreased physical activity are obesity and acquired insulin resistance, followed by beta-cell failure and onset T2DM. Skeletal muscle takes 80% of insulin-dependent glucose uptake. Hence muscle insulin resistance conserves glucose for utilization by the central nervous system decreasing the amount of muscle protein needed to be converted to glucose (neogluconeogenesis). It is postulated that the more insulin resistance an individual, the more efficient will be their ability to decrease proteolysis (and preserve lean body mass) when faced with caloric deprivation. Although a useful survival advantage or primitive man this phenotype predicts an inability to maintain normal glucose homeostasis in modern human (Reaven, 1998).

However, available evidence strongly supports the view that muscle insulin resistance is, at least to some extent, a genetically determined characteristic.

### 3 The role of Physical Exercise and the Effects on Insulin Resistance

Although the absolute caloric intake of modern-day humans is likely lower compared with our hunter-gatherer ancestors, it is nevertheless in positive caloric balance in the majority of the adult population mainly due to the increased sedentary lifestyle in present society (Chakravarthy & Booth, 2004).

Physical activity was obligatorily required for food procurement (Cordain et al., 1998), which in turn was necessary for the biological existence of our species. It is postulated that 95% of human biology, and presumably some human behaviors, was naturally selected during the late-Paleolithic era (50,000 – 10,000 BC).

Inherited genes allowing greater fat oxidation lowers the rate of muscle glycogen usage lengthening the exercise time to exhaustion and work time. It is therefore speculated that many genes involved in the upregulation of enzymes processing free fat acid oxidation in skeletal muscle with endurance training could be ‘thrifty’ gene candidates. In this sense the hunter-gatherers had a greater capacity to turn spare muscle glycogen with fasting, likely had a survival advantage. Another potential survival advantage for a better conservation of glucose in starvation would be diminishment of gluconeogenesis, which would spare muscle proteins (Chakravarthy & Booth, 2004).

During the past century, humans in industrialized societies made advances so that food could be produced with minimal physical work compared with earlier centuries, and they also devised transportation and storage methods such as food became available 24h/day. As a result, there is an even greater and perhaps unhealthy storage of fuel (Chakravarthy & Booth, 2004).

For example, a deficiency in caloric expenditure of at least 107 kcal/day by the elimination of walking from >21min/day at speeds >4.5km/h to not walking at all is associated with increased prevalence of mortality and many health conditions from diabetes (Hu et al., 2001). T2DM prevalence is 1.1% in present hunter-gatherer, rudimentary horticultural, simple agricultural and pastoral societies (Diamond, 2003).

Prediabetic conditions in healthy humans (decreased oral glucose tolerance with increased fasting plasma glucose and insulin concentrations) occur within 3 days of commencing continuous bed rest and no later than 10 days when trained individuals stop exercising, thereby suggesting that physical activity deficiency plays a key role in the rapid development of insulin resistance (Chakravarthy & Booth, 2004).

From an evolutionary perspective, those with thrifty or frugal genes who now eat too much or do not get enough exercise are at risk of T2DM. All mechanisms of developing insulin resistance can be reversed by physical activity. Exercise training activates a member of signaling pathways that regulate expression of the co-activator of peroxisome proliferator activated receptor gamma (PGC-1α) known to regulate mitochondrial bio-
genesis and β-oxidation enzymes (Ventura-Clapier et al., 2007).

It has been shown that both caloric restriction (via insulin) and muscle contraction (via AMP-activated protein kinase) enhance glucose uptake through translocation of glucose transporter type 4 (GLUT-4) protein. Besides acting directly on GLUT-4 translocation process AMPK has two other mechanisms which may reduce insulin resistance. One by stimulating IL-6 synthesis and therefore blocking TNF-α mRNA and the other by stimulating PGC-1α, increasing fatty oxidation and reducing the cellular fat levels (Huang & Czech, 2007; Ventura-Clapier et al., 2007).

Short-term fasting (15-40h) or a single exercise bout initiated a common adaptive response in skeletal muscle to increase the expression of a subset of metabolic genes (pyruvate dehydrogenase kinase 4, lipoprotein lipase, carnitine palmitoyltransferase I, and uncoupling protein 3 mRNA) in human skeletal muscle, it would seem to minimize glucose utilization in peripheral tissues (Pilegaard et al., 2003a; Pilegaard et al., 2003b), whereas mRNA for GLUT-4, hexokinase II, PGC-1α and fatty acid translocase (FAT/CD36) were not altered (Pilegaard et al., 2003a; Steensberg et al., 2002). Finally, exercise training increases mitochondrial density in skeletal muscle whereas fasting likely does not.

One of the most efficacious modes to prevent the development of insulin resistance is exercise of large muscle masses to lower skeletal muscle stores of glycogen and triglycerides. Reintroduction of physical activity, even when the muscle is already insulin resistant secondary to lack of utilization of excessively stored fuel, can restore metabolic flexibility potentially reversing insulin resistance (Chakravarthy & Booth, 2004).

4 The Botucatu Study on Healthy Lifestyle Promotion

Lifestyle is directly related to the incidence of type 2 diabetes (DM2) and several studies have shown that it is possible to achieve primary prevention of type 2 diabetes by changing lifestyle (diet and exercise) in subjects with impaired glucose tolerance (Tuomilehto et al., 2001; Knowler et al., 2002). Brazilian epidemiologists emphasize the importance of primary prevention for DM2 in Brazil (Sartorelli & Franco, 2003) by promoting healthy lifestyle.

The Botucatu Study on Healthy Lifestyle Promotion as a primary care for non-communicable chronic diseases (Move for Health – Mexa-se Pró-saúde) is an ongoing epidemiological study conducted by professionals from the Nutritional and Exercise Metabolism Centre (CeMENutri) of the UNESP Medical School (Botucatu, SP, Brazil). Patients are screened for chronic diseases and are submitted to assessments of physical activity readiness (PAR-Q), clinical, anthropometric, dietary, physical activity, blood analysis, fitness (aerobic, strength and flexibility), and postural at baseline and after intervention (daily sessions of supervised exercises and dietary counseling). Dietary counseling is provided by dietitians that meet with all participants at baseline to discuss the dietary intervention. The dietary intervention consists of a weekly group discussion about benefits of a healthy diet to achieve an adequate body weight. The weekly group section encourages participants to increase the daily intake of fruit and vegetables, whole grain cereals, legumes, low-fat dairy products, and lean meat, fish or poultry as recommended in the Food Guide for the Brazilian population (Brasil, 2008). The follow-up assessments occur every 10-12 weeks.

4.1 Cross Sectional Studies

A recent study conducted with 1003 individuals clinically selected to participate on our lifestyle changing program “Move for Health” aimed to identify biochemical and anthropometric factors associated with impaired fasting glucose (IFG) and T2DM. The results showed that abdominal obesity (elevated waist circumference), high blood pressure, elevated plasma concentrations of triglycerides, uric acid, and low density lipoprotein cholesterol, and decreased plasma concentration of high density lipoprotein cholesterol are associated with an increased risk for IFG and T2DM (Torezan, 2012).

Mota et al. (2011a) found positive associations of insulin resistance (HOMA-IR) with waist circumference, dietary fat intake, low dietary fiber intake, low muscle mass, elevated plasma concentration of uric acid, and presence of metabolic syndrome on adults. The determinants of insulin resistance among these individuals were related with modifiable factors that could be preventable with an effective lifestyle intervention program.

4.2 Longitudinal Studies
According to our data, eight weeks of physical exercise and food energy adequacy increased insulin sensitivity in high-insulinemic obese women (Barrile et al., 1999). Moreover, lifestyle modification associated with physical conditioning is able to reduce efficiently the prevalence of IFG on hyperglycemic-overweight adults (Mota et al., 2011b), and lead to important changes in dietary intake, such as an increase in protein and dietary fiber intake and a decrease in sugar and vegetable oil intake.

The additional effects of restricted energy intake to a physical exercise protocol on the exogenous glucose tolerance were investigated in free-living overweight women. The sample was initially composed by 150 individuals registered at the BLS program from 1993 to 1994. Of these individuals, 43 were eligible for the study (BMI < 35kg/m² and minimal of physical exercise sessions 3x/week for 2 months). The study protocol was divided in two parts and in each part the intervention lasted 2 months. At the first part of the study (M0) individuals were only submitted to physical exercises for 90 minutes/day, 5 times a week. At the second part (M1) individuals were additionally submitted to a dietary-energy restriction (25kcal/kg/day). Anthropometric and biochemical data were assessed at the beginning and at the end of each part of the study (M0 and M1). Glucose load test (GLT) was measured after a 75g glucose load as dextrosol (maltose) at baseline, and after 30, 60, 90, 120 and 180 minutes. The glycemic and insulinenic responses to GLT were determined by the area under the curve (AUC). Plasma removal rate of exogenous glucose was estimated by the AUC above the glucose baseline. The insulin cost of the loaded glucose was calculated by the ration between AUC of plasma glucose appearance/disappearance to the insulin increase/decrease both over the baseline. Paired-t test (student) was used to compare the responses of each individual of the study.

Energy intake (kcal/kg/day) was kept constant throughout the first part of the study, decreasing (11%) thereafter with dietary-energy restriction (second part of the study). The first two months of physical exercise slightly reduced body weight without significant changes on body mass index. When the individuals were submitted to physical exercises plus dietary-energy restriction, both body weight and BMI were reduced (0.9kg and 1.1kg/m², respectively). Physical exercise alone did not change plasma fasting levels of glucose or insulin, and neither the AUC values of glucose. However, the insulin to the exogenous glucose appearance decreased but the ratio of insulin/glucose over the baseline was maintained. Dietary-energy restriction associated to physical exercise reduced significantly fasting plasma glucose and its AUC, without significant changes on insulin levels. The overall responses were significant for reducing fasting plasma glucose which decreases insulin requirements for glucose appearance from the GLT. Thus, adequacy of energy intake (25kcal/kg/day) followed by body weight loss strengthened the insulin sensitivity action of physical exercises in removing the plasma glucose born from exogenous glucose loading.

5 Conclusion
Lifestyle is directly related to the incidence of T2DM, a risk dramatically elevated by obesity and inactivity. Obesity is considered a subclinical inflammatory condition that increases pro-inflammatory factors related to insulin resistance. The Botucatu Study on Healthy Lifestyle Promotion (cross sectional and longitudinal studies discussed) showed strategies (diet and physical activity interventions) that successfully improved plasma glucose control and insulin sensitivity as a result of an effective lifestyle intervention program. Several studies have verified that educational interventions, generally referred to a change in lifestyle, can delay the onset of T2DM. Despite the evidence that T2DM can be preventive, there is still limited availability of effective prevention programs.

References


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