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Prevention and Treatment of Type 2 Diabetes: Current Role of Lifestyle, Natural Product, and Pharmacological Interventions

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Abstract

Common complications of Type 2 diabetes (T2D) are eye, kidney and nerve diseases, as well as an increased risk for the development of cardiovascular disease and cancer. The overwhelming influence of these conditions contributes to a decreased quality of life and life span, as well as significant economic consequences. Although obesity once served as a surrogate marker for the risk of T2D, we know now that excess adipose tissue secretes inflammatory cytokines that left unchecked, accelerate the progression to insulin resistance and T2D. In addition, excess alcohol consumption may also increase the risk of T2D. From a therapeutic standpoint, lifestyle interventions such as dietary modification and/or exercise training have been shown to improve glucose homeostasis but may not normalize the disease process unless weight loss is achieved and increased physical activity patterns are established. Furthermore, utilization of natural products may serve as a significant adjunct in the fight against insulin resistance but further research is needed to ascertain their validity. Since it is clear that pharmaceutical therapy plays a significant role in the treatment of insulin resistance, this review will also discuss some of the newly developed pharmaceutical therapies that may work in conjunction with lifestyle interventions, and lessen the burden of behavioral change as the only strategy against the development of T2D.

1. Introduction

The widespread prevalence of type 2 diabetes (T2D) in the United States of America (US) has been consistently increasing over the past three decades, now accounting for annual health care costs of ~$132 billion dollars (Hamdy et al. 2001; Hogan et al. 2003). The disease has also reached epidemic proportions around the world, and with a predicted global prevalence of over 300 million by 2025. T2D is strongly associated with significant increases in morbidity and mortality, and directly linked to pathogenic consequences in the eyes, kidney and nerves as well as microvascular and macrovascular complications that promote cardiovascular disease.

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2. Complex Etiology of Type 2 diabetes

Primary Culprits

Obesity and/or lack of physical activity are two of the main determining factors in the development of insulin resistance that precede the diagnosis of T2D (Committee 1999). Insulin resistance is characterized by the impaired suppression of endogenous glucose production (glucose R_a) and/or the disposal of glucose into skeletal muscle (Stumvoll et al. 2005). Typically, β-cell compensation would initially facilitate an increase in insulin levels and prevent hyperglycemia. Unfortunately, as insulin resistance worsens, β-cell compensation become less and less effective and hyperglycemia of progressively greater magnitude occurs (Weyer et al. 1999). The result of the impossibility to maintain normal glycemic levels is a deleterious decline in the functional interplay between organ systems under worsening insulin resistance, and eventual evolution to frank T2D.

Although excess body weight and an elevated body mass index (BMI) have been clearly identified as risk factors for T2D, the underlying pathogenetic mechanisms by which obesity contributes to the etiology of diabetes are very complex, and still partially undetermined. The contributory influence of obesity is closely associated with the adverse impact of visceral and deep abdominal subcutaneous fat on lipolysis and the disproportionate release and/or influence of pro-inflammatory cytokines. Although studies that have examined the relationship between regional fat depots and insulin sensitivity have not been entirely conclusive with respect to the identification of the most pathogenic fat depot (Abate et al. 1995; Garg 2004), lipolytic activity is consistently higher in visceral and deep abdominal subcutaneous compared to superficial subcutaneous adipoctyes (Bergman & Ader 2000; Boden 1997). As a result, these adipoctyes contribute to higher free fatty acid (FFA) levels in the circulation and promote ectopic fat storage in non-adipose cells such as hepatocytes and myocytes (Machann et al. 2004; Seppala-Lindroos et al. 2002). It is also interesting to note that while studies employing the removal of subcutaneous fat in animals and humans did not change the degree of insulin resistance (Gabriely et al. 2002; Klein et al. 2004), a similar decrease in visceral fat resulted in an efficacious reduction in the level of insulin resistance (Gabriely et al. 2002; O'Leary et al. 2006). Hence, it seems plausible that higher amounts of abdominal fat in diabetic patients compared to age and BMI-matched non-diabetic subjects may contribute directly to the development of insulin resistance and chronic disease (Rattarsan et al. 2004).

Increased adiposity is also often accompanied by a disproportionate increase in pro-inflammatory adipokines (Carey et al. 2004). Expression and release of TNF-α (Hotamisligil et al. 1994) and release of monocyte chemoattractant protein (MCP-1), IL-6 and IL-8 from adipose tissue are increased in obesity and have been implicated in the development of insulin resistance (Bastard et al. 2000; Christiansen et al. 2005; Dyck et al. 2006b). Convincing evidence for the pathogenetic importance of TNF-α is derived from studies in which the genetic blockade of TNF-α completely restored insulin sensitivity (Ventre et al. 1997). Additional studies in obese humans found that treatment with anti-TNF-α agents also improved insulin sensitivity (Yazdani-Biuki et al. 2004). Elevations in TNF-α have been shown to reduce the expression of genes important to the electron transport chain, and inhibit lipid oxidation in human adipocytes (Dahlman et al. 2006). In addition, TNF-α may further amplify lipolytic signals, contributing to the development of hyperlipidemia in the metabolic syndrome (Cawthorn & Sethi 2007).

It seems that visceral adipose tissue may be responsible for a large fraction of circulating IL-8 (Bruun et al. 2004), and MCP-1 (Bruun et al. 2005). MCP-1 is a well recognized mediator of monocyte recruitment (Rollins 1997), impairs insulin signaling in skeletal muscle (Sell et al. 2006), and the overexpression of MCP-1 in mice contributes to systemic insulin resistance (Kanda et al. 2006). In mice fed a high fat diet, increased MCP-1 (among other macrophage

specific genes) resulted in a dramatic elevation in macrophage infiltration, promoting the downstream secretion of hormones, adipokines and lipids that are known to initiate and amplify insulin resistance (Xu et al. 2003). A recent study also provided evidence for the role in the development of insulin resistance of another inflammatory adipokine called acute-phase serum amyloid A (A-SAA), through paracrine stimulation of TNF-α, IL-6 and MCP-1 (Yang et al. 2006). The several lines of evidence presented above, while constituting only a representative fraction of the rapidly expanding body of literature available in this field, clearly document the established role of pro-inflammatory cytokines and chemokines in the development of insulin resistance.

Other molecules expressed in adipose tissue display primarily anti-diabetic properties. A notable example is adiponectin (Kern et al. 2003), whose protective effect on carbohydrate metabolism in skeletal muscle and liver (Dyck et al. 2006a) is paralleled by a significant inverse correlation with plasma TNF-α and TNF-α expression in abdominal adipose tissue (Kern et al. 2003). Incubation of adipose tissue fragments with either TNF-α or IL-6 reduced adiponectin mRNA (Bruun et al. 2003), indicating a potentially reciprocal relationship between pro-inflammatory cytokines (ie., TNF-α and IL-6) and adiponectin. Independent of weight loss or dietary restriction, adiponectin may also be a contributing mechanism by which physical exercise improves insulin sensitivity. For example, a recent study demonstrated that despite only modest changes in the systemic concentrations of high molecular weight (HMW) adiponectin, an exercise intervention induced a ~60% increase in insulin sensitivity and concomitant 1.9 and 3.5 fold increases in skeletal muscle mRNA expression of the adiponectin receptors, Adipo R1 and Adipo R2 (O'Leary et al. 2007).

Leptin is another adipose tissue-derived cytokine with protective effects on carbohydrate and lipid homeostasis, through inhibitory signals for food intake and energy metabolism (Dyck et al. 2006a). While elevated leptin physiologically suppresses the desire for nutrient intake, obesity is associated with high leptin levels, due to central and/or peripheral leptin resistance (Lonnqvist et al. 1995). For example, in rats fed a high fat diet for 4 weeks, the suppressive influence of leptin on hepatic glucose production was reduced (Wang et al. 2001) and the stimulatory influence of leptin on fat utilization was ameliorate$_{[p1]}$d (Steinberg & Dyck 2000). Therefore, the beneficial influence of leptin on insulin action may be largely mediated through its promotion of FFA oxidation (Shimbukuro et al. 1997) and the reduction of ectopic fat in muscle (Minokoshi et al. 2002). Despite the need to further clarify the complex roles of these cytokines in the regulation of metabolism, it is clear that insulin resistance develops and worsens in the presence of a chronic low-grade inflammatory state, in which dysregulation of adipose tissue-derived cytokines$_{[p2]}$ are likely to play a significant role.

While$_{[p3]}$ insulin resistance exerts its detrimental influence on glucose homeostasis, β-cell failure also plays a pivotal role in the gradual development of T2D (Weyer et al. 1999). Insulin resistance is progressive in nature, and the reduction in β-cell function seems congruent with this pattern in terms of disease etiology. Typically, by the time the patient is diagnosed with T2D, β-cell function has already been reduced by ~ 50% (Holman 1998). The reduction in β-cell function is also well correlated with β-cell mass. In persons with impaired glucose tolerance, β-cell mass may be reduced by 40%, while individuals with T2D may lose up to 60% of their original β-cell mass (Butler et al. 2003). Loss of β-cell mass has been largely attributed to beta cell apoptosis, and not deficiencies in β-cell replication or new islet formation.

Although the relative contributions of insulin resistance and impaired insulin secretion have not been completely resolved, there is an inverse relationship between insulin sensitivity and β-cell function (Wajchenberg 2007). The product of these parameters is referred to as the disposition index, and reflects the compensatory ability of the β-cells to overcome insulin resistance (Bergman 1989). For example, the acute insulin response (AIR) and the metabolic

action of insulin to stimulate glucose disposal (M) work together in a healthy metabolic scenario to preserve or maintain a relative degree of glucose homeostasis. As the severity of insulin resistance increases, normal compensation of AIR is not sufficient to overcome the steady increases in glycemia and usually results in the diagnosis of T2D (Stumvoll et al. 2003). While not all individuals with insulin resistance develop T2D, longitudinal studies in Pima Indians demonstrated that impaired β-cell function was an predictor of the development of T2D, independent of obesity and/or insulin resistance (Pratley & Weyer 2001). In fact, a 5-year study in 48 Pima Indians found that almost half of these individuals progressed from normal glucose tolerance to T2D. In this time, insulin secretion declined by 78% while insulin sensitivity only decreased by 14%. In those individuals who did not develop T2D, insulin sensitivity decreased similarly (ie., 11%) while a 30% increase in insulin secretion reduced the risk of T2D (Weyer et al. 1999). Therefore, a decline in β-cell function or an impaired AIR may precede the development of chronic hyperglycemia. As such, the etiological progression of T2D represents a combination of hepatic and peripheral insulin resistance as well as progressive β-cell failure that cannot keep up with the pathogenic development of insulin resistance. For the purpose of this review, we will focus primarily on intervention- and pharmaceutical-based studies and their influence on the pathogenesis of insulin resistance, while appreciating the importance of β-cell dysfunction in the pathogenesis of T2D.

Genetic predisposition is another factor of primary importance in the development of T2D. The prevalence of T2D varies widely among different ethnic groups, and the incidence of T2D in Pima Indians (extremely high risk for T2D) is inversely related to the degree of interbreeding with Caucasians of European origin (Barroso 2005). While different ethnicities often also differ in non-genetic environmental and cultural behavior that can independently affect the risk to develop T2D, increased susceptibility to the disease persists in selected ethnic groups with comparable environmental backgrounds. Family history also points to the importance of genetic background: the lifetime risk of developing T2D is about 40% in children with one diabetic parent, while that risk almost doubles when both parents have been diagnosed with T2D (Groop & Tuomi 1997). Further, concordance of T2D in identical twins (the likelihood of one twin to develop T2D after the other one has been diagnosed) is ~ 30-40%, almost twice as high as in type 1 diabetes (Kaprio et al. 1992).

Determination of the specific genes responsible for this predisposition remains elusive, due in large part to the complexity of the involved genetic interactions. Unlike other pathologies (such as cystic fibrosis) in which a single gene or a small number of genes are responsible for disease onset, only a small percentage of cases of diabetes can be considered monogenetic. In the majority of cases, a large number of genes are possibly involved, and while some promising candidates have been identified (most notably TCF7L2, the p12A variant of PPARG, the E23K variant of KCNJ11, CAPN10, HNF1A, HNF4A, GCK, LMNA, ENPP1, etc.), no specific gene cluster has been associated with disease consistently enough to prove a cause-effect relationship (Owen & McCarthy 2007).

3. Negative Influence of Alcohol Consumption on Glucose Metabolism

Several large epidemiological studies have demonstrated that alcohol consumption is associated with impaired glucose tolerance and/or T2D prevalence in a U-shaped fashion, with a decreased risk observed among individuals with light to moderate alcohol intake (up to ~30 g/d) compared to individuals reporting either excessive intake or abstinence (Beulens et al. 2005; Carlsson et al. 2000; Koppes et al. 2005; Wannamethee et al. 2003). A recent study in older women extended these findings by reporting that lifetime moderate alcohol consumption was also associated with a reduced risk of T2D (Beulens et al. 2005). Further, low to moderate alcohol consumption has been associated with reduced insulin resistance as estimated using homeostasis model assessment (HOMA), after adjustment for potentially confounding lifestyle

factors (Kiechl et al. 1996). A 2-week intervention study in 17 diabetic subjects found that 360mL/day of red wine consumption resulted in a 44% improvement in insulin-stimulated glucose disposal (ISGD) as assessed using the hyperinsulinemic euglycemic clamp technique (Napoli et al. 2005). Data regarding the specific type of alcoholic beverage associated with decreased T2D risk is inconsistent; both a greater effect of red wine versus beer or liquor consumption, and no difference in benefit among different beverages, have been described (Beulens et al. 2005; Conigrave et al. 2001; Wannamethee et al. 2003). While the potential mechanism by which moderate alcohol consumption may influence insulin sensitivity is unknown, elevated expression of cardiac Akt protein has been demonstrated following alcohol administration in mice (Zhou et al. 2002), suggesting that alcohol may directly affect intracellular insulin signaling. Despite the uncertainty regarding the specific mechanisms by which insulin resistance may be modulated by alcohol intake, the consistent epidemiological evidence linking moderate alcohol consumption with lower T2D risk and overall mortality supports a recommendation allowing light to moderate alcohol drinking as part of an appropriate prevention and treatment plan for T2D.

4. Impact and/or Efficacy of Lifestyle Interventions

4.1. Role of Caloric Restriction

The overwhelming majority of caloric restriction-based weight loss studies have focused almost entirely on insulin sensitivity in skeletal muscle (Goodpaster 1999; Joseph et al. 2001; Kelley et al. 1993b; Ross et al. 2000). Although some of these well-controlled studies have reported significant improvements in ISGD (Goodpaster et al. 1999; Kelley et al. 1993a; Ross et al. 2000), this improvement was normally less than it would have been needed for a complete normalization of insulin sensitivity in skeletal muscle; (a recent study, for instance, reported that a 25% reduction in excess BMI corrected only ~50% of the altered insulin sensitivity in overweight subjects (Goodpaster et al. 1999). The reason for the lack of normalization may be due to the fact that the BMI remained elevated in the overweight to obese range depending upon the specific study. More importantly, abdominal fat was still 50-100% higher than non-obese controls. Despite the encouraging data (Goodpaster et al. 1999; Kelley et al. 1993b; Ross et al. 2000), normalization of insulin sensitivity in the skeletal muscle may require a reduction in BMI that approaches non-obese levels.

In studies by Barzilai et al., the removal of visceral fat has been shown to improve hepatic insulin sensitivity in rodent models (Barzilai et al. 1999). [p4]In a comparable human study, a 7% body weight loss in human subjects with T2D resulted in 59±21 % improvement in insulin sensitivity (Toledo et al. 2007). However, it is important to mention that the results of these animal and human studies are difficult to interpret since 1) insulin levels were different from pre- to post-intervention, and/or 2) glucagon levels were not measured or systematically controlled. These issues are important since changes in hormone concentrations can initiate the action of glucoregulatory feedback loops responsible for control of glucose homeostasis (Cherrington 1999). Furthermore, hyperglucagonemia has been shown to influence exaggerated rates of gluconeogenesis and glycogenolysis in people with T2D (Gastaldelli et al. 2001). In our laboratory, we have addressed these issues using an octreotide infusion to inhibit pancreatic hormone secretion, and replaced basal glucagon while selectively adjusting the insulin concentration to study hepatic insulin action. Using this well-controlled approach, our data suggests that moderate weight loss through caloric restriction (ie., 25% reduction of excess BMI) promotes only 30% of the change necessary to normalize hepatic insulin sensitivity (Coker et al. 2006b). Even though moderate weight loss (Δ in BMI from 32 to 30 kg/m^2) does not normalize hepatic insulin sensitivity, data from our laboratory supports an inverse relationship between BMI and the suppression of glucose R_a ($r=-0.72$, $P<0.001$), and

this may indicate the potential for normalization of hepatic insulin sensitivity as BMI approaches 25 kg/m^2 (Yeo et al. 2006).

Caloric restriction-induced weight loss has also been shown to increase the oxidative capacity of skeletal muscle (Kern et al. 1999), potentially dampening the negative influence of excess lipid in skeletal muscle on peripheral insulin action (Bergman & Ader 2000). CR-induced weight loss is also known to decrease FFA levels, and this may be largely responsible for favorable improvements in insulin sensitivity (Machann et al. 2004). In studies that examined the weight loss dependent and independent influence of orlistat (an intestinal lipase inhibitor), subjects randomized to the orlistat treatment reduced their plasma FFA levels and increased peripheral insulin action to a greater extent (Kelley et al. 2004). Even in studies where FFA levels were only acutely elevated, a reduction in glucose uptake was demonstrated (Boden et al. 1994). Thus, it is presumable that weight loss-induced reductions in plasma FFA may decrease the accumulation of intramyocellular lipid (IMCL) and increase insulin sensitivity in skeletal muscle. On the contrary, caloric restriction-based weight loss (~16 lbs) in individuals with T2D resulted in no change in IMCL or peripheral insulin action, suggesting that more aggressive weight loss may be necessary to reduce excess IMCL, or that caloric restriction becomes less effective in the presence of more profound insulin resistance (Petersen et al. 2005). In obese volunteers with no history of T2D, a relatively aggressive caloric restriction-induced weight loss (~20 lbs) study demonstrated a trend towards a decrease in IMCL, but the decline did not reach significance (Larson-Meyer et al. 2006). Currently, it is not known how much weight loss via caloric restriction is necessary to normalize IMCL and facilitate the amelioration of insulin resistance in skeletal muscle.

It has been demonstrated that the accumulation of excess intrahepatic lipid (IHL) contributes directly to insulin resistance in the liver (Oakes et al. 1997; Song et al. 2001). This is a serious clinical concern since several investigative groups have demonstrated dramatic elevations in IHL in obese individuals compared to non-obese counterparts (Larson-Meyer et al. 2006; Lewis et al. 2006 Kelley, 2003 #4880; Thomas et al. 2005). The etiology of hepatic insulin resistance seems to be promoted by an enhanced supply of FFA from the portal system due to direct systemic access and the enhanced lipolytic activity of visceral adipose tissue (Montague & O'Rahilly 2000). In turn, the excess supply of FFA promotes the accumulation of long chain fatty acyl CoA, diacyglyerol and/or triglycerides in hepatic tissue that may promote the activity of protein kinase C-δ, and potentially lead to an inhibition of insulin-mediated suppression of glucose R_a (Lam et al. 2003). Encouraging results from studies performed by Petersen et al. using MRS recently concluded that ~16 lbs of caloric restriction -induced weight loss initiated a reduction in IHL, and resulted in greater suppression of glucose R_a in persons with T2D (Petersen et al. 2005). In another weight loss study using caloric restriction to induce a 22% reduction of excess BMI, there was a 42% reduction in the IHL levels (Lewis et al. 2006). Despite these encouraging results, IHL levels were not normalized and remained at least threefold higher than the levels in non-obese controls. Unfortunately, the amount of CR-induced weight loss necessary to normalize IHL through caloric restriction is not known[p5].

4.2. Role of Exercise Training

Exercise Training without Weight Loss—Since exercise training does not normally result in weight loss, training-induced increases in ISGD in the absence of weight loss (Coker et al. 2006a; Devlin et al. 1987) are relevant to the prevention of T2D in persons with IGT. Training-induced improvements in ISGD without a reduction in body weight or decrease in fat composition are likely due to increased GLUT-4 content (Hughes et al. 1993), elevated glycogen synthesis or increased oxidative enzyme activity (Coker et al. 2006a; Ebeling et al. 1993). Despite these training-induced changes in glucose metabolism in obesity (Segal et al. 1991), IGT (Hughes et al. 1993), and T2D (Dela et al. 1995), improvements in ISGD due to

exercise training are usually short lived, often returning to pre-training levels of insulin resistance within a week after cessation of training (Dela et al. 1995). This raises the question of whether weight loss is not a greater factor in the normalization of glucose metabolism in persons with IGT. It is known that insulin resistant skeletal muscle is characterized by decreased oxidative capacity (Simoneau et al. 1998) and lower rates of FFA oxidation under post-absorptive conditions (Kelley et al. 1999). Therefore, the efficacy of exercise training without weight loss is documented by positive changes in oxidative enzyme capacities, capillary density, and the proportion of Type 1 skeletal muscle fibers. As a result, exercise training may promote functionally relevant adaptations involved in facilitating an increase in ISGD. It would seem that an increased capacity for efficient lipid utilization would reduce the impact of excess IMCL serving as a surrogate for other metabolites such as fatty acyl CoA (Kelley & Goodpaster 2001), known to be implicated in insulin resistance (Ruderman et al. 1998). In slight contrast, recent studies measuring oxygen flux/mitochondrial DNA using permeabilized muscle fibers from patients with T2D suggest that mitochondrial function is normal (Boushel et al. 2007), and that reduced oxygen flux is due to reduced mitochondrial content. As such, the mechanisms responsible for exercise training-induced improvements are most likely multiplicative and may be closely associated with glycogen flux.

Exercise Training with Weight Loss—In studies that focused on the influence of weight loss and/or exercise training on ISGD, the improvement in ISGD was slightly greater with weight loss (induced by caloric restriction or exercise training) compared to exercise training without weight loss (Ross et al. 2000). In these studies, ISGD was measured 72 hours after the last training session. With exercise-induced weight loss, the improvement in ISGD was not different from caloric restriction-induced weight loss (Ross et al. 2000). Unfortunately, the results of these studies are difficult to interpret since dietary control and exercise training was provided according to a behavioral modification study design. In studies utilizing dietary control, short-term (4 weeks) moderate weight loss of 3.0 kg had no influence on ISGD (Joseph et al. 2001), while greater amounts of weight loss regardless of the inclusion/exclusion of increased physical activity resulted in significant improvements in ISGD (Hays et al. 2006). Therefore, it is very difficult to distinguish the separate influence of exercise training from weight loss when one considers the level of control needed to answer this important question. Nonetheless, this is an important question that needs to be addressed, considering the notion that only 20% of people who attempt weight loss actually utilize exercise training (Weiss et al. 2006).

In addition to the detrimental influence of obesity on hepatic insulin action, elevations in visceral adipocyte-derived FFA are linked to accelerated gluconeogenesis and excessive glucose R_a in individuals with IGT or T2D (Bergman & Ader 2000). Further, this abnormality is partially due to the reduction in the ability of insulin to suppress lipolysis, especially in visceral adipocytes (Arner 2002; Fisher et al. 2001). The efficacy of training-induced weight loss is supported by the results of recent study that found reductions in the portal vein concentration of FFA and mesenteric fat in rats (Nara et al. 1997). Cross-sectional studies in humans have also demonstrated greater hepatic insulin sensitivity in trained versus untrained subjects (Rodnick et al. 1987). Therefore, training-induced weight loss may decrease the deleterious influence of excess portal FFA on hepatic insulin action. However, it is not known whether weight loss is a necessary component of an exercise training program in order to improve insulin-mediated suppression of excess glucose R_a.

5. Natural Products

Data from recent US national surveys indicate that use of complementary and alternative medicine is widespread, with as many as 1 in 3 adults reporting the use of therapies such as acupuncture, chiropractic care, massage, relaxation techniques, yoga, and herbal remedies in

the prevention and/or treatment of specific conditions including T2D (Barnes et al. 2004; Egede et al. 2002; Tindle et al. 2005). Despite this popularity, limited scientific evidence exists regarding the efficacy, safety, and mechanisms of action of these interventions in disease treatment. Chromium, garlic, ginseng and α-lipoic acid and various herbal dietary supplements [p6]are several commonly used natural product interventions for T2D treatment and/or prevention, although more than 50 products have been identified as potentially therapeutic (Table 1) (Faculty 2006). Given that no conclusive data are available to support or refute the use of these interventions, individuals who use these natural products should notify their health care providers of therapies that are undertaken, and consider them as adjuncts to the other types of lifestyle and pharmacological interventions reviewed above (Association 2003; Association 2004).

While compelling evidence exists to support an important role for dietary chromium intake in the restoration of normal glucose tolerance among chromium-deficient individuals (Stoecker 2006), the ability of chromium to improve insulin action remains controversial (Althuis et al. 2002). Randomized, placebo-controlled clinical trials of chromium supplementation have shown conflicting results on fasting and plasma glucose and insulin data (Crawford et al. 1999; Joseph et al. 1999; Pasman et al. 1997). Additional placebo-controlled randomized trials in well-characterized populations are required to more fully understand the potential efficacy of chromium supplementation in T2D treatment and prevention.

The purported physiological effects of ginseng are very broad, and different species of plants from the genus Panax are used in U.S. supplements, with the most common being Asian and American ginseng. While a number of studies using animal models have generally demonstrated anti-diabetic properties, relatively few clinical studies in humans have been reported (Xie et al. 2005). In a small study (n = 19) examining the blood glucose response following administration of a single 3g dose of ginseng or placebo with a 25-g oral glucose challenge, Vuksan et al. (Vuksan et al. 2000) reported that ginseng consumed prior to the glucose challenge resulted in a decrease in the post-challenge glycemic response in both non-diabetic and T2D patients. An early longer-term (8 weeks) supplementation trial (Sotaniemi et al. 1995) suggested that 200mg of ginseng improved fasting blood glucose and HbA_{1c} status in T2D patients, but simultaneous body weight losses confound the interpretation of these results. Taken together, these data suggest that ginseng likely has a beneficial effect on certain metabolic parameters in T2D. However, it is difficult to make standardized recommendations because of the large reported variability in metabolic response to different ginseng species (Sievenpiper et al. 2004), different batches of the same species (Sievenpiper et al. 2003), and different parts of the ginseng plant (Dey et al. 2003).

Numerous cell culture and in vivo animal studies have demonstrated that treatment with the water soluble antioxidant α-lipoic acid (also known as thioctic acid) is associated with improved skeletal muscle glucose transport activity, reduced whole-body insulin resistance, and reduced oxidative stress (Henriksen 2006). In addition, chronic administration of α-lipoic acid over 2 weeks in obese Zucker rats has been shown to result in increased insulin receptor substrate (IRS)-1 protein expression (Saengsirisuwan et al. 2004), an important signaling factor mediating skeletal muscle glucose uptake. Similar changes in insulin signaling factors and glucose metabolism were not observed following α-lipoic acid treatment in insulin-sensitive, lean rats (Saengsirisuwan et al. 2002), suggesting that the ability of this antioxidant to improve glucose disposal is limited to conditions of insulin resistance. Although relatively few human clinical trials have been reported, Jacob et al., described a significant improvement in glucose clamp-derived ISGD in T2D patients following oral supplementation of α-lipoic acid versus placebo (Jacob et al. 1999). The combination of compelling in vitro and in vivo animal data but limited clinical data provides support for further research in human subjects, but does not presently support a general recommendation for α-lipoic acid supplementation.

Increased dietary intake of omega-3 long-chain polyunsaturated fatty acids has been associated with reduced mortality and morbidity (Bucher et al. 2002). In prospective studies of various populations with high intakes of fatty fish (a rich source of omega-3 fatty acids) demonstrate a lower incidence of T2D compared to populations with less frequent fish consumption (Feskens et al. 1991) but not all (Meyer et al. 2001; van Dam et al. 2002). Subsequent intervention-based studies using fish oil supplementation, however, showed worsening of glucose tolerance (Borkman et al. 1989), which has been suggested to be due to the very high doses (~10g/day) of fish oil often administered in some early studies (Nettleton & Katz 2005). More recent studies using smaller supplemental doses (≤ 4g/day) have not resulted in negative changes in glucose tolerance, but also little benefit, as indicated by a lack of effect on either serum glucose, plasma insulin, or HbA_{1c} concentrations (Grundt et al. 1995; Sirtori et al. 1998). However, positive changes in lipid profile and blood pressure demonstrated by these and other studies (Grundt et al. 1995; Nettleton & Katz 2005; Sirtori et al. 1998) suggest that omega-3 supplementation may be of benefit in reducing cardiovascular disease risk in T2D patients, even if no direct improvement in insulin or glucose homeostasis has been conclusively demonstrated.

Multiple cohort and cross-sectional studies in U.S., European, and Asian populations have identified an inverse association between coffee consumption and markers of T2D risk (van Dam & Hu 2005). This association appears to be dose-dependent and independent of potentially confounding dietary or other lifestyle factors. The specific mechanism responsible for this reduced T2D risk is currently unknown, although constituents of coffee such as caffeine, antioxidants (e.g. chlorogenic acid), and magnesium have each been suggested (van Dam & Hu 2005). Caffeine in particular has been identified as a potential mechanistic factor, despite evidence that acute administration of a moderate dose of caffeine results in reduced insulin sensitivity in humans (Greer et al. 2001; Keijzers et al. 2002). However, several large, prospective studies found reduced T2D risk even among drinkers of decaffeinated coffee (Pereira et al. 2006; Salazar-Martinez et al. 2004), suggesting that coffee constituents other than caffeine may be primarily responsible for the protective effect.

Green tea is another caffeine- and antioxidant-containing beverage that is of interest because of the possible protection it affords against diabetes, cardiovascular disease and cancer (Crespy & Williamson 2004). In a study of 19,487 middle-aged men and women living in Japan, individuals that reported the highest intakes of green tea (≥ 6 cups/day) or coffee (≥ 3 cups/day) had 33% and 42% lower risk for T2D over a 5 year follow-up, respectively, compared to those who did not consume these beverages {Iso, 2006 #1685}. Inverse associations between T2D and high intakes of either black or oolong tea were not observed in this study (Iso et al. 2006), although the variation in consumption patterns of these beverages was less than for green tea and coffee. Additional evidence for a green tea protective effect was reported by Tsuneki et al., (Tsuneki et al. 2004), who administered 1.5g of green tea powder in hot water to 22 young, healthy volunteers and observed improved glucose tolerance following a standard OGTT. In contrast, Yamaji et al., (Yamaji et al. 2004) found no association between reported green tea intake and glucose tolerance status as assessed by OGTT in 3224 Japanese men, although greater coffee consumption was associated with better glucose tolerance in this study[p7].

6. Pharmacological Therapy

The pharmaceutical industry has produced a wealth of effective medications to help control the deleterious influence of T2D. As we have discussed the influence of lifestyle interventions ranging from diet and exercise to the use of natural products, it is also logical to review some of the most innovative diabetes medications. Since it is beyond the scope of this review to provide a completely comprehensive evaluation of pharmaceutical therapy for the prevention/

treatment of T2D, we have chosen to review those medications whose actions may mimic the influence of lifestyle interventions. For example, diet and/or exercise may improve beta cell compensation, suppression of exaggerated glucose R_a, and reduce tissue lipotoxicity. All of these factors are important in the etiological progression of T2D, and we will review, in this regard, the effectiveness of, metformin, a representative thiazolidinedione (pioglitizone) pramalitide, and exenatide.[p8]

6.1. Metformin, AMP-activated protein kinase (AMPK) and Hepatic Metabolism

The clinical use of metformin has gained widespread utilization in the treatment of T2D, and it has also proven its therapeutic efficacy to decrease the risk of T2D in obese individuals (Viollet et al. 2006). In fact, computerized searches of databases from 29 clinical trials revealed that metformin has consistently demonstrated a favorable influence on glycemic control (Saenz et al. 2005). While exaggeration of glucose R_a commonly occurs in T2D, metformin utilizes AMPK signals to suppress exaggerated rates of glucose R_a, and in turn, lower blood glucose levels (Zhou et al. 2001). In addition, adiponectin has been shown to influence AMPK activation in the liver, and play a regulatory role in the control of glucose R_a (Satoh et al. 2004; Yamauchi et al. 2002). The primary role of hepatic AMPK in the maintenance of glycemia is further confirmed by the results from animal experiments detailing the specific importance of the AMPKα2 isoform. In these studies, liver-specific AMPKα2-/- mice demonstrated exaggerated glucose R_a that contributed to hyperglycemia and IGT (Andreelli et al. 2006). As such, these results outline the critical importance of the hepatic AMPKα2 isoform in the metformin-activated pharmacological manipulation of glucose R_a under conditions of prevailing insulin resistance.

While metformin's action on hepatic metabolism seems relatively straightforward, its action on peripheral glucose metabolism has not been easily described or understood. As mentioned previously, it has been demonstrated to improve glycemic control (Saenz et al. 2005). However, improvements in GLUT 4 transport expression and ISGD were not shown unless metformin therapy was combined with exercise training (Smith et al. 2007a). While metformin alone had no effect, metformin plus exercise training did induce changes in peroxisome proliferator-activated receptor-γ (PPAR-γ), citrate synthase, and β-hydroxyacyl-CoA dehydrogenase activity. This is important since PPAR-γ and oxidative enzymes may modulate optimal fat utilization in muscle and dampen the detrimental influence of lipid accumulation (Smith et al. 2007a).

Regardless of the non-specific influence that metformin may have on skeletal muscle, several studies have demonstrated its clinical utility in improving glycemic control in obese adults at risk for T2D (Saenz et al. 2005). This may also be true in other segments of the population. For example, it is interesting to note that metformin monotherapy in obese adolescents promoted a progressive decline in fasting plasma glucose and plasma insulin levels (Freemark & Bursey 2001). These results are especially provocative when compared with worsening fasting plasma glucose levels in non-treated individuals. The combine effects of metformin therapy therefore seems to directly influence AMPK activation in the liver, improve hepatic glucose metabolism, and potentiate overall glycemic control in persons with T2D, and in multiple segments of the population at risk for T2D.

6.2. Pioglitazone, Adipose Tissue, and PPAR-γ

Pioglitazone is a member of the thiazolidinedione class (also including Rosiglitazone and the now withdrawn Troglitazone). It is a well-recognized PPAR-γ agonist that is primarily expressed in adipose tissue but it also found in small amounts in skeletal muscle (Vidalpuig et al. 1997). It has recently been shown in patients with T2D that pioglitazone treatment improves fasting plasma glucose and HbA_{1c} levels while also facilitating increases in plasma adiponectin

and ISGD (Bajaj et al. 2007). In previous studies from the same laboratory, a two-step clamp procedure was utilized to demonstrate the effectiveness of pioglitazone in reducing hepatic insulin resistance in persons with T2D (Miyazaki et al. 2002). The decreased plasma triacylglycerol and hepatic fat content in individuals treated with pioglitazone (Bajaj et al. 2007) further exemplifies this drug's positive influence on hepatic metabolism. Recent studies also support a possible pioglitizone's role in improving β-cell compensation in persons with T2D (Gastaldelli et al. 2007). However, these results are not conclusive, and may only affect those individuals with the lowest insulin sensitivity or those already with T2D (Rasouli et al. 2007).

While it is relatively clear that pioglitazone has a favorable influence on systemic insulin resistance, the indirect influence of pioglitazone on adipose tissue versus its direct effects has posed an interesting question as to where the compound exerts its most powerful action. In persons with IGT who were administered pioglitazone for a10 wk period, glucose tolerance was improved and S_i was increased. This was coupled with a concomitant reduction in IMCL in Type 1 fibers (Rasouli et al. 2005). It is also interesting that in these studies pioglitazone resulted in a 2.6 kg weight gain while facilitating a significant decrease in the visceral-to-subcutaneous adipose tissue ratio (Rasouli et al. 2005). Therefore, pioglitazone-induced improvements in systemic insulin sensitivity (Miyazaki et al. 2002) appear at least in part mediated by the diversion of lipids from skeletal muscle and visceral depots into subcutaneous adipose depots (Miyazaki et al. 2002; Rasouli et al. 2005),

Treatment with pioglitazone also increases the secretion of HMW adiponectin from human adipose tissue (Bodles et al. 2006a), an important effect since plasma adiponectin and adiponectin mRNA in skeletal muscle has been linked to greater insulin sensitivity (Kern et al. 2003). In addition, pioglitazone was shown to induce a ~50% reduction in macrophage infiltration (ie., CD-68 and MCP-1 mRNA), and a significant reduction in systemic TNF-α (DiGregorio et al. 2005), whose expression and secretion are associated with the inflammatory state that influences the development of insulin resistance (Kern et al. 2001). Later studies from the same laboratory also demonstrated that pioglitazone can directly initiate macrophage apoptosis in human adipose tissue, potentially reducing the detrimental, chronic inflammatory effects of these cells (Bodles et al. 2006b). The results of the numerous human studies summarized above, therefore, indicates how pioglitazone can ameliorate insulin sensitivity through multiple mechanisms, including an improved balance of por- and anti-inflammatiory cytokines and a redistribution of lipid storage depots.

6.3. Pramlintide, Weight Control and Long-Term Glycemic Control

Pramalitide is a synthetic analog of human amylin, a pancreatic islet cell hormone colocalized within the beta cells with insulin. Amylin complements the influence of insulin on the regulation of postprandial glucose concentrations (Weyer et al. 2001), contributes to the suppression of glucagon secretion (Gedulin et al. 1997), and reduces rates of gastric emptying (Young et al. 1995). Due to the β-cell dysfunction that occurs in later in the progression of T2D, amylin availability may be also compromised, and the beneficial amylin-derived effects may be lost.

Administraion of pramlintide in humans with T2D, therefore, has significantly improved postprandial glycemia (Buse et al. 2002; Edelman & Weyer 2002; Weyer et al. 2001), abated hyperglucagonenmia (Fineman et al. 2002), and decreased the rate of gastric empyting (Vella et al. 2002). Studies utilizing a 6-week dose of this medication also suggest that this compound may decrease 24-hour caloric intake and binge eating (Smith et al. 2007b). Additional studies incorporating a longer treatment periods found even greater weight loss, significant reductions in waist circumference, improvements in appetite control (Aronne et al. 2007; Hollander et al. 2004), and a proportionate decline in the daily insulin requirement (Hollander et al. 2004).

Among the subjects for these studies, patients with a BMI of >40 kg/m^2 or those also treated with metformin experienced the greatest reductions in body weight (Hollander et al. 2004). Therefore, an additional benefit of pramlintide treatment as an adjunctive therapy is its potential ability to prevent the weight gain commonly associated with other classes of andti-diabetic drugs, such as sulfonylureas (Group 1998).

6.4. Exenatide, Body Weight, and Insulin Sensitivity

As mentioned previously, oral insulin secretagogues or sensitizers are associated with weight gain (Aviles-Santa et al. 1999; Lewitt et al. 1989). This is important since the risk of diabetes is increased by 9% for every 1-kg increase in body weight (Mokdad et al. 2000). Due to a need for pharmacological approaches for diabetes that do not exacerbate the problems of weight gain, the incretin mimetic exenatide has gained in popularity as an adjunctive treatment for T2D. Exanatide has also been demonstrated to enhance β-cell proliferation and islet neogenesis in rodents but not yet in humans (Nielsen et al. 2004). Similar to glucagon-like peptide-1, exanatide helps to suppress excess glucagon secretion, slows gastric emptying, and reduces food intake (Buse et al. 2004; Defronzo et al. 2005; Degn et al. 2004; Kendall et al. 2005; Kolterman et al. 2005). In fact, exanatide therapy has effectively reduced HbA_{1c} levels to ≤% 7 in ~40% of patients when maximal doses of metformin and/or sulfonylureas were not effective (Buse et al. 2004; Defronzo et al. 2005; Kendall et al. 2005). A longer term (ie., 2 years) study has also demonstrated significant improvements in HbA_{1c} paralleled by a reduction in body weight of ~4.7 kg (Buse et al. 2007).

It is interesting to note that exanatide-treated rodents, even if fed a high-fat diet, displayed significant weight loss, due exclusively to fat mass loss (Mack et al. 2006). Additional effect of exeatide may include activation of phosphatidylinositol-3-kinase (PI-3 kinase) (Idris et al. 2002), and increase insulin sensitivity, as documented by a 224% increase following 6 weeks of exenatide administration (Gedulin et al. 2005), accompanied by a β-cell mass reduction proportional to the reduced insulin demand (Gedulin et al. 2005). Therefore, the results of clinical studies that demonstrate exenatide as a effective adjunctive therapy towards achieving weight loss and improving long term glycemic control are coupled with data from animal studies suggesting beneficial effects on insulin sensitivity and islet function.

7. Summary

The epidemic proportions of T2D have become an increasing problem in terms of its influence on public health and the cost of healthcare in the US. Despite the efforts and resources that have been allocated towards the prevention and treatment of T2D and its co-morbidities, the widespread trends of increased obesity and decreased physical activity have overwhelmed our population with a debilitating and deadly disease. We have learned that adipose tissue is no longer considered an inert depot but serves as an organ capable of secreting inflammatory cytokines into the bloodstream that may exacerbate the development of insulin resistance and lead to the progression of T2D. In fact, the reciprocal relationship between pro-inflammatory cytokines (ie., TNF-α and IL-6), and adiponectin and leptin may largely control the progression of insulin resistance in hepatic and muscle tissue, and ultimately beta-cell failure. [p9]

While poor lifestyle choices are largely to blame for the development of T2D in the overwhelming majority of the population, interventions such as diet and exercise as well as the utilization of natural products may help reduce the risk of metabolic disease. Even short-term exercise and dietary interventions have yielded various degrees of positive results, with the greatest improvement in insulin sensitivity of skeletal muscle reported when exercise is combined with weight loss. Unfortunately, however, the vast heterogeneity in the methods of assessment and subject populations has resulted in considerable inconsistencies across studies

in this regard. In addition, the effects of lifestyle interventions on hepatic and pancreas tissue are not clear. Lastly, at least 50 natural product interventions (Table 1) have been proposed to facilitate therapeutic outcomes. Of these, gingseng and ∝-liopic acid seem to provide relatively promising results, but like many natural product interventions, the required amounts and frequency of administration for these supplements has not been well charcaterized. On the contrary, excessive of consumption of alcohol may have an underappreciated negative influence on glucose metabolism.

Several newly advocated pharmaceutical alternatives and/or adjunct therapies are also available. For example, the combination of pramlintide therapy with the administration of sulfonylureas may minimize weight gain and lessen the associated cardiovascular risk. Also, metformin may help facilitate greater reductions in body weight and lessen systemic insulin resistance. Similar to pramlintide, exanatide may enhance β-cell function and prevent unnecessary weight gain, and in turn, help to improve glycemic control. From a different angle, pioglitazone seems to divert lipids away from muscle and reduce the chronic inflammatory state aasociated with insulin resistance.

Therefore, poor lifestyle choices such as obesity and lack of physical activity, can be held largely responsible for the development of insulin resistance, and ultimately lead to T2D. Treatment of insulin resistance through lifestyle change represents an efficacious alternative in terms of prevention but interventions must be aggressive in nature and serve to promote weight loss. In addition, other medications and/or excess alcohol consumption may also negatively contribute to the pathogenesis of insulin resistance and T2D. Lastly, novel medications, in conjunction with existing therapies, may moderate the onset and progression of insulin resistance in population at increased risk to develop T2D, or slow the evolution of the disease in already diagnosed T2D patients.

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Table 1

Putative natural therapeutic products for T2D

Product	Effectiveness rating (1)			
	Possibly Effective	Possibly Ineffective	Likely Ineffective	Insufficient Data
Alcohol	X			
Aloe gel				X
Alpha-lipoic acid	X			
Ascorbic acid		X		
Banaba				X
Beta-carotene		X		
Biotin				X
Bitter melon				X
Branched-chain amino acids				X
Buckwheat				X
Caffeine	X			
Calcium				X
Cinnamomum cassia				X
Chromium				X
Coenzyme Q_{10}				X
Cranberry		X		
Diacylglycerol				X
Docosahexaenoic acid		X		
Eicosapentaenoic acid		X		
Eugenia jambolana		X		
Fenugreek				X
Fig				X
Fish oil			X	
Garlic		X		
Ginseng	X			
Ginkgo biloba				X
Glucomannan	X			
Guar gum	X			
Gymnema sylvestre				X
Holy basil				X
Ivy gourd				X
Lutein		X		
Lycopene		X		
Magnesium	X			
Maitake mushroom				X
Milk thistle				X
Niacin / niacinamide	X			
Oat bran	X			
Olive				X
Prickly pear cactus	X			
Psyllium seed husk (blonde)	X			
Salacia				X
Table X continued				
Soy	X			
Stevia				X
Tomato		X		
Vanadium				X
Vitamin D				X
Vitamin E				X
Wheat bran		X		
Xanthan gum	X			

Note:

(1) Ratings are defined as follows: possibly effective = reputable references suggest that the product might work for the given indication based on one or more clinical trials giving positive results for clinically relevant end-points; possibly ineffective = reputable references suggest that the product might not work for the given indication based on one human study giving negative results for clinically relevant end-points; likely ineffective = reputable references generally agree that the product is not effective for the given indication, based on two or more randomized, controlled, clinical trials giving negative results for clinically relevant end-points and published in established, refereed journals.

The effectiveness ratings come from the Natural Medicines Comprehensive Database (www.naturaldatabase.com) accessed on 29 July 2006, copyright © 1995-2006, Therapeutic Research Faculty (all rights reserved). Used with permission.