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Minimizing Postprandial Oxidative Stress in Type 2 Diabetes: The Role of Exercise and Selected Nutrients

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1. Introduction

Approximately 25.8 million Americans (8.3% of the population) are currently living with diagnosed (18.8 million) or undiagnosed (7.0 million) diabetes (World Health Organization, 2011), most of whom are type 2 in pathology. An additional 79 million Americans are estimated to have pre-diabetes (World Health Organization, 2011). Unfortunately, the overall prevalence of these conditions continues to rise, as indicated by the 1.9 million newly diagnosed cases of diabetes in 2010 within people aged 20 years and older (World Health Organization, 2011). A similar situation presents itself within other nations around the world, with an estimated 220 million individuals currently living with diabetes (World Health Organization, 2011).

The onset and progression of diabetic disorders, as well as the related complications, are linked to impairments in glucose and lipid metabolism (O'Keefe & Bell, 2007), both of which are strongly associated with increased production of reactive oxygen and nitrogen species (RONS) (Ceriello & Motz, 2004; Fisher-Wellman & Bloomer, 2009b). Increased RONS production coupled with impaired antioxidant defense (a common finding among patients with diabetes) promotes oxidation of specific biomolecules (e.g., lipids, proteins, DNA), which can lead to an exacerbation of diabetic complications (Giacco & Brownlee, 2010). While variables such as blood glucose and blood triglycerides have traditionally been measured in a fasted state, increasing evidence suggests that measurement of *postprandial* glycemia, lipemia, as well as oxidative stress biomarkers, may provide more important clinical information concerning an individual's susceptibility to both type 2 diabetes mellitus (T2DM) onset and disease progression—as well as related conditions (O'Keefe & Bell, 2007; Pastromas et al., 2008).

For example, increased postprandial oxidative stress has been implicated in the pathophysiology of diabetes (Wright et al., 2006) and cardiovascular disease (Ceriello, 2004), which may be linked to the strong association between the postprandial rise in blood glucose and triglycerides and the generation of RONS. Moreover, randomized controlled trials indicate that reducing postprandial triglycerides appears to slow atherosclerotic progression and may improve long-term cardiovascular prognosis (O'Keefe & Bell, 2007). Therefore, methods to reduce the postprandial rise in glycemia and lipemia may help to prevent oxidative stress related complications in T2DM patients.

Drugs to treat hyperglycemia (e.g., sulfonylureas) and hyperlipidemia (e.g., statins) have been reported in some studies to promote favorable outcomes related to minimizing the postprandial rise in blood glucose and triglycerides (Nakajima, 2010; O'Keefe et al., 2011). However, non-pharmacological approaches also exist and have been discussed previously (Davi et al., 2010; Tucker et al., 2008). In particular, both acute and chronic exercise, as well as specific nutrient *intake* (e.g., certain macronutrients, antioxidants, glucose regulatory and insulin mimetic agents, lipid lowering agents) or *proscription* (e.g., saturated fat and simple sugar) may be considered in an attempt to minimize postprandial oxidative stress.

Specific to the above, exercise and selective nutrient intake may aid in attenuating postprandial oxidative stress in three distinct ways. First, exercise stimulates an increase in endogenous antioxidant enzyme activity and other protective mechanisms (e.g., heat shock proteins (Geiger & Gupte, 2011)). Exogenous antioxidant intake in the form of whole foods and nutritional supplements may provide additional protection against RONS production following a meal (Neri et al., 2005; Neri et al., 2010). Second, exercise improves blood glucose clearance via enhanced glucose-4-transport protein (GLUT 4) translocation and protein content (McGee & Hargreaves, 2006; Rockl et al., 2008), as well as enhanced insulin-insulin receptor binding and post-receptor signaling (McGee & Hargreaves, 2006). Nutrients acting to minimize the rise in blood glucose (e.g., fiber (Sierra et al., 2002)) or to enhance glucose clearance (e.g., herbal extracts (Yin et al., 2008)) may also provide benefit. Third, exercise improves blood triglyceride clearance via enhanced lipoprotein lipase activity (Seip & Semenkovich, 1998) and a reduction in chylomicron-triglyceride half-life (J. C. Cohen et al., 1989). Nutrients acting to minimize the rise in blood triglycerides or to enhance triglyceride clearance may also prove beneficial (Cottin et al., 2011), as well as altering nutrient intake to favor lower intake of saturated fat and simple sugar and higher intake of "healthy" fats and dietary fiber (Bloomer, Kabir, Canale et al., 2010; Jenkins et al., 2007; Marin et al., 2011).

In this chapter we provide an overview of the role of RONS in diabetic complications and provide a rationale for the inclusion of both exercise and selected nutrients to combat postprandial oxidative stress in those with T2DM. It is likely that these non-pharmacological approaches may not only improve glycemic control in a rested and fasted state, but also in response to feeding. If so, these methods should be strongly considered and implemented into the clinical treatment plan of type 2 diabetics in an effort to not only considerably improve the long-term prognosis of such individuals, but also to significantly reduce the financial burden associated with the chronic treatment of this disease.

2. Diabetes overview

Diabetes is present in multiple forms, but most commonly diagnosed as type 2 in pathology (World Health Organization, 2011). Diabetes is associated with multiple medical complications ranging from increased risk of cardiovascular disease to amputations and blindness. As the incident rate continues to rise, the economic burden associated with this disease also continues to grow. For example, the combined direct and indirect cost associated with diabetes has been estimated at $174 billion in 2007 within the United States alone (World Health Organization, 2011), with estimated and projected future costs being considerably higher. Related to the direct costs of $116 billion, after adjusting for population age and sex differences, the average medical expenditures among individuals with diagnosed diabetes were 2.3 times higher than what expenditures would have been in the

absence of diabetes. Indeed, diabetes is not only associated with significant impairments in both the quality and quantity of life in most patients, but poses a major burden to the healthcare economy.

3. Oxidative stress description

Oxidative stress is a term used to describe a condition of imbalance that exists between prooxidants and antioxidants, in such a way that prooxidant production overwhelms antioxidant defenses (Bloomer, 2008). This may lead to the oxidation of lipids, proteins, DNA, glutathione, and other molecules in ways that impair cellular function (Bloomer, 2008). Although excessive production of prooxidants (also referred to as reactive oxygen and nitrogen species [RONS]) may be problematic, RONS generation occurs in part as a consequence of normal cellular metabolism (Halliwell & Cross, 1994) and serves several vital functions *in vivo*. For example, RONS play an important role in cell signaling (Haddad, 2002), cellular immunity (Fialkow et al., 2007), apoptosis (Lee & Wei, 2007), and redox regulation of gene transcription (H. Liu et al., 2005). Hence, RONS are essential for normal physiological function. It is important to note that under normal physiologic conditions, the endogenous antioxidant defense system, in conjunction with exogenous antioxidants consumed through whole food and nutritional supplements, serve to protect small and large molecules from oxidative modification via RONS.

3.1 Association with disease

Increased biomarkers of oxidative stress have been noted in those living with disease (Dalle-Donne et al., 2006), as well as in various tissues extracted upon autopsy. It is possible that during repeated exposure to stressful conditions in which RONS production is increased, and during which time adequate protection is not available, the antioxidant defense system may be overwhelmed. The resultant oxidative stress may lead to progressive oxidation of cellular constituents, eventually leading to functional decline of vital components (e.g., vascular endothelium) and disease (Dalle-Donne et al., 2006). However, while associations between various oxidative stress biomarkers, impairments in cellular function, and frank disease have been noted in many studies, direct *cause and effect* data are scarce (Maiese et al., 2007). For example, in many cases the evidence consists only of observations of increased levels of oxidative stress biomarkers (e.g., lipid, protein, and DNA oxidation) in persons with a particular disease such as diabetes (Baynes & Thorpe, 1999) or cardiovascular disease (Tsimikas, 2006). In other cases, subjects with certain diseases such as T2DM have demonstrated improved markers of health following antioxidant therapy (Wu et al., 2007), suggesting that RONS may have been a possible cause of disease or disease progression. However, when considering the multi-factorial pathology of most disease states, it is likely that systems aside from those associated with RONS are also involved. Additional study is needed before conclusions can be made pertaining to the specific role of RONS in human disease—and whether RONS are a major cause of disease or merely a consequence of the disease process.

3.2 Formation of Reactive Oxygen and Nitrogen Species (RONS)

As discussed earlier, a state of "oxidative stress" is created when RONS production exceeds antioxidant defense. Both non-radical and radical species are considered to be RONS, the latter which are often referred to as "free radicals", defined as any species capable of

independent existence containing one or more unpaired electrons (Halliwell, 1991). The majority of biological molecules are non-radicals and contain only paired electrons. However, if a single electron is unpaired within an orbital, it is said to be "free". Free radicals are typically regarded as highly reactive (hence the term "reactive" oxygen and nitrogen species), because they seek to accept electrons from other molecules. The donation of electrons can then produce additional free radicals, leading to a chain reaction of radical generation, which may continue until a chain terminating reaction occurs.

Although RONS are generated as a component of normal cellular metabolism, they can also be produced through exposure to a wide variety of stimuli. These include, but are not limited to exposure to environmental toxins (Matsuoka et al., 2010), cigarette smoke (Edirisinghe & Rahman, 2010), ozone (Bocci et al., 2009; Yang & Omaye, 2009), intense physical exercise (Bloomer, 2008; Fisher-Wellman & Bloomer, 2009a), and ingestion of certain nutrients (Sies, Stahl, & Sevanian, 2005). Specifically, a state of oxidative stress may be mediated through a disruption of the electron transport system leading to increased formation of superoxide radicals, an increase in the activity of RONS generating enzymes (e.g., xanthine oxidase), activation of cyclooxygenases, lipoxygenases, phagocytes, and phospholipases, as well as through an acute or chronic decrease in antioxidant protection (Jackson et al., 2007).

3.2.1 Exercise conditions

More than 300 original investigations have been performed in relation to exercise-induced oxidative stress (Fisher-Wellman & Bloomer, 2009a). The results of this work are mixed, with many studies documenting an acute oxidative stress, while others fail to demonstrate such findings. The opposing results are likely due to discrepancies in the exercise protocols, the training status and age of subjects, the biomarkers measured, and the timing of blood collection relative to the exercise bout (Fisher-Wellman & Bloomer, 2009a). Regardless, there are multiple potential sites for RONS formation in relation to an acute bout of exercise. These include primary sources in which RONS are generated in direct response to a given condition (e.g., formation of superoxide within the respiratory chain, prostanoid metabolism, catecholamine autoxidation, heightened xanthine oxidase activity), as well as secondary sources in which RONS production might occur in response to muscle damage (e.g., neutrophil respiratory burst activity, disruption of iron containing proteins) (Bloomer, 2008). It is important to note that despite the potential for oxidative stress arising from acute exercise, such a condition is generally short lived. That is, any post-exercise elevation in oxidative stress biomarkers typically returns to baseline within minutes to hours following the cessation of exercise. Moreover, this acute increase in RONS is necessary to allow for the up-regulation in antioxidant defense—in accordance with the principle of hormesis (Radak et al., 2008). For these reasons, concern over an acute increase in RONS as a consequence of strenuous exercise should be minimal.

3.2.2 Feeding conditions

The generation of RONS and the ensuing oxidative stress following a meal is referred to as *postprandial* oxidative stress. This appears directly linked with the rise in blood glucose (Monnier et al., 2006) and triglycerides (Bae et al., 2001) following feeding. Individuals with diabetes and pre-diabetes appear more susceptible to postprandial oxidative stress due to the fact that they experience prolonged periods of hyperglycemia (Ceriello et al., 2002; Y. Miyazaki et al., 2007; Schindhelm et al., 2007) and hypertriglyceridemia (Ceriello et al., 2002;

Nappo et al., 2002) following meals, as compared to those with normal blood glucose control. Elevations in both glucose and triglycerides are directly linked to superoxide production (Bae et al., 2001; Nishikawa et al., 2000), a potent RONS which is known to react with other molecules causing additional RONS generation (Brownlee, 2005). It is likely that superoxide is generated within the mitochondria during the process of substrate oxidation following the ingestion of energy dense meals—in particular those high in saturated fat (Fisher-Wellman & Bloomer, 2009b). Therefore, methods of attenuating postprandial glycemia and lipemia (e.g., ingestion of lower calorie meals, decreased intake of saturated fat and simple sugar) may be associated with a decrease in RONS generation. Moreover, because the blood glucose (Monnier et al., 2006) and triglyceride response (Bloomer, Ferebee et al., 2009) to feeding is at least partly mediated by the fasting levels of these variables, a decrease in fasting blood glucose or triglycerides should result in lower postprandial oxidative stress. A lifestyle approach of modifying dietary intake might be considered a "first line" defense to decrease both fasting and postprandial oxidative stress. It should be noted that unlike exercise, for which the oxidative stress response is typically short lived, the oxidative stress response following a high calorie, high fat meal may persist for several hours (e.g., 4-6) following feeding (Bloomer, Cole et al., 2009; Bloomer, Fisher-Wellman et al., 2009; Melton et al., 2009; Saxena et al., 2005), and the response is exacerbated in those who are obese (Bloomer & Fisher-Wellman, 2009).

3.2.2.1 Meal composition and size

It is evident that the dietary practices of many individuals are not ideal, with consumption of dietary fat and simple sugars meals being prevalent (Drewnowski, 2007; Livesey et al., 2008). The sheer size of individual meals is often larger than what is needed based on energy demands, which may exacerbate and prolong postprandial glycemia and lipemia (Zilversmit, 1979)—allowing for greater RONS production. The severity of the oxidative load imposed appears dependent on the magnitude and rate of glycemia and lipemia experienced post-feeding (O'Keefe & Bell, 2007). Indeed, moderate to strong correlations exist for both glucose (Monnier et al., 2006) and triglycerides (Bae et al., 2001; Bloomer, Ferebee et al., 2009; Bloomer & Fisher-Wellman, 2010; Fisher-Wellman & Bloomer, 2010; Saxena et al., 2005) and oxidative stress biomarkers post-feeding.

Studies have included a variety of meals to induce an oxidative stress, ranging from isolated protein, carbohydrate, and fat, to mixed meals involving some combination of macronutrients. However, in most postprandial oxidative stress studies, the meal of choice is predominantly lipids. Such a meal reliably induces a state of oxidative stress, with a corresponding increase in blood triglycerides. We have recently compared the oxidative response to four different isocaloric meals (protein, carbohydrate, lipid, and mixed) and found that the lipid meal resulted in the greatest increase in postprandial oxidative stress (Fisher-Wellman & Bloomer, 2010). We have replicated these findings with regards to the lipid meal compared to a carbohydrate meal (Bloomer, Kabir, Marshall et al., 2010), noting that the oxidative stress response is dependent on meal size (i.e., increased calories = greater oxidative stress). Taken together, these data indicate that both meal composition and size impact postprandial oxidative stress.

3.3 Cellular dysfunction

The rise in circulating glucose and triglycerides, and the ensuing postprandial oxidative stress, triggers a harmful biochemical cascade throughout the circulation, including inflammation, endothelial dysfunction, hypercoaguability, and sympathetic hyperactivity,

all of which may promote further RONS generation and oxidative damage (Fisher-Wellman & Bloomer, 2009b). The specific mechanisms of RONS generation in the postprandial state have yet to be elucidated due to the complexity of the cellular signaling cascade that exits *in vivo*. However, it appears that RONS initiate pathways of gene transcription, inflammation, and cellular adhesion, which induce further RONS generation and cellular damage (Fisher-Wellman & Bloomer, 2009b). When an excess of substrate enters the mitochondria, an accumulation of superoxide is generated from the electron transport chain (E. J. Anderson et al., 2009; Brownlee, 2005; Koves et al., 2008).

Within the peripheral tissue, this oxidative disruption can activate several pro-inflammatory transcription factors (nuclear factor κB [NF- κB] and tumor necrosis factor α [TNF-α]), which may induce further RONS production and insulin resistance (Aljada et al., 2006; Sinha et al., 2004). It is proposed that this form of RONS mediated insulin resistance is a means for peripheral tissue to reduce the amount substrate after excessive nutrient intake (Ceriello & Motz, 2004). In turn, substrate may accumulate within the circulation leading to hyperglycemia and hyperlipidemia (Fisher-Wellman & Bloomer, 2009b).

Within the vasculature, the endothelium may produce RONS by similar mechanics as peripheral tissue under conditions of hyperglycemia and hyperlipidemia (Ceriello & Motz, 2004). The increased RONS generation leads to the migration of phagocytic cells (leukocytes and neutrophils) to the endothelium, which produce additional RONS via NADPH oxidase (Mohanty et al., 2000; Mohanty et al., 2002; Van Oostrom et al., 2003). Moreover, this can lead to the release of inflammatory cytokines (Aljada et al., 2006) and cellular adhesion molecules (Ceriello et al., 2004; Rubin et al., 2008), which may be contributing factors to atherosclerosis, myocardial infarction, and stroke (Aljada et al., 2006).

3.3.1 Methods of assessing RONS formation

Since radicals are highly reactive and short lived (e.g., 10^{-5} seconds for superoxide), they are difficult to measure in biological systems. However, direct measurement techniques do exist; the most common being electron spin resonance (ESR) spectroscopy involving spin traps (Knight, 1999). Unfortunately, the equipment needed for such measurements is sophisticated and costly and the procedures are labor intensive, making the analysis of large numbers of samples difficult. More common is the use of indirect methods to measure oxidized biomolecules such as lipids, proteins, and DNA—resulting from exposure to RONS. By measuring these oxidative stress biomarkers, the degree of RONS generation and antioxidant capacity can be inferred, although specific information related to the type and extent of RONS remains unknown.

Due to the vast growth in this area of study, a variety of analysis procedures have been used to measure oxidative stress biomarkers (Rimbach et al., 1999), ranging from spectrophotometric assays to procedures using gas chromatography-mass spectroscopy (GC-MS) and high performance liquid chromatography (HPLC) coupled with electrochemical or chemiluminescence detection. Several commercially available assay kits are now available, while some companies offer oxidative stress related reagents and assay kits exclusively—while also providing analytical services for these procedures. Analyses can be performed using several body fluids (e.g., blood, urine, saliva), as well as muscle and organ tissue.

3.3.2 Common biomarkers of oxidative stress

Numerous biomarkers have been used in oxidative stress related research. Although a complete discussion of these markers is beyond the scope of this chapter, the biomarkers

indicated below appear most commonly used. It should be understood that due to the growing interest in this line of work, new biomarkers and assay procedures emerge each year.

With regards to lipids, the following assays are commonly used: isoprostanes, lipid hyroperoxides, malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), oxidized low density lipoproteins (ox-LDL-C), conjugated dienes, and hexanoyl lysine. With regards to proteins, the following assays are commonly used: protein carbonyls, nitrotyrosine, individual oxidized amino acids, and advanced oxidation protein products. With regards to DNA, the following assays are commonly used: 8-hydroxy-2'-deoxyguanosine (8-OHdG) and individual oxidized DNA strand breaks (comet assay).

In addition to the above, numerous individual antioxidants (e.g., ascorbate, tocopherols), antioxidant enzymes (e.g., superoxide dismutase), and antioxidant capacity markers can be measured. In relation to the latter, the following four assays are common: Trolox equivalent antioxidant capacity (TEAC), Oxygen Radical Absorbance Capacity (ORAC), Ferric Reducing Ability of Plasma (FRAP), and Total Radical-Trapping Antioxidant Parameter (TRAP).

Enzymes such as xanthine oxidase and peroxides such as hydrogen peroxide can also be measured. Other biomarkers thought to be associated with oxidative stress (e.g., inflammatory markers, obesity markers) are often included in postprandial studies. Finally, markers of endothelial function such as nitrate and nitrite (surrogate markers of nitric oxide) and flow mediated dilation are often included in studies of postprandial oxidative stress—due to the association between increased RONS production, decreased nitric oxide bioavailability, and endothelial dysfunction.

4. Minimizing and protecting against postprandial RONS

In an attempt to decrease the potential harm of RONS following acute feedings, it appears most prudent to attempt to simply avoid any significant elevation in RONS to begin with. This may be best accomplished by decreasing the overall calorie load within any given meal (Bloomer, Kabir, Marshall et al., 2010), while reducing the amount of saturated fat and simple sugar and replacing such calories with "healthy" fat and dietary fiber (Jenkins et al., 2007). In addition, the use of selected micronutrients may prove helpful. Finally, the performance of regular exercise may act to minimize postprandial oxidative stress. Beyond this prophylactic approach involving alterations in both nutrient intake and physical activity, the plan becomes one of treatment (i.e., handling the increased production of RONS due to the spike in blood glucose and blood triglycerides).

The remainder of this chapter focuses on the role of exercise and selected nutrient intake in an attempt to attenuate postprandial oxidative stress. While some studies have focused exclusively on diabetic patients, many others have not. However, because the potential mechanisms of actions in relation to glucose and triglyceride uptake, as well as the up-regulation in antioxidant defense may be similar for diabetic and non-diabetic individuals, we have included studies specific to both populations. Where possible, distinctions are made between studies.

5. Exercise and postprandial oxidative stress

Aerobic exercise has been shown to ameliorate postprandial oxidative stress and hyperlipidemia, with consumption of a high fat meal (Clegg et al., 2007; McClean et al.,

2007); however few studies have been conducted to address this issue. This effect may be due to an acute improvement in both triglyceride and glucose clearance, as well as an increase in antioxidant enzyme activity resulting from the exercise bout (McClean et al., 2011). The following text outlines findings specific to these areas of investigation.

5.1 Acute exercise

5.1.1 Triglyceride metabolism

It is well documented that exercise improves multiple aspects of human health and reduces both morbidity and mortality. Over the past few decades, a great amount of attention has been given to exercise as a therapeutic tool to reduce circulating triglyceride levels, both at rest and following meal consumption. Although, the exact mechanisms involved in attenuation of postprandial lipemia with exercise are not fully understood (Katsanos, 2006), exercise has been shown to decrease circulating triglyceride levels (Pronk, 1993), as well as help to reduce the amount of triglyceride secretion by the liver (Borsheim et al., 1999; Gill et al., 2001).

As highlighted earlier, reducing postprandial triglyceride levels is of particular importance, as this rise in circulating lipids post-feeding may be associated to increased risk for cardiovascular disease, possibly linked to the formation of RONS (Bae et al., 2001). It is well documented that a positive correlation exists between postprandial triglyceride levels and oxidative stress biomarkers (Bae et al., 2001; Bloomer, Ferebee et al., 2009; Bloomer & Fisher-Wellman, 2010; Fisher-Wellman & Bloomer, 2010; Saxena et al., 2005). Therefore, if exercise is successful at reducing postprandial triglycerides, it may also be associated with a decrease in oxidative stress.

Exercise has been reported to increase the activity of lipoprotein lipase (LPL) (Seip & Semenkovich, 1998), and thus improve triglyceride clearance. Lipoprotein lipase is expressed on adipocytes and skeletal muscle cells, with a main function of removing triglyceride from circulating lipoproteins. In the early postprandial period, adipose LPL activity increases while muscle LPL activity decreases (Seip & Semenkovich, 1998), which is most likely due to the rise in post-meal insulin. Exercise is believed to increase muscle LPL activity via decreased circulating insulin levels and increased catecholamine levels (Seip & Semenkovich, 1998). In support of this, acute exercise was investigated with participants cycling for 60-90 min at 55-70% VO_{2max} (Seip et al., 1997). The investigators reported a significant increase in LPL activity at four and eight hours post-exercise, with a return to baseline values at 20 hours post-exercise. This increase corresponded with a significant decrease in triglycerides, an increase in norepinephrine and epinephrine, and a reduction in circulating insulin. Other investigators have noted an increase in LPL activity at 24 hours (Ferguson et al., 1998; Grandjean et al., 2000) and 48 hours (Grandjean et al., 2000) post-exercise, while triglycerides have been noted to be lower at 24 hours (Cullinane et al., 1982; Grandjean et al., 2000), 48 hours (Grandjean et al., 2000), and 66 hours (Ferguson et al., 1998) following exercise.

In addition to an increase in LPL activity following exercise, a decreased secretion of very low density lipoprotein (VLDL) may be another mechanism that results in lower circulating levels of triglycerides (Borsheim et al., 1999; Gill et al., 2001). With regards to VLDL, it appears that intensity plays a major role in decreasing secretion of VLDL. This is supported by the work of Borsheim et al. (Borsheim et al., 1999) who noted a decrease in VLDL at 4.5 hours after cycling for 90 minutes at ~58% VO_{2max}, while Magkos et al. (Magkos et al., 2008) reported no significant changes for 6 hours post-exercise when treadmill walking was

performed for 90 minutes at intensity of ~30% VO_{2max}. One investigation reported no change in VLDL immediately and one hour following exhaustive cycling exercise performed at 115% VO_{2max} (Lira et al., 2010). One potential limitation to this study was that the sampling time course was only sustained for one hour post-exercise. This is considerably less than prior work demonstrating an effect of exercise on VLDL lowering when measured 4.5 hours post-exercise (Borsheim et al., 1999).

Resistance training has also been shown to have an effect on postprandial lipemia. Singhal et al. (Singhal et al., 2009) investigated the role of intensity on postprandial lipemia by performing 10 resistance exercises at either 50% of eight repetition maximum (RM) or at 100% of eight RM (the lower intensity group performed 16 repetitions and the higher intensity group performed eight repetitions, and both groups performed three sets). A high fat meal was administered 15.5 hours post-exercise and there was found to be no significant difference between intensities. Both exercise bouts resulted in a similar reduction in postprandial lipemia and increase in fat oxidation. Another investigation compared resistance exercise with aerobic exercise by matching energy expenditure between exercise type (Petitt et al., 2003). Resistance exercise was comprised of 10 exercises performed for three sets of 10 repetitions, at the participants' 10 RM, while the aerobic exercise involved walking for the same duration as resistance exercise, and at an intensity estimated to elicit an identical energy expenditure. The results indicated that resistance exercise more favorably impacted baseline triglyceride concentrations, as well as the total postprandial triglyceride response, as compared to aerobic exercise and control.

5.1.2 Glucose metabolism

Given that the hallmark characteristic of diabetes is elevated blood glucose, consumption of high caloric meals composed of processed carbohydrates should be cautioned, if not avoided completely. The post-meal hyperglycemia has been shown to elicit a subsequent rise in RONS (Fisher-Wellman & Bloomer, 2010; Mohanty et al., 2000; Monnier et al., 2006). While young, healthy, non-diabetic individuals may not be negatively affected by high "simple" carbohydrate meals (Bloomer, Kabir, Marshall et al., 2010), research has shown that obese and metabolically diseased populations (e.g., obese, diabetic) consuming such feedings may be at increased risk for postprandial oxidative stress (Bloomer & Fisher-Wellman, 2009).

Individuals with insulin resistance have noted improvements in glucose homeostasis following both acute exercise and chronic exercise training, resulting in numerous metabolic and hemodynamic changes that may contribute to improved glucose disposal. These adaptive responses include enhanced insulin action on the skeletal muscle glucose transport system, reduced hormonal stimulation of hepatic glucose production, improved blood flow to skeletal muscle, and normalization of an abnormal blood lipid profile (Henriksen, 2002).

There are two main mechanisms responsible for enhanced glucose disposal following an acute exercise bout. First, an observed stimulation of GLUT4 to the cell membrane is noted, which allows for glucose uptake into the cytosol from the vasculature. Second, an increase in insulin sensitivity within contracting skeletal muscle is noted, ultimately allowing for GLUT4 translocation. Both of these effects are welcome following the ingestion of a high carbohydrate meal in which blood glucose is elevated.

Under normal physiologic conditions, GLUT4 is translocated from the cytosol to the cell surface through an insulin signaling mechanism. This is accomplished when insulin binds to the insulin receptors of the cellular wall of the muscle, which in turn activates a cascade of protein kinases that eventually translocate GLUT4 (Rockl et al., 2008). However, muscular

contraction also induces this translocation independently of the initial insulin signaling, possibly through calcium and/or AMP kinase (Henriksen, 2002). An immediate increase in plasma GLUT4 transport protein content following moderate (Kristiansen et al., 1999) and high (Green et al., 2008; Kristiansen et al., 1996) intensity aerobic exercise has been noted. The increase in GLUT4 translocation in response to exercise may be necessary to allow for adequate glycogen replenishment (Thompson et al., 2001).

In terms of improved insulin sensitivity in response to exercise, it has been reported that insulin transduction through insulin receptor IRS-1/2 and PI3-kinase is enhanced post-exercise (Peres et al., 2005). This increase in skeletal muscle insulin sensitivity has been shown to last for up to 16 hours post-exercise (Chibalin et al., 2000; Ren et al., 1994). The enhanced removal of excess glucose from within the vasculature may be in conjunction with insulin independent increases of GLUT4 translocation, which in turn may relate to both reduced RONS production and maintenance of endothelial function.

The majority of acute investigations related to increased glucose clearance have focused on moderate intensity aerobic exercise, with multiple studies reporting favorable effects, as reviewed elsewhere (Praet & van Loon, 2007). To our knowledge, only one investigation has focused on the effect of high intensity sprint exercise on glucose metabolism. Brestoff et al. (Brestoff et al., 2009) had subjects perform five 30 second sprints at 125% VO_{2peak} with four minutes rest between sprints or 45 minutes of continuous exercise at 75% VO_{2peak}. An oral glucose tolerance test (OGTT) was administered 12-16 hours after exercise, and blood samples were taken every 30 minutes for a two hour period following the OGTT. There was no significant effect of the sprint exercise with regards to blood glucose lowering; however, the endurance protocol significantly lowered the insulin response. One possible reason for the lack of significance regarding the sprint exercise bout may be due to the bout being performed 12-16 hours prior to the OGTT—a time that may have been too distant from exercise to elicit an effect. Kraniou et al. (G. N. Kraniou et al., 2006) also reported no significant differences in GLUT4 protein gene expression with higher intensity aerobic exercise (27 minutes at 83% VO_{2peak}) compared to lower intensity aerobic exercise (60 minutes at 39% VO_{2peak}). Despite no significant difference between trials, both intensities resulted in a significant increase in GLUT4 protein and gene expression immediately and three hours post-exercise. Collectively, improvements in GLUT4 translocation immediately post-exercise (Kristiansen et al., 1997; Thorell et al., 1999), with significant increases in both gene expression (G. N. Kraniou et al., 2006; Y. Kraniou et al., 2000) and insulin sensitivity (Thong et al., 2003) lasting up to three hours post-exercise, may provide evidence for exercise to be performed closer to the actual test meal.

In addition to aerobic and sprint exercise protocols, resistance exercise has also been used in an attempt to improve postprandial glucose metabolism. One investigation had subjects exercise 14 hours prior to consuming a carbohydrate-rich meal (Andersen & Hostmark, 2007). Resistance exercise consisted of seven exercises performed for three sets of 10 repetitions at an intensity of 50% 1RM. The authors reported that postprandial glucose response was significantly reduced in the exercise group when compared to the control group. Fluckey et al. (Fluckey et al., 1994) investigated the effects of resistance exercise on glucose tolerance in non-diabetic subjects and in those with non-insulin dependent diabetes mellitus (NIDDM) by performing three sets of 10 repetitions at 75% 1RM, 18 hours prior to an OGTT. It was concluded that a single resistance exercise session significantly enhanced insulin clearance, but not insulin secretion, in both control and NIDDM subjects.

5.1.3 Antioxidant capacity

Although both a lowering of circulating triglycerides and blood glucose are thought to lead to lower production of RONS, improved antioxidant capacity may also serve to minimize the potential harm of increased RONS postprandially. Besides including more global markers of total antioxidant status, such as TEAC and ORAC, performing assays for individual antioxidant enzymes is another method to assess oxidative stress (e.g., superoxide dismutase [SOD], glutathione peroxidase [GPx], catalase [CAT], or glutathione reductase [GR]), as these enzyme may be up-regulated by an acute bout of exercise or may be acutely lowered owing to their combating nature against RONS.

Many investigations have been performed to confirm the post-exercise change in antioxidant capacity. Although these investigations generally note a decrease in antioxidant status post-exercise (Di Massimo et al., 2004; Tozzi-Ciancarelli et al., 2002), this is usually transient, as defenses either return to, or exceed, their pre-exercise values shortly after exercise cessation (Alessio et al., 2000; Fatouros et al., 2004; Michailidis et al., 2007; Quindry et al., 2003; Steinberg et al., 2006; Vider et al., 2001; Watson et al., 2005). These findings confirm the short-term activity of antioxidants in handling RONS, as well as propose a hypothesis for the stimulatory effect of acute exercise on chronic antioxidant status. However, despite the increase in antioxidant status noted in some studies, other authors have reported no increase (Sen et al., 1994; H. K. Vincent et al., 2004), which may be attributed to sampling times related to the acute session.

When focusing specifically on individual antioxidant enzymes, investigations have reported increases in SOD (Buczynski et al., 1991; M. F. Chen et al., 1994; Elosua et al., 2003), GPx (Buczynski et al., 1991; Elosua et al., 2003; Fatouros et al., 2004; Laaksonen et al., 1999), and CAT (Buczynski et al., 1991; Michailidis et al., 2007; Vider et al., 2001) following exercise. This increase in antioxidant enzyme activity may function to combat any increase in RONS resulting from ingestion of dietary nutrients. Only a few studies have reported null findings for SOD (Tozzi-Ciancarelli et al., 2002), GPx (Akova et al., 2001), and GR (Elosua et al., 2003).

Although not directly considered to be an antioxidant, heat shock proteins (HSPs) have been shown to be important mediators of skeletal muscle insulin sensitivity, as well as aid in protection against oxidative stress (Geiger & Gupte, 2011). With acute exercise, HSPs have been shown to increase in response to body temperature variations, inflammation, and RONS production (K. L. Hamilton et al., 2003; Nishizawa et al., 1999; Smolka et al., 2000). Therefore, HSPs are sometimes considered as "complementary" to antioxidant function (Finaud, Lac, & Filaire, 2006; Smolka et al., 2000), due to protecting cells and intracellular proteins against RONS-induced damage (Fehrenbach & Northoff, 2001; K. L. Hamilton et al., 2003; Nishizawa et al., 1999). It's important to note that within certain disease states, especially those associated with insulin resistance and aging, HSPs are decreased. This becomes an unfavorable situation considering that HSPs have been shown to decrease oxidative stress, inhibit inflammatory pathways, and enhance metabolic characteristics in skeletal muscle (Geiger & Gupte, 2011). Therefore, methods of increasing HSP production should be considered, with exercise being one such method.

5.2 Chronic exercise

5.2.1 Triglyceride metabolism

As with acute exercise, chronic exercise training also results in beneficial changes in lipid metabolism and increased LPL activity (Peltonen et al., 1981); at least within a sample of non-diabetic subjects. However, when focusing on investigations using patients with T2DM,

the results are mixed. Two investigations have reported that patients with T2DM experienced a decrease in total cholesterol and low-density lipoprotein-cholesterol (LDL-C), as well as elevations in high-density lipoprotein-cholesterol (HDL-C) with aerobic training (consisting of mainly walking or running on a treadmill, cycling and calisthenics involving the upper and lower limbs) (Kadoglou et al., 2007; Ronnemaa et al., 1988) or walking (Araiza et al., 2006). However, other investigations with T2DM participants have noted no effect on the blood lipid profile following a period of exercise training (Loimaala et al., 2009; Sigal et al., 2007; Tudor-Locke et al., 2004).

Some investigations have aimed to increase physical activity in an effort to attenuate triglyceride levels. Despite being successful in their objective to increase physical activity, this increase was not associated with any significant reductions in triglycerides (Loimaala et al., 2009; Sigal et al., 2007; Tudor-Locke et al., 2004). It is possible that exercise alone (particularly if low volume), without a concomitant change in dietary intake and decrease in weight loss, might not be adequate to significantly improve blood lipids in those with T2DM. For example, Barnard et al. (Barnard et al., 1982) completed a 26 day intervention involving exercise and dietary modification and noted that both total cholesterol and triglycerides were reduced compared to baseline. However, these changes appeared mediated by an average weight loss of 4.3 kg. Using a similar exercise and nutritional intervention, Barnard and colleagues (Barnard et al., 1992) later noted a reduction in total cholesterol, LDL-C, and the ratio of total cholesterol: HDL-C. However, like the earlier investigation, these effects may have been more mediated by the weight loss than by the exercise. These data highlight the potential role of combination treatment (i.e., exercise and weight reduction—possibly involving dietary modification) to improve blood lipids in those with T2DM.

5.2.2 Glucose metabolism

Aerobic exercise has been the primary mode prescribed for diabetes prevention and management. It has been shown that only one week of aerobic training can improve whole-body insulin sensitivity in individuals with T2DM (Winnick et al., 2008). Although only persisting for a period of hours to days, moderate and vigorous aerobic training has been shown to improve insulin sensitivity (Bajpeyi et al., 2009; Evans et al., 2005; Galbo et al., 2007; Houmard et al., 2004). The responsiveness of skeletal muscles to insulin has been shown to be enhanced with training due to the increases in expression and/or activity of proteins involved in glucose metabolism and insulin signaling (Christ-Roberts et al., 2004; Holten et al., 2004; O'Gorman et al., 2006; Y. Wang et al., 2009). Glycogen synthase activity and GLUT4 protein expression has been shown to increase from moderate training (Christ-Roberts et al., 2004). Another key aspect related to improved insulin action and glycemic control is mediated through fat oxidation, and chronic training induces increased lipid storage in muscle, as well as increased fat oxidation capacity (Duncan et al., 2003; Goodpaster et al., 2003; Kelley & Kelley, 2007; Pruchnic et al., 2004).

In addition to aerobic training, blood glucose control and insulin action has also been shown to be favorably impacted by resistance training (N. D. Cohen et al., 2008; Dunstan et al., 2002; Ibanez et al., 2005; Ibanez et al., 2008; Ishii et al., 1998). One investigation consisted of twice-weekly progressive resistance training for 16 weeks by older men with newly diagnosed T2DM (Ibanez et al., 2005). The authors reported a 46% increase in insulin action, 7% reduction in fasting blood glucose, and a significant loss of visceral fat. Muscle mass

increases from resistance training may also aid in blood glucose uptake due to the actual increase in mass, and heavy resistance training may also help to reverse or prevent further loss of skeletal muscle due to disuse and aging (Castaneda et al., 2002; Willey & Singh, 2003).

5.2.3 Antioxidant capacity

Participating in regular physical activity has been shown to be an effective means of increasing antioxidant defense (Ji, 1999; Kojda & Hambrecht, 2005). Exercise, in particular of aerobic nature (Elosua et al., 2003; Marzatico et al., 1997; May et al., 1996; H. Miyazaki et al., 2001; Selamoglu et al., 2000), may lead to up-regulation in antioxidant enzymes that are situated at the muscular, plasmatic, hepatic, and cardiac levels (Chevion et al., 2003; Venditti & Di Meo, 1997). With regards to muscle, the effect may be strongest for tissue with high oxidative power (e.g., type I fibers) (Hollander et al., 1999; Inal et al., 2001; Leeuwenburgh et al., 1999). It should be noted that the absolute magnitude of change in antioxidant enzymes may differ, with SOD and GPx noted to increase more than CAT (Hollander et al., 1999; Leeuwenburgh et al., 1999; H. Miyazaki et al., 2001; Ohno et al., 1988; Powers et al., 1999).

There are less data pertaining to the impact of anaerobic exercise on antioxidant capacity. However, it has been reported that anaerobically trained individuals have lower oxidative stress and experience less muscular damage after exercise when compared with untrained individuals (Ortenblad et al., 1997; Selamoglu et al., 2000). Moreover, anaerobic trained participants have been reported to have higher antioxidant enzyme activity in blood and working muscle (Hellsten et al., 1996; Marzatico et al., 1997; Ortenblad et al., 1997; K. R. Vincent et al., 2002); however, exceptions to this finding exist (Selamoglu et al., 2000). Heat shock proteins have also been shown to increase as a result to chronic anaerobic training (Carmeli et al., 2010), suggesting that cellular protection is increased as an adaptation to this form of exercise.

5.3 Summary of exercise

Although exercise may elicit a transient increase in RONS, it is clear from multiple studies that both acute and chronic exercise may improve certain aspects of metabolic function—including enhanced triglyceride and glucose clearance, as well as increased antioxidant defense. Because elevated triglyceride and glucose (in particular in response to high fat and/or high carbohydrate feeding) is associated with increased production of RONS, any decrease in circulating triglyceride and glucose may be related to lower postprandial oxidative stress. Few studies have directly measured postprandial oxidative stress in association with acute or chronic exercise. Therefore results need to be inferred based on the observed changes in triglyceride and glucose. Further work is needed to provide more convincing evidence for such an effect.

6. Nutrients and postprandial oxidative stress

The multifaceted etiology of diabetes has given rise to a number of interventions in an attempt to minimize disease progression. Regular exercise (Praet & van Loon, 2007; Tucker et al., 2008), weight control (Mavian et al., 2010), pharmaceuticals (Nakajima, 2010; O'Keefe et al., 2011), and selected nutrients (Badimon et al., 2010; Davi et al., 2010; Nahas & Moher, 2009) have been scientifically supported to aid in diabetes management. Considering that inhabitants of the Western world spend up to 16 hours of the day in the postprandial state

(de Koning & Rabelink, 2002), and that postprandial oxidative stress is hypothesized to be the pathogenic mechanism underlying diabetes and cardiovascular disease (Ceriello & Motz, 2004; Fisher-Wellman & Bloomer, 2009b), the use of selected nutrients as a therapeutic tool to help control diabetes should be considered. Of course, the fundamentals of optimal dietary intake inclusive of the consumption of a nutrient dense, moderate to low calorie diet, ideally consumed over multiple balanced meals throughout the day (Bloomer, Kabir, Marshall et al., 2010), and inclusive of fruits and vegetables (S. Liu et al., 2000), whole grains (S. Liu et al., 1999), and relatively low amounts of saturated fats should be considered first. However, beyond the foundational plan, there exist a number of nutraceuticals, functional foods, and dietary strategies that have been shown to attenuate the postprandial rise in triglycerides, glucose, and subsequent oxidative stress, as well as improve antioxidant status. Therefore, intake of selected nutrients may be considered as a preventive measure, as well as a treatment option, for individuals with impaired glucose tolerance (IGT).

The focus of this section is to highlight nutrients that have a potential influence on ameliorating the rise in postprandial oxidative stress. As mentioned previously in this chapter, postprandial oxidative stress appears contingent upon the magnitude and rate of postprandial glycemia and triglyceridemia (O'Keefe & Bell, 2007). Individuals who are obese or have metabolic or cardiovascular disease appear to be more susceptible to postprandial oxidative stress, and they typically experience more robust and prolonged periods of hyperglycemia (Y. Miyazaki et al., 2007; Schindhelm et al., 2007; Serin et al., 2007) and hypertriglyceridemia (Ceriello et al., 2002; Nappo et al., 2002) post-feeding, as compared to non-diseased individuals. Again, elevations in blood glucose and triglycerides are directly associated with superoxide production (Bae et al., 2001); hence, a greater increase in either blood glucose or triglyceride post-feeding may be associated with a greater increase in postprandial oxidative stress. This has been reported previously in patients with T2DM (Saxena et al., 2005), as well as in those with coronary artery disease (Graner et al., 2006).

The following sections are focused primarily on highlighting nutrients that enhance triglyceride and glucose clearance, are associated with lower biomarkers of oxidative stress, improve antioxidant status, and augment endothelial function. Specific attention is given to literature focused on outcomes in the postprandial period, given that fasting is not the usual physiological state of modern humans, especially in the Western world. It should be understood that due to the vast and increasing study in this area of investigation, the present chapter does not exhaust the literature pertaining to this line of work. However, several well-studied nutrients are included for discussion. Moreover, while we provide brief information pertaining to the potential mechanisms of actions for selected nutrients, a complete discussion is beyond the scope of this chapter. We refer readers to the individual manuscripts for more information on possible mechanisms of action.

6.1 Nutritional supplements

The use of nutrition supplements for purposes of aiding postprandial metabolism is widespread. Although a variety of ingredients and finished products have been studied, those with greatest interest appear to be antioxidants and insulin mimetic agents. The text below illustrates the varying effects of several antioxidants, in diabetic and healthy populations. Additional ingredients used primarily for purposes of altering glucose, and in some cases lipid, metabolism, are also presented. The mixed findings across studies extend to some longitudinal intervention studies (some of which may include the use of sub-optimal dosing of nutrients (Sesso et al., 2008)), indicating that more research is needed to

elucidate the optimal dosage and duration of supplementation, as well as the population who might benefit most from supplementation.

6.1.1 Vitamin C

Vitamin C supplementation (800mg·day^{-1}) in T2DM patients with low plasma vitamin C for four weeks was found not to be effective at improving endothelial dysfunction and insulin sensitivity, despite increasing endogenous vitamin C levels (H. Chen et al., 2006). Similarly, 1.5g·day^{-1} of vitamin C for three weeks did not improve fasting plasma concentrations of oxidative stress biomarkers, blood glucose, lipid profile, or blood pressure, despite also increasing endogenous concentrations of vitamin C (Darko et al., 2002). In contrast to these null findings, 1g·day^{-1} of vitamin C for three days completely abolished the postprandial oxidative stress insult, and blunted the deterioration of endothelial function, to a high fat meal in patients with T2DM (R. A. Anderson et al., 2006). Moreover, pharmacological infusion with vitamin C has been found to acutely improve endothelial dysfunction in patients with insulin-dependent DM (Timimi et al., 1998), NIDDM (Ting et al., 1996), and healthy subjects (Beckman et al., 2001). Finally, intravenous infusion of vitamin C improved endothelial function and insulin sensitivity in patients with coronary spastic angina following an OGTT (Hirashima et al., 2000).

6.1.2 Vitamin E

Like vitamin C, vitamin E (α-tocopherol) supplementation has been similarly ambiguous with regards to improving biomarkers of oxidative stress and cardiovascular risk factors. On the one hand, vitamin E supplementation was associated with significant reduction in biomarkers of oxidative stress in NIDDM patients supplemented with 600mg·day^{-1} for two weeks (Davi et al., 1999). Additionally, 98 Korean patients with T2DM treated with continuous subcutaneous insulin infusion and 200mg·day^{-1} vitamin E for two months had significantly decreased red blood cell lipid peroxide concentrations (Park & Choi, 2002). However, Winterbone and colleagues (Winterbone et al., 2007) found that 1200IU·day^{-1} of vitamin E for four weeks in T2DM patients resulted in a significant prooxidant effect mediated through DNA damage to mononuclear cells after an OGTT, despite no changes in fasting oxidative measures. The ability of vitamin E to act as a pro-oxidant and increase the peroxidation of lipids has been established *in vitro* (Bowry et al., 1992; Santanam & Parthasarathy, 1995); while the work of Winterbone et al. (Winterbone et al., 2007) suggests the possibility that a high dose of vitamin E is also potentially damaging *in vivo* in patients with T2DM.

6.1.3 α-lipoic acid

The antioxidant α-lipoic acid (ALA) has illustrated efficacy when prescribed to patients with T2DM. Three weeks of treatment with ALA (600, 1200, or 1800 mg·day^{-1}) resulted in a significant increase in insulin-stimulated glucose disposal compared to placebo (Jacob et al., 1999). Three weeks of treatment with intravenous infusion of ALA (600mg·day^{-1}) in subjects with impaired fasting glucose (IFG) illustrated a significant increase in endothelium-dependent arterial dilation and a significant decrease in plasma TBARS (Xiang et al., 2011). Acutely, in patients with IGT, plasma glucose levels were similar between the ALA group (300mg) and placebo group during an OGTT. However, at 1 and 2 hours, flow mediated

dilation was significantly elevated in the ALA group compared to the placebo group, and plasma glucose levels were negatively correlated with endothelial function. After supplementation with ALA, the power of this association decreased. Similarly, flow mediated dilation decreased in association with an increase in TBARS, and the strength of this association also decreased after supplementation with ALA (Xiang et al., 2008).

6.1.4 Coenzyme Q_{10}

Coenzyme Q_{10} (CoQ_{10}) is a critical intermediate of mitochondrial electron transport chain activity that regulates cytoplasmic redox potential and can inhibit superoxide generation by endothelial cells (Beyer, 1990; McCarty, 1999). Two separate human trials, one with hyperglycemic T2DM patients and one with statin-treated T2DM patients, elicited approximately parallel results. Specifically, twelve weeks of supplementation with 200mg of CoQ_{10} or placebo resulted in significant increases in plasma $CoQ_{10,}$ respectively, and improved flow mediated dilation (S. J. Hamilton et al., 2009; Watts et al., 2002). However, neither trial found an alteration in biomarkers of oxidative stress or antioxidant capacity, lipid profiles, glycemic control, or blood pressure after supplementation.

6.1.5 Carnitine

Carnitine is an essential compound that assists in the transport of long-chain fatty acids into the mitochondrial matrix for subsequent oxidation. Additionally, *in vitro* and *in vivo* evidence supports the role of carnitine as an antioxidant (Calo et al., 2006). Endothelial function, assessed by flow mediated dilation in the brachial artery was improved after a high-fat meal consumed with 2g L-carnitine and preceded by three weeks of carnitine supplementation in healthy, young men and women (Volek et al., 2008). There was no significant postprandial differences in triglycerides, inflammatory markers, interleukin-6 (IL-6), TNF-α, or MDA between placebo and treatment. In pre-diabetics (fasting blood glucose: 100-125 $mg \cdot dL^{-1}$) $3g \cdot day^{-1}$ acetyl L-carnitine arginate resulted in a significant increase in fasting nitrate/nitrite, suggesting a possible impact on vascular function (although not specifically determined). However, little other effects were noted for a variety of oxidative stress biomarkers (Bloomer et al., 2009).

6.1.6 Lycopene

Lyopene is a highly unsaturated carotenoid found predominantly in tomato products (Clinton, 1998). Four weeks of lycopene supplementation (tomato-derived Lyc-O-Mato) at $30mg \cdot day^{-1}$ in obese patients was not found to favorably influence markers of inflammation and oxidation biomarkers, despite a significant increase in plasma cartenoids, and specifically lyopene (Markovits et al., 2009). One week of lyopene supplementation ($80mg \cdot day^{-1}$) was found again to increased endogenous capacity of plasma lipid-soluble antioxidants (lycopene, β-carotene, and α-tocopherol); however, biomarkers of vascular oxidative stress and inflammation were unaffected in the fasted state, as well as post consumption of a high fat meal, in young, healthy subjects (Denniss et al., 2008). Finally, both acute (24 hour) and long-term (seven day) tomato puree consumption had no effects on endothelial dysfunction after consumption of a meal, despite a significant increase in plasma lyopene levels in healthy postmenopausal women (Stangl et al., 2011).

6.1.7 Catechins

Tea is made from the leaves of the evergreen *Camellia sinensis*. Tea is a rich source polyphenolic compounds called catechins, especially epigallocatechin gallate (EGCG), which are hypothesized to have multiple health-promoting effects (Higdon & Frei, 2003), including a potential impact on T2DM (Thielecke & Boschmann, 2009). Chronic green tea supplementation has been shown to significantly decrease lipid peroxidation and a trend to lower LDL-C (non-significantly) when supplemented for eight weeks in obese subjects with metabolic syndrome (Basu et al., 2010). On the other hand, three months of supplementation with an extract of green and black tea was found to elicit non-significant differences in glycosylated hemoglobin (HbA_{1c}) between treatment groups in a placebo controlled multiple-dose study in patients with T2DM (Mackenzie et al., 2007).

Tea catechins consumed acutely have been shown to decrease incremental area under the curve (AUC) for triglycerides in a dose dependent manner in men with mild or borderline hypertriglyceridemia. Moreover, tea catechin supplementation resulted in a significant suppression of remnant-like particle cholesterol at an early postprandial stage, but this failed to achieve statistical significance for overall incremental AUC (Unno et al., 2005). In healthy subjects, 300mL of green tea was shown to have no glucose or insulin-lowering effects (Josic et al., 2010).

6.1.8 Red wine (polyphenols)

Consumption of 300mL of red wine taken in conjunction with an acute high fat meal was found to significantly preserve antioxidant defenses and reduce both LDL-C susceptibility to oxidation and thrombotic activation, in T2DM patients (Ceriello et al., 2001). Also, a trend was seen for decreased triglycerides across the 3 hour postprandial time period; however, glucose and insulin appeared to be unaffected. In healthy subjects, 250mL of red wine in conjunction with an acute high fat meal significantly reduced the oxidative insult (increased antioxidant capacity and decreased oxidative stress biomarkers), without significantly modifying lipid profile (Ventura et al., 2004). Finally, 300mg of grape seed proanthocyanidins was given to healthy volunteers before the consumption of a test meal. It was found that grape seed extract minimizes the postprandial oxidative stress by decreasing oxidants and increasing antioxidant levels, tending to protect LDL-C from oxidative modification (Natella et al., 2002).

In relation to the above, the consumption of red wine may be linked to the 'French Paradox' (Renaud & de Lorgeril, 1992): derived from an examination of World Health Organization (WHO) epidemiological data, identifying that subjects in France, despite of diet highly comprised of saturated fat, comparable cholesterol and similar risk factors, showed considerably lower incidence of death from coronary heart disease compared with other countries such as the USA. Further analysis suggests that alcohol consumption, in particular red wine, might provide superior protection compared with other nutrients and beverages. Although the specific mechanism behind the French paradox has not been identified, *in vitro* data has proposed that the flavonoid components in red wine have strong antioxidant properties (Demrow et al., 1995; Sun et al., 2009), possibly contributing to observed cardiovascular benefits.

Some subsequent applied human research has supported these claims. For example, moderate red wine consumption (118 $mL \cdot day^{-1}$) for 12 months, in subjects with T2DM who had sustained their first non-fatal myocardial infarction, was associated with significant

improvements in oxidative stress, inflammatory response, and insulin sensitivity (Marfella et al., 2006). However, triglycerides and other markers of glycemic control were unaffected. Four weeks of grape seed extract (600mg·day^{-1}) in obese T2DM patients was associated with significantly improved markers of inflammation, glycemia, and the sole marker of oxidative stress (Kar et al., 2009). However, no significant changes were shown in endothelial function, insulin sensitivity, or total antioxidant status. Similarly, 360mL·day^{-1} of red wine showed no improvement in endothelial function after two weeks, in patients with T2DM (Napoli et al., 2005). In contrast, insulin-mediated whole body glucose disposal improved significantly. Finally, 400mL·day^{-1} of red wine for two weeks significantly increased total antioxidant status and significantly decreased MDA and reduced glutathione (GSH) of both young and old subjects, assumed to be healthy (Micallef et al., 2007). No significant effects were found for blood glucose or lipid parameters.

6.1.9 Combination antioxidant treatment

Combination treatments of antioxidants have been more efficacious in lowering oxidative stress biomarkers, most likely through a synergetic mechanism and their ability to function within different body compartments (e.g., aqueous for vitamin C vs. lipid for vitamin E). For example, vitamin C can assist in maintaining vitamin E in the reduced and active state (Packer et al., 1979). Neri et al. (Neri et al., 2005) investigated the effects of 15 days antioxidant supplementation with 600mg·day^{-1} N-acetylcysteine (NAC), 300mg·day^{-1} vitamin E, and 250mg·day^{-1} vitamin C on postprandial oxidative stress in patients with T2DM, IGT, and healthy volunteers. Antioxidant supplementation was associated with significant improvements in redox balance in all three groups, along with a reduced postprandial increase in biomarkers of oxidative stress, as well as plasma levels of von Willebrand factor (vWF), vascular cell adhesion molecule-1 (VCAM-1). Neri and colleagues (Neri et al., 2010) conducted a follow up investigation with an antioxidant cocktail of similar composition (600 mg·day^{-1} of NAC, 50 mg·day^{-1} of vitamin E, and 500 mg·day^{-1} of vitamin C) on postprandial oxidative stress. Again the trial was 15 days in duration with patients with T2DM, patients with IGT, and healthy controls. It was found that antioxidant supplementation lowered oxidative stress biomarkers in the control group and significantly decreased it in the IGT group after feeding. It was also noted that antioxidant supplementation was able to improve endothelial function, but only in healthy and IGT subjects. It should be noted that antioxidant supplementation did not alter any of the lipid variables in any of the groups. Finally, the acute intake of a combination vitamin C (2g) and vitamin E (800IU) was found to prevent the transient decrease in flow mediated dilation in healthy subjects following the OGTT, despite no significant effects being noted for biomarkers of oxidative stress (Title et al., 2000).

6.1.10 Omega-3 fatty acids

Evidence exists for the cardio-protective effects of the fatty acids found in fish (Cottin et al., 2011), which include the omega-3 fatty acids eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). Therefore, fish oil supplementation has considerable potential for diabetic individuals. In a randomized, double-blinded, placebo controlled trial in treated, hypertensive T2DM patients, 4g·day^{-1} of purified EPA or DHA elicited a fall in urinary F2-isoprostane excretion following six weeks of supplementation (Mori et al., 2003). Moreover,

baseline urinary F2-isoprostanes were positively associated with indices of diabetic control and the changes in urinary F2-isoprostanes were positively associated with changes in TNF-α and HbA_{1c}. In another study with T2DM patients with treated hypertension, 4g·day^{-1} EPA, DHA, or olive oil for six weeks decreased serum triglycerides by 19% and 15% in the EPA and DHA groups respectively, but neither had significant effects on glycemic control (Woodman et al., 2002). Purified omega-3 fatty acids at 2g·day^{-1} for 10 weeks decreased fasting triglycerides relative to placebo, and ApoB-100, and MDA relative to baseline and placebo (Shidfar et al., 2008). Again, omega-3 fatty acids had no effect on glycemic control. Finally, 2g·day^{-1} of N-3 polyunsaturated fatty acids for 12 weeks in offspring of patients with T2DM, significantly improved flow mediated dilation that was accompanied by a significant decrease in triglycerides and TNF-α (Rizza et al., 2009).
Acute combination treatment of omega-3 fatty acids (400mg EPA and 200mg DHA) and isoflavones (150mg glycoside isoflavones) did not attenuate the postprandial rise in triglycerides after a high fat meal in obese hypertriglyceridemic men (Hanwell et al., 2009). Moreover, they did not induce any significant changes in oxidative stress biomarkers. On the other hand, 1g of EPA and DHA consumed by healthy subjects was able to preserve endothelial function following a high fat meal (Fahs et al., 2010).

6.1.11 Vitamin D

Investigations have shown that vitamin D helps to reduce the risk of bone fractures, falls, autoimmune diseases, cardiovascular disease and cancer (S. Wang, 2009), and has also been shown to be inversely associated with risk of T2DM (Pittas et al., 2006). Cholecalciferol (vitamin D_3) supplemented at 1332 IU·day^{-1} for one month in women with T2DM was shown to improve insulin secretion, with a tendency to decrease fasting plasma glucose (Borissova et al., 2003). On the other hand, supplementation with 40,000 IU·week^{-1} of cholecalciferol for six months in T2DM subjects treated with metformin and bed-time insulin had no significant effects on fasting glucose, insulin, C-peptide, fructosamine, and HbA_{1c} levels (Jorde & Figenschau, 2009). Finally, supplementation with 500mg·day^{-1} calcium citrate and 700IU·day^{-1} cholecalciferol in apparently healthy, older subjects (≥ 65 years), for three years, prevented increases in fasting plasma glucose and insulin resistance in the subgroup of participants with impaired fasting glucose at baseline. There was no effect among those with normal fasting glucose (Pittas et al., 2007).

6.1.12 Magnesium, Chromium, Vanadium

Certain elements have been proposed to have glucoregulatory effects, such as magnesium, chromium, and vanadium. In T2DM patients with low serum magnesium levels, 50mL·day^{-1} $MgCl_2$ solution given for 16 weeks was shown to improve fasting measures of insulin sensitivity, blood glucose, and HbA_{1c} (Rodriguez-Moran & Guerrero-Romero, 2003). Supplementation with 600mg·day^{-1} magnesium pidolate for 12 weeks in mildly-hypertensive patients was shown to have multiple benefits (Hadjistavri et al., 2010). Specifically, supplementation was shown to lower fasting insulin, heighten fasting insulin sensitivity, reduce postprandial measures of glucose and insulin AUC, ameliorate postprandial measures of insulin sensitivity, and improve total cholesterol, LDL-C, HDL-C, and triglycerides. Finally, chronic magnesium supplementation (2.5g·day^{-1} $MgCl_2$) for three months has been reported to result in improvements in fasting insulin sensitivity

and the lipid profile in non-diabetic subjects with insulin resistance (Guerrero-Romero et al., 2004).

Opposite to the beneficial effects of magnesium, chronic supplementation with chromium picolinate has been relatively ineffective in improving metabolic features of patients with IGT (Ali et al., 2011; Iqbal et al., 2009), despite being commonly marketed as a hypoglycemic agent, and with efficacious data obtained in animals (Abdourahman & Edwards, 2008) and cell culture (Y. Q. Wang & Yao, 2009). It has been noted that the beneficial effects of chromium supplementation might be related to the severity of insulin resistance, with clinical response being more likely in individuals with more elevated fasting glucose and HbA_{1c} (Cefalu et al., 2010).

Finally, vanadium has been used with mixed success in prior trials in an attempt to lower blood glucose. The mechanism supporting vanadium supplementation is likely linked to its ability to promote increased insulin-mediated glucose disposal. Like chromium, vanadium efficacy appears to also depend on the degree of diabetic complications, with T2DM patients (N. Cohen et al., 1995; Cusi et al., 2001; Goldfine et al., 2000; Halberstam et al., 1996) reporting greater efficacy compared to non-diabetics (Halberstam et al., 1996; Jacques-Camarena et al., 2008; Jentjens & Jeukendrup, 2002).

6.1.13 Inositol phosphoglycans

Inositol phosphoglycans are potentially important post-receptor mediators of insulin action (Kelly et al., 1987; Larner et al., 1998). Pinitol (3-*O*-methyl-D-chiro-inositol) was identified in putative insulin mediator fractions that had hypoglycemic activity, and appears to mimic the effects of insulin by acting downstream in the insulin signaling pathway (Fonteles et al., 1996). After pinitol treatment ($20mg \cdot kg^{-1} \cdot day^{-1}$) in poorly controlled T2DM patients, fasting glucose, postprandial glucose, and HbA_{1c} were all significantly decreased. However, an effect on lipid profiles or adipocytokine levels was not noted (Kim et al., 2007). Acutely, pinitol supplemented at 1000mg 60 minutes before an OGTT was not shown to influence any indices of whole-body glucose tolerance and insulin sensitivity, or the activation of the skeletal insulin receptor in older, non-diabetic adults (Stull et al., 2009).

6.1.14 Cinnamon

Cinnamon is widely used as a spice, and research has suggested that it may have potential effects in improving not only glucose metabolism, but also lipid metabolism and antioxidant status. Kahn et al. (A. Khan et al., 2003) demonstrated that consumption of 1, 3, or $6g \cdot day^{-1}$ of cinnamon for 40 days reduces serum glucose, triglycerides, LDL-C, and total cholesterol in patients with T2DM. Moreover, lower serum glucose and lipid were maintained even when the individuals were not consuming cinnamon for 20 days. In a randomized, placebo-controlled double-blind clinical trial, intake of $2g \cdot day^{-1}$ of cinnamon for 12 weeks significantly reduces HbA_{1c} and systolic and diastolic blood pressure among poorly controlled T2DM patients compared to placebo (Akilen et al., 2010). Moreover, fasting blood glucose was significantly decreased compared to baseline. In opposition to these findings, Vanschoonbeek and colleagues (Vanschoonbeek et al., 2006) concluded that that cinnamon supplementation for 6-7 weeks at $1.5g \cdot day^{-1}$ does not improve fasting plasma glucose or insulin concentrations, whole body oral glucose tolerance, or lipid profiles in postmenopausal women with T2DM.

The antioxidant benefit of cinnamon has also been elucidated, suggesting a potential *in vivo* mechanism by which cinnamon acts. Subjects with impaired fasting glucose were assigned either 500mg·day^{-1} of an aqueous cinnamon extract or placebo for 12 weeks (Roussel et al., 2009). The cinnamon extract was shown to increase FRAP and plasma thiol groups, while decreasing MDA levels. In healthy humans, cinnamon supplementation at 3g·day^{-1} for 14 days reduced the glucose and insulin response to an OGTT (Solomon & Blannin, 2009). However, these effects were lost following cessation of cinnamon supplementation. Acutely, cinnamon ingestion reduced plasma glucose AUC and improved insulin sensitivity in inactive, healthy men (Solomon & Blannin, 2007).

6.1.15 Turmeric

Another spice proposed to have glucoregulatory effects is *Curcuma longa* (turmeric), due to its active component, curcumin. Curcumin is believed to have antioxidant and anti-inflammatory properties (Hsu & Cheng, 2007). A four week intervention study revealed no changes in fasting glucose or lipid profiles when 2.8g·day^{-1} turmeric was given to healthy subjects (Tang et al., 2008). However, acute ingestion of 6g *Curcuma longa* in healthy subjects had a significant effect on postprandial insulin levels, without influencing glucose (Wickenberg et al., 2010).

6.1.16 Banaba and Berberine

Lagerstroemia speciosa L. (banaba) standardized to 1% corosolic acid (Glucosol™) at daily dosages of 32 and 48mg·day^{-1} for two weeks showed a significant reduction in blood glucose in T2DM patients (Judy et al., 2003). Acutely, corosolic acid also attenuated the postprandial rise in blood glucose post-OGTT, in a mixed sample of IGT, IFG, and healthy subjects (Fukushima et al., 2006). Berberine is a natural plant alkaloid isolated from the Chinese herb, *Coptis chinensis* (Huanglian). Chronically supplemented at 1g·day^{-1} to dyslipidemic T2DM patients for three months, berberine was associated with significantly improved levels of fasting and postprandial blood glucose, HbA_{1c}, triglycerides, total cholesterol, LDL-C, blood pressure and IL-6, compared to placebo (Zhang et al., 2008). Moreover, markers of insulin sensitivity were improved in the berberine group, albeit, non-significantly. A similar investigation comprised of two components (study A and study B) also evaluated the efficacy of berberine in T2DM patients for 3 months (1.5g·day^{-1}) (Yin et al., 2008). Study A found that berberine had similar hypoglycemic effects to the anti-diabetic drug metformin. Significant decreases were noted in fasting and postprandial blood glucose, HbA_{1c}, and triglycerides were observed in the berberine group and in the metforin group (as expected). Study B consisted of the combination therapy, berberine (1.5g·day^{-1}) added to subjects' usual anti-diabetic medicine, again for 3 months. Significant reductions compared to baseline were found in fasting and postprandial blood glucose, HbA_{1c}, fasting insulin, insulin sensitivity, and lipid profile, including triglycerides, total cholesterol, and LDL-C. A proprietary blend of Phellodendron (which contains the active ingredient berberine) and Crape Myrtle (banaba; *Lagerstroemia speciosa* L.) has been shown to lower the postprandial glucose response to a modified OGTT, while resulting in a non-significant attenuation in insulin response, in a small sample of healthy, exercise-trained men (Canale et al., In Review). It is possible that a combination of nutrients may provide the most favorable effect on postprandial glucose response.

6.1.17 Fenugreek

Two months of supplementation with *Trigonella foenum graecum* (fenugreek) seeds in newly-diagnosed T2DM patients significantly attenuated incremental AUC of blood glucose and insulin, as well as demonstrating a trend to improve fasting and two hour postprandial glucose (Gupta et al., 2001). The rise in triglycerides and cholesterol were also significantly improved, along with insulin sensitivity and HDL-C after supplementation. Moreover, 12 weeks of supplementation with Fenugreek elicited significant decreases in fasting blood glucose, postprandial blood glucose, and HBA_{1c} (Lu et al., 2008). Acutely, Fenugreek added to two slices of bread (5% fenugreek), and fed to a small sample of T2DM patients, was shown to significantly reduce the AUC for insulin (Losso et al., 2009). Glucose AUC also tended to be improved.

6.1.18 Stevia

Steviol glycosides (or stevioside), isolated from the plant *Stevia rebaudiana Bertoni* and taken for three months ($250mg \cdot day^{-1}$) by patients with T1DM and T2DM, as well as by healthy controls, was not shown to elicit any significant differences in markers of glycemic control or blood pressure (Barriocanal et al., 2008). Acutely however, 1g of steviol glycosides reduced postprandial blood glucose levels in T2DM patients and increased the insulinogenic index ($AUC_{insulin}/AUC_{glucose}$) (Gregersen et al., 2004). The differences in dosages used in each respective study may be the reason for these conflicting results.

6.1.19 Gymnema sylvestre

Early intervention trials with *Gymnema sylvestre* ($400mg \cdot day^{-1}$) were associated with improved glycemic control in NIDDM patients (Baskaran et al., 1990) and insulin-dependent DM patients (Shanmugasundaram et al., 1990). Moreover, there was a significant improvement in terms of insulin response and lipid profiles, encompassing cholesterol, triglycerides, and free fatty acids. A more recent investigation, illustrated that $1g \cdot day^{-1}$ for 60 days of Om Santal Adivasi®, a novel high molecular weight *Gymnema sylvestre* extract, induced significant increases in circulating insulin and C-peptide, which were associated with significant reductions in fasting and postprandial blood glucose (Al-Romaiyan et al., 2010).

6.1.20 Cissus quadrangularis

Cissus quadrangularis is a relatively novel ingredient in the clinical setting; however, the few investigations that do exist exhibit a remarkable efficacy. In three clinical investigations (J. E. Oben et al., 2006; J. E. Oben et al., 2007; J. E. Oben et al., 2008), c*issus quadrangularis* supplemented to obese and overweight persons for 6-8 weeks has elicited significant net reductions in weight, body fat, fasting blood glucose, total cholesterol, LDL-C, triglycerides, C-reactive protein, biomarkers of oxidative stress, as well as a significant increase in HDL-C. As all work was conducted by the same group of investigators, additional studies performed by other research groups are needed to corroborate these findings.

6.1.21 Coccinia indica

Coccinia indica (*Coccinia cordifolia*) supplemented to T2DM patients for 90 days elicited a significant reduction in fasting and postprandial blood glucose and HbA_{1c}; however, there was no significant change in serum lipids, except for LDL-C (Kuriyan et al., 2008). In an

earlier study, *Coccinia indica* powder, from crushed, dried leaves, significantly improved glycemic control following six weeks use in patients with poorly controlled or otherwise untreated T2DM (A. K. Khan et al., 1980). Moreover, animal data suggests that *Coccinia indica* has potentially beneficial antioxidant properties (Venkateswaran & Pari, 2003).

6.1.22 Nopal

The literature pertaining to *Opuntia Streptacantha* (Nopal or Prickly Pear Cactus) has been available for several years, and demonstrates efficacy in a dose-dependent manner, when its stems are broiled and provided to T2DM patients (Frati-Munari, Del Valle-Martinez et al., 1989). However in a follow up study, Nopal extract in encapsulated form did not reduce fasting glycemia in T2DM patients; however, the extract did diminish the increase of postprandial glucose following an OGTT (Frati-Munari, de Leon et al., 1989). Chronically, the efficacy of Nopal requires additional clarification (Frati Munari et al., 1992).

6.1.23 Ginseng

Ginseng has received considerable attention, dating back to ancient Chinese medicine (Y. Z. Xiang et al., 2008). Chronically, Korean red ginseng (*Panax ginseng*) supplemented for 12 weeks (6g·day^{-1}) in well controlled T2DM patients, significantly improved fasting insulin and insulin sensitivity, as well as postprandial glucose and insulin following an OGTT (Vuksan et al., 2008). However, supplementation did not significantly improve the primary endpoint HbA_{1c}. In healthy subjects, *Panax ginseng* supplemented for 57 days (200mg·day^{-1}), in a randomized crossover design, had no effect on fasting or postprandial measures of glucose regulation (Reay et al., 2009). Acutely, American ginseng (*panax quinquefolius* L.) has been shown to be beneficial in reducing postprandial glucose in T2DM patients irrespective of dose (3g, 6g, or 9g) (Vuksan, Stavro et al., 2000) or timing of consumption (40 minutes before a test meal or immediately preceding) (Vuksan, Sievenpiper et al., 2000). On the other hand, in healthy subjects, the postprandial response to supplementation was dependent on the timing of administration (Vuksan, Sievenpiper et al., 2000; Vuksan et al., 2001); however, like diabetic subjects, the dose did not influence the findings (1g, 2g, 3g) (Vuksan et al., 2001).

6.1.24 Russian tarragon

Russian tarragon (*Artemisia dracunculus* L.) is a relatively novel ingredient and to date only one reported investigation is available regarding its anti-diabetic effects in humans. An aqueous extract of Russian tarragon provided to a sample of healthy, exercise-trained men, did not significantly influence glucose or insulin response to an OGTT (Bloomer, Canale et al., 2011). However, approximately two-thirds of subjects ingesting the Russian tarragon did experience attenuation in both the glucose and insulin in response to the OGTT. It is possible that more favorable effects would be noted in a sample of diabetic subjects, as has been the case for animal (Zuberi, 2008) and cell culture (Z. Q. Wang et al., 2008) studies using Russian Tarragon.

6.1.25 Bitter Mellon

Despite being a frequently used ingredient within insulin mimetic and hypoglycemic agents sold as dietary supplements, *Momordica charantia* (bitter melon) has been shown to be relatively ineffective in attenuating measures of glycemia chronically in T2DM patients

(Dans et al., 2007) or acutely, following an OGTT (Kasbia, et al. 2009), in a sample of non-diabetic overweight men. Nonetheless, animal studies support its potential at ameliorating glycemic control, lipid profiles, and antioxidant status (Chaturvedi & George, 2010) and one recent human study supports a modest hypoglycemic effect at 2000 mg·day^{-1} for four weeks in T2DM patients (Fuangchan et al., 2011).

6.1.26 Garlic

Treatment with garlic (*Allium sativum*) has also elicited beneficial anti-diabetic effects. A garlic tablet taken at 600mg·day^{-1} for 12 weeks was shown to significantly reduce total cholesterol and LDL-C, and moderately raise HDL-C compared to placebo (Ashraf et al., 2005). In a later trial, a time-released garlic tablet, Allicor (600mg·day^{-1}), was investigated for four weeks using a double-blinded placebo controlled study with T2DM patients (Sobenin et al., 2008). Allicor was shown to significantly lower fasting blood glucose levels, serum fructosamine, and triglyceride levels.

6.1.27 Vinegar

Vinegar has been successfully added to feedings to ameliorate the glycemic response. In patients with T2DM, 20g of wine vinegar has been shown to reduce postprandial glucose and insulin AUC when added to a high, but not to a low, glycemic index meal (Liatis et al., 2010). In a four part investigation, the anti-glycemic properties of vinegar were investigated (Johnston et al., 2010). Pertinent for the present discussion, trial 4 examined whether a "vinegar pill" (i.e., the neutralized salt of acetic acid, sodium acetate) possessed anti-glycemic effect in individuals with T2DM, when compared to 20g of traditional vinegar (1g acetic acid), and placebo. Treatments were administered two minutes before a test meal and the results indicated that only acetic acid was effective at attenuating postprandial blood glucose. The other results from this overall investigation consisted of healthy subjects; however, trial 1 found that 10g of vinegar (0.5 acetic acid) was better at reducing postprandial blood glucose compared to 20g vinegar and 2g vinegar. Trial 2 indicated that vinegar (20g) ingested at meal time elicited a greater attenuation of postprandial glucose compared to five hours before the meal, albeit non-significantly. Finally, trial 3 indicated that the anti-glycemic effect of vinegar is best realized when ingested with food composed of complex carbohydrates and that vinegar may not attenuate postprandial glucose following the consumption of foods sweetened with dextrose, as is the case for many processed beverages and foods.

6.2 Macronutrients

6.2.1. Amino acids

The postprandial oxidative stress response to a macronutrient protein meal has been shown to be relatively diminutive in comparison to an isoenergetically comprised carbohydrate, lipid, and mixed composition meals (Fisher-Wellman & Bloomer, 2010). Moreover, endothelial dysfunction has been shown to be neutralized when proteins are added to a high fat meal (Westphal et al., 2006). Therefore, it is not surprising that amino acids, in particular L-arginine (one of the precursors to nitric oxide), have been investigated as a nutritional intervention for diabetes control. Amino acids (L-leucine; L-lysine; L-isoleucine; L-valine; L-threonine; L-cysteine; L-histidine; L-phenylalanine; L-methionine; L-thyrosine; and L-tryptophan) supplemented to elderly T2DM patients for 60 weeks (8g·day^{-1}) significantly

decreased HbA_{1c}, fasting and postprandial blood glucose, fasting insulin, and insulin resistance (Solerte et al., 2008). Intravenous infusion of L-arginine ($0.52mg \cdot kg^{-1} \cdot min^{-1}$) in a mixed sample of NIDDM, obese, and healthy subjects restored the impaired insulin-mediated vasodilation observed in obese and NIDDM patients (Wascher et al., 1997). Moreover, insulin sensitivity was improved significantly in all three groups. In healthy subjects, an oral dose of L-arginine as low as 2.5g and as high as 15g, supplemented concomitantly with a high fat meal, has been shown to significantly improve endothelial function (Borucki et al., 2009; Lin et al., 2008) and favorably impact biomarkers of oxidative stress (Lin et al., 2008).

6.2.2 Nuts

The consumption of nuts could provide a benefit to those with T2DM given that nuts have an excellent nutritional profile, are high in monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), contain polyphenols, and are a fair source of vegetable protein. However, results have been conflicting in diabetic and healthy populations with regards to the impact of nut intake on measures of glycemic regulation. In two studies (presented within one manuscript) Lovejoy et al. (Lovejoy et al., 2002) assessed the effect of almond-enriched diets on insulin sensitivity and lipids in patients with T2DM or healthy volunteers. Study one determined the effect of almonds on insulin sensitivity in healthy volunteers who received $100g \cdot day^{-1}$ of almonds for four weeks. Results indicated that total cholesterol and LDL-C decreased significantly; however, there was no effect on insulin sensitivity. Study two was a randomized crossover design that compared 4 diets in T2DM patients, each diet being four weeks in duration. The high-fat, high-almond diet had the greatest decrease in total cholesterol; however, no diet impacted fasting glucose, postprandial glucose (following an OGTT), or HbA_{1c}. Tapsell et al. (Tapsell et al., 2004) found that a moderate-fat diet inclusive of walnuts for six months, significantly increased the plasma HDL-C: total cholesterol ratio and HDL-C, and significantly decreased plasma LDL-C in subjects with T2DM. Additionally, triglycerides showed a trend to be improved in the intervention group. However, there were no significant differences between treatment groups regarding total antioxidant capacity or HbA_{1c} levels. In subjects with metabolic syndrome, Davis et al. (Davis et al., 2007) noted non-significant effects in oxidative stress biomarkers after an 8 week walnut or cashew diet, despite ORAC being significantly higher compared to the control diet. Twelve weeks of mixed nut consumption ($30g \cdot day^{-1}$) in 50 subjects also with metabolic syndrome was found to decrease DNA damage compared to the control group (Lopez-Uriarte et al., 2010). The nut group also tended to have less oxidative stress, as indicated by reductions, albeit non-significantly, in ox-LDL-C, conjugated diene formation, and 8-isoprostanes in urine. Null findings were reported for antioxidant capacity, endothelial function, and lipid profiles. Finally, in healthy subjects, walnut consumption for six weeks did not significantly change the plasma antioxidant capacity (McKay et al., 2010). Interestingly, plasma total cholesterol, LDL-C, and triglyceride levels decreased significantly compared to baseline in the lower dose group ($21g \cdot day^{-1}$).

In healthy volunteers, acute almond intake has been shown to reduce glucose AUC after consuming 50g of white bread, in a dose dependent manner, as well as lowering total cholesterol levels (Josse et al., 2007). Moreover, almonds were shown to decrease the glycemic and insulinemic responses to white bread, and increase the serum protein thiol concentration, indicating less oxidative protein damage. Acute consumption of pecans by

healthy subjects has been shown to significantly decrease ox-LDL-C, and increase the flavonoid EGCG (Hudthagosol et al., 2011). Additionally, the molar ratio of MDA: triglyceride was significantly lower as compared to baseline following the pecan meals (pooled data).

6.2.3 Fiber

Viscous fiber affects metabolism by its actions within the proximal digestive tube (Hunt et al., 1993). In the colon, soluble fibers bind, absorb, or sequester bile acids, products of fat digestion, fatty acids, and monglycerides during passage through the intestinal luman (Hunt et al., 1993). Moreover, soluble fibers delay gastric emptying and increase unstirred water in the small bowl producing satiety (Gray, 1995). These effects appear to make dietary fiber a beneficial intervention for patients with T2DM. Three doses of 5g·day^{-1} psyllium for six weeks was shown to significantly reduce fasting plasma glucose, total cholesterol, LDL-C, and triglycerides, as well as significantly increase HDL-C in patients with T2DM (Rodriguez-Moran et al., 1998). Similarly, 14g·day^{-1} of psyllium for six weeks significantly decreased postprandial glucose absorption, fructosamine, total cholesterol, and LDL-C cholesterol in T2DM patients (Sierra et al., 2002). Other markers of glycemic control also tended to be lower, albeit non-significantly. Guar gum for 48 weeks at 15g·day^{-1} in subjects with NIDDM has been shown to improve long-term glycemic control, postprandial glucose tolerance, and LDL-C (Groop et al., 1993). Finally, dietary assignment to food products that contained oat β-glucan in hypertensive subjects showed a favorable effects on postprandial glucose and insulin levels, as well as blood pressure, after 12 weeks of treatment. (Maki, Galant et al., 2007). However, these beneficial effects were independent of differences in oxidative stress biomarkers.

Acutely, high-viscosity hydroxypropylmethylcellulose (HV-HPMC) has been found to blunt postprandial glucose and insulin in a dose-dependent manner in subjects at risk for the development of T2DM (Maki et al., 2007; Maki et al., 2009). Moreover, triglyceride incremental AUC during the postprandial period was significantly lower after the consumption of 15g psyllium compared to 3g, and chylomicron levels were also influenced in this dose-dependent manner in overweight and obese men (Khossousi et al., 2008).

6.3 Whole food dietary intervention

Although supplementation with isolated ingredients provides unique insight into the beneficial effects of selected nutrients on human health, dietary interventions in which whole food intake is significantly altered in an attempt to improve health may have even more impact. One dietary approach that has received considerable attention is the Mediterranean diet—a plan rich in the intake of olive oil.

Acutely, extra virgin olive oil has been shown decrease postprandial inflammatory markers and up-regulate antioxidant capacity (Bogani et al., 2007). As a consequence of proposed benefit of olive oil, coupled with the supporting evidence for the consumption of red wine, the Mediterranean diet has been met with a good degree of success. For example, in overweight men followed for 24 months, the Mediterranean diet, with or without caloric restriction, resulted in improved fasting measures of glucose, insulin, oxidative stress, total cholesterol, blood pressure, and adiponectin (Esposito et al., 2010). In elderly subjects, consumption of the Mediterranean diet for four weeks was shown to induce a reduction in endothelial dysfunction and improve the regenerative capacity of the endothelium (Marin et al., 2011). Specifically it was found that the Mediterranean diet led to lower total

microparticle, activated endothelial microparticle, and apoptotic endothelial microparticle concentrations, and a higher number of endothelial progenitor cells compared to the other diets. Moreover, the Mediterranean diet was associated with lower oxidative stress and elevated β-carotene concentrations. Finally, in an elderly population, the Mediterranean diet alone for four weeks was found to improve postprandial oxidative stress with a higher increase in capillary flow and nitric oxide levels, lower lipid peroxidation products, and a lower postprandial decrease in HDL-C compared to a diet rich in saturated fat (Yubero-Serrano et al., 2010). Moreover, CoQ_{10} supplemented to the Mediterranean diet further improved postprandial levels of oxidative stress and elicited a superior increase in capillary flow and nitric oxide levels, with respect to the other diets.

We have recently demonstrated the beneficial metabolic and cardiovascular effects of a dietary restriction model known as the Daniel Fast. The Daniel Fast involves a 21 day *ad libitum* food intake period, devoid of animal products and preservatives, and inclusive of fruits, vegetables, whole grains, legumes, nuts, and seeds. In our first study, the Daniel Fast elicited a significant lowering of total cholesterol, LDL-C, HDL-C, SBP, and DBP. Moreover, insulin, HOMA-IR, and C-reactive protein all showed a trend for improvement (Bloomer, Kabir, Canale et al., 2010). Improvements were also noted in several measures of oxidative stress and antioxidant capacity (Bloomer, Kabir, Trepanowski et al., 2011). In a follow-up study involving this model, both resting and postprandial biomarkers were favorably impacted (unpublished findings), suggesting that this form of eating (e.g., stringent vegan diet) may be associated with multiple favorable effects on metabolic and cardiovascular health. Longer term studies are needed to determine the potential impact of the acute changes on health and disease over time.

Other dietary interventions exist that have been investigated and proposed to have beneficial effects on metabolic and cardiovascular risk factors. The Portfolio Diet developed by Jenkins et al. (Jenkins et al., 2007) consists of using combinations of cholesterol-lowering foods within one diet, rather than single foods, to achieve more favorable effects on serum cholesterol. The dietary portfolio currently contains four main elements with proven cholesterol lowering efficacy, some of which have been highlighted in the preceding text. These include soy, viscous fibers, plant sterols, and nuts. In a similar manner as the Daniel Fast, the Portfolio Diet encourages the consumption of foods that are traditionally found in a vegetarian/vegan plan, which may prove beneficial for controlling and preventing T2DM (Tonstad et al., 2009). Readers are referred to the following papers for more information on such diets (Jenkins et al., 2003; Key et al., 2006).

Finally, although emphasis in this section is on specific nutrients and types of dietary approaches to improve metabolic health, it should be noted that a reduction in dietary energy and modification of portion sizes should be considered. Indeed, the literature pertaining to caloric restriction is lengthy, with multiple known benefits with a reduction in normal dietary energy intake (Civitarese et al., 2007; Redman et al., 2009).

6.4 Summary of nutrients

As illustrated above, results for improvement in selected markers of cardiovascular and metabolic health through dietary manipulation in individuals with T2DM have been mixed. Some potential reasons for conflicting findings across studies include the degree of diabetic complication, the timing and dosage of dietary supplement or food, the duration of treatment, and the fact that some individuals are noted "responders" and others are "non-

Exercise	What to Include	What to Consider
Aerobic	• Walking, Jogging, Cycling, Stepping, Swimming, etc. • (Most or all days of week; 30-60 minutes; 50-80% of VO_{2max})	• Interval training – light running (50-60% of VO_{2max}) combined with short, fast bursts of running (1-2 days per week; 20-40min) • Sports and physical activities (e.g., soccer, basketball)
Anaerobic	• Resistance exercise: free weights and/or machines • (2-3 days per week; 30-45 minutes; 50-80% 1RM)	• Maximal-intensity repetition training (1 day per week; 80-100% 1RM—focus on development of muscular strength)

Whole Food Intake	What to Include	What to Consider	What to Avoid
	Whole grains, fruits, vegetables, beans, nuts, seeds, low fat or fat free dairy, lean poultry, fish, olive oil, vinegar	Red wine (in moderation), tea (green or black)	Saturated fat, processed carbohydrate, packaged foods, sugar-rich carbonated beverages
Nutritional Supplements	**What to Consider (Suggested Dosage)**		**What Requires More Research***

	• Amino acids (8.0g·day^{-1})
	  • L-arginine (2.5-15g·day^{-1})
	• Antioxidants
	  • α-Lipoic acid (0.3-1.8g·day^{-1})
	  • Vitamin C (1.0-2.0g·day^{-1})
	  • Vitamin E (0.6-0.9g·day^{-1})
	• Banaba/corosolic acid (*Lagerstroemia speciosa* L.) (0.1-0.5g·day^{-1})
	• Berberine (1.0-1.5g·day^{-1})
	• Cinnamon (0.5-6.0g·day^{-1})
	• Fenugreek (*Trigonella foenum graecum*) (8.0-10.0g·day^{-1})
	• Fish oil (omega-3 fatty acids; EPA, DHA) (1.0-4.0g·day^{-1})
	• Ginseng (*Panax ginseng* or *Panax quinquefolius* L.) (1.0-6.0g·day^{-1})
	• Garlic extracts (0.6g·day^{-1})
	• Magnesium (0.6-2.5g·day^{-1})
	• Multi-vitamins (≥1.0g·day^{-1})
	• Tea catechins (0.6-1.0g·day^{-1})
	• Vitamin D (≥700IU·day^{-1})
			• Coenzyme Q_{10}
			  • Lycopene
			  • Bitter melon (Momordica charantia)
			• Carnitine
			• Chromium
			• Cissus quadrangularis
			• Coccinia indica
			• Gymnema sylvestre
			• Inositol phosphoglycans (pinitol)
			• Nopal or Prickly Pear Cactus (*Opuntia Streptacantha*)
			• Russian tarragon (Artemisia dracunculus L.)
			• Selenium
			• Steviol glycosides (Stevia rebaudiana Bertoni)
			• Turmeric (Curcuma longa)
			• Vanadium

*Current concerns exist regarding efficacy—especially in diabetic populations, paucity of data, dosage, or safety.

Table 1. Lifestyle approach to improving metabolic health at rest and in response to feeding

responders" to treatment (in the same manner as certain individuals respond better to certain drugs than do others). Additional, well-controlled investigations are needed to clarify which nutrients and which dietary models may be most conducive to improving the metabolic profile at rest and in response to feeding—in particular as related to oxidative stress.

7. Conclusions and practical application

As there currently exists no cure for diabetes, lifestyle factors should be strongly considered as the first line treatment for this disease—as these activities may improve fasting and postprandial lipid and glucose metabolism, as well as antioxidant capacity. Collectively these effects may help to minimize postprandial oxidative stress. The rationale for regular and structured exercise (Praet & van Loon, 2007; Tucker et al., 2008), coupled with the intake of a nutrient dense, macronutrient balanced, and portion controlled eating plan (Bloomer, Kabir, Canale et al., 2010; Bloomer, Kabir, Trepanowski et al., 2011; Jenkins et al., 2007), complete with use of selected nutrients to aid in both glucose and triglyceride processing (Badimon et al., 2010; Davi et al., 2010; Nahas & Moher, 2009), appears well supported. Suggestions are provided in Table 1. Adherence to these guidelines, or those which are similar, may be associated with improved metabolic control in both the fasting and fed state. This may be met with a reduction in RONS production and ensuing oxidative stress, which may be correlated to improved health and quality of life (Frisard & Ravussin, 2006), and a reduction in disease progression over time (Ceriello & Motz, 2004).

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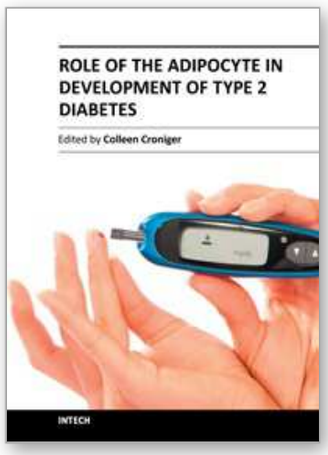
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Role of the Adipocyte in Development of Type 2 Diabetes

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Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

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