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Macronutrient intake induces oxidative and inflammatory stress: potential relevance to atherosclerosis and insulin resistance

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Abbreviations: 13-HODES, 13-hydroxyoctadecadienoic acid; AMI, acute myocardial infarction; AP-1, activator protein-1; BP, blood pressure; CCL-2, CC chemokine ligand 2; CCR-2, CC chemokine receptor 2; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DART, diet and reinfarction trial; DHA, docosahexaenoic acid; Egr-1, early growth response 1; EPA, eicosapentaenoic acid; GGT, gamma-glutamyl transpeptidase; GISSI, gruppo Italiano per lo studio della sopravvivenza nell'Infarto miocardico; GSK-3β, glycogen synthase kinase-3β; HFHC, high fat high carbohydrate; HNF, hepatic nuclear factors; ICD, implantable cardioverter-defibrillator; IKK, IκB kinase; IRS-1, insulin receptor substrate 1; IRS-2, insulin receptor substrate 2; JELIS, Japan EPA lipid intervention study; LXR, liver X receptor; MCP-1, monocyte chemoattractant protein-1; MI, myocardial infarction; MMP-2, matrix metalloproteinases 2; MRFIT, multiple risk factor intervention; mTOR, mammalian target of rapamycin; PECAM, platelet endothelial cell adhesion molecule; PGI3, prostacyclin I3; PI3-kinase, phosphoinositide 3-kinase; PPAR, peroxisome proliferator activated receptors; RCTs, randomized controlled trials; ROS, reactive oxygen species; RR, relative risk; RXR, retinoid X receptors; S-6-K, ribosomal protein S6 kinase; SCFA, short chain fatty acids; SOCS-3, suppressor of cytokine signaling-3; SREBP-1c, sterol regulatory binding protein-1c; TBARS, plasma concentrations of thiobarbituric acid-reactive species; TF, tissue factor; TLR-4, toll-like receptor 4; t-PA, tissue plasminogen activator; VT, ventricular tachycardia

Abstract

With the global increase in the epidemic of obesity and type 2 diabetes with a concomitant increase in atherosclerotic disease, an investigation into the effects of various macronutrients and food products has become necessary. Such investigation will allow us to better understand the relationship between the intake of various macronutrients and the pathogenesis of mechanisms underlying the regulation of insulin sensitivity and resistance, oxidative stress and inflammation, the regulation of hunger and satiety and atherogenesis. This review covers the first decade of work in this area relating the intake of usual foods and diets to their immediate and long term outcomes. The review also covers the exciting novel area of anti-inflammatory effects of certain foods. Hopefully, a comprehensive understanding of these actions of macronutrients and their long term effects will allow us to formulate food combinations which will lead to healthy eating habits and improvement in our overall health status.

Keywords: atherosclerosis; inflammation; insulin resistance; micronutrients; oxidative stress; diabetes mellitus, type 2

Introduction

The association of obesity with chronic low grade inflammation and insulin resistance is well established (Hotamisligil *et al*., 1993; Festa *et al*., 2000). The facts that obesity is the most powerful risk factor for type 2 diabetes and that increased concentrations/expression of inflammatory mediators in the obese predicts the occurrence of future diabetes are also well established (Pradhan *et al*., 2001). In addition, type 2 diabetes is also known to be associated with chronic inflammation (Pickup *et al*., 1997). Recent data also demonstrate that inflammatory mediators may interfere with insulin signal transduction (Hotamisligil *et al*., 1996; Ghanim *et al*., 2007a). These facts reinforce the importance of inflammation in the pathogenesis of insulin resistance and type 2 diabetes. So, what is the link between these facts and what is the origin

of this inflammation?

Macronutrient intake, oxidative stress and inflammation

Since the relationship between obesity and insulin resistance is a dynamic one and weight gain leads to increased resistance and weight loss to a reduction in insulin resistance, it is possible that macronutrient intake may be crucial and central to these relationships. This concept led us to investigate whether macronutrient intake leads to an increase in inflammation and caloric restriction leads to a reduction in inflammation. Since oxidative stress and reactive oxygen species (ROS) generation lead to the activation of redox sensitive pro-inflammatory transcription factors (Woronicz *et al*., 1997; Wang *et al*., 1999), we also studied the effect of macronutrient intake and caloric restriction on ROS generation and oxidative stress.

The first demonstration that a macronutrient induces ROS generation was made when it was shown that the intake of glucose by normal subjects leads to an increase in ROS generation by polymorphonuclear (PMN) and mononuclear (MNC) leucocytes (Mohanty *et al*., 2000). This could be inhibited by diphenyl iodonium, an inhibitor of NADPH oxidase and was measured by chemiluminescence with luminol in the medium. It was, therefore, concluded that this increase in superoxide (ROS) generation was from the leukocyte membrane and that superoxide was released into the extracellular medium. Consistent with this, there was an increase in the expression of p47phox, a key subunit of the enzyme NADPH oxidase which converts molecular O_2 into superoxide. A similar effect was also observed with saturated fat (cream) and to a much smaller extent with protein (casein) (Mohanty *et al*., 2002). Although the magnitude of this effect (area under the curve) was similar for glucose and cream, the peak effect of glucose was at 2 h with a decline at 3 h. The progression of this effect was slower for cream and there was a persistence of this effect at 3 h without a significant decline. A high fat high carbohydrate (HFHC) meal induced a similar effect with an increase in ROS generation and an increase in $p47^{phox}$ expression (Aljada *et al*., 2004b). The other source of ROS following glucose intake is the mitochondrion. Superoxide radicals are generated from the electron transport chain during the metabolism of glucose and other metabolites.

Since, as stated above, several of the pro-inflammatory transcription factors are redox sensitive, and it seemed likely that the stimulation of ROS generation would be associated with the activation of these transcription factors, we investigated them and the genes which would be stimulated by them. NF-κB, activator protein-1 (AP-1) and early growth response 1 (Egr-1) are activated by the intake of glucose; accompanying this activation, there is an increase in the expression of TNFα, matrix metalloproteinases 2 (MMP-2), matrix metalloproteinases 9 (MMP-9) and tissue factor (TF) (Aljada *et al*., 2004a). The activation of NFκB has also been shown by an HFHC meal (Aljada *et al*., 2004b). This is achieved through the activation of IκB kinase (IKK) and the phosphorylation of IκBα (IκBα). Since the binding of IκBα to NFκB is required for the prevention of the nuclear translocation of NFκB and since the phosphorylation of IκBα leads to the dissociation of IκBα from NFκB, NFκB translocates into the nucleus and activates the transcription of pro-inflammatory genes including TNFα (Barnes and Karin, 1997). Similarly, the activation of AP-1 leads to the transcription of MMP-2 and MMP-9 and that of Egr-1 to the transcription of TF. Thus, the intake of glucose leads to oxidative and inflammatory stress and a prothrombotic state. Our more recent work shows that a large HFHC meal induces a more intense and prolonged oxidative and inflammatory stress response in the obese than that in normal weight subjects (Patel *et al*., 2007). This is consistent with the fact that obesity is a pro-inflammatory state (Ghanim *et al*., 2004). These data also raise the question whether obesity is also associated with increased oxidative stress.

Increased oxidative stress with obesity and its reversal following caloric restriction and weight loss

Indeed, human obesity is associated with both inflammatory and oxidative stress. Plasma concentrations of thiobarbituric acid-reactive species (TBARS), 9-hydroxyoctadecadienoic acid (9-HODES) and 13-hydroxyoctadecadienoic acid (13-HODES), and ortho-tyrosine and meta-tyrosine concentrations are elevated in the obese in the fasting state (Dandona *et al*., 2001a; Ghanim *et al*., 2004). These indices as well as ROS generation by mononuclear and polymorphonuclears fall dramatically with caloric restriction and weight loss over a relatively short period of two weeks (Dandona *et al*., 2001b). Plasma concentrations of TNFα and adipose tissue expression of TNFα are also increased in the obese and tend to decrease with caloric restriction and weight loss (Dandona *et al*., 1998). These data are further reinforced by the fact that even in normal subjects, a 48 h fast results in the reduction of ROS generation by $>50\%$, with a

reduction of 35% at 24 h (Dandona *et al*., 2001c). This is associated with a parallel reduction in p47phox expression.

Non-inflammatory and anti-inflammatory foods

In view of these dramatic acute effects of macronutrient intake in inducing oxidative and inflammatory stress and equally impressive effects of caloric restriction and weight loss in reversing it, the question of whether there are some non-inflammatory foods is raised. Three sets of data have been obtained confirming this concept. Firstly, alcohol (300 Calories) does not induce oxidative and inflammatory stress (Dhindsa *et al*., 2004). Secondly, orange juice (300 Calories) does not induce oxidative and inflammatory stress (Ghanim *et al*., 2007b). Thirdly, a high fiber and fruit meal based on AHA guidelines does not induce either oxidative or inflammatory stress when compared to an equicaloric HFHC (900 Calorie) meal (Ghanim *et al*., 2009).

Our most recent data demonstrate that the intake of orange juice with a high fat high carbohydrate meal leads to the total neutralization of the pro-inflammatory effects of the meal (AJCN, in press). In this study, we observed that the concomitant intake of orange with a HFHC meal led to an almost total inhibition of ROS generation, the increase in NFκB binding, the increase in MMP-9 concentration and the increase in the expression of several pro-inflammatory genes. Since two major flavonoids contained in orange juice, naringenin and hesperidin, exert a powerful ROS suppressive effect, it is likely that they contribute to this effect (Ghanim *et al*., 2007b). Thus, it is possible in principle to choose non-inflammatory or anti-inflammatory foods to minimize post-prandial oxidative stress and inflammation. This search must, therefore, continue and include substances like flavonoids to reduce post prandial oxidative and inflammatory stress. Red wine intake with a HFHC meal has also been shown to exert a neutralization of its pro-inflammatory effect.

Ethanol (=300 Calories) administered as vodka has also been shown not to induce ROS generation or an increase in NFκB binding (Dhindsa *et al*., 2004).

Anti-inflammatory micronutrients

As discovered in our experiments with orange juice, the flavonoids contained in it, naringenin and hesperidin, were shown to exert a powerful inhibition of ROS generation (Ghanim *et al*., 2007b). Naringenin and hesperidin may thus be potentially be used to prevent post prandial oxidative and inflammatory stress. Our recent work shows that resveratrol also exerts an ROS suppressive and an anti-inflammatory effect. Thus resveratrol could also potentially provide a means for preventing post prandial inflammation. In addition, resveratrol suppresses several pro-inflammatory kinases which interfere with insulin signal transduction (presented at ADA, 2008). It is clear that these compounds need to be investigated extensively for their interesting effects so that scientifically based rational food choices directed at healthy living can be made.

The potent anti-inflammatory effect of Curcumin, the product of turmeric, the yellow Indian spice Curcuma longa is already well recognized (Aggarwal and Harikumar, 2009). Indeed, turmeric has been used for its anti-inflammatory properties in traditional Indian medicine for millennia and curcumin is currently being investigated for several of its potential therapeutic properties. It has been shown to suppress at least two major pro-inflammatory transcription factors, AP-1 and NFκB. It has also been shown to have some cancer suppressive properties, probably through a contribution from its anti-inflammatory actions.

Inflammation may contribute to insulin and leptin resistance

Since inflammatory mediators are known to increase the expression and activity of molecules which interfere with insulin signal transduction, we have also investigated whether these molecules increase post prandially (Hotamisligil *et al*., 1996; Hirosumi *et al*., 2002). Indeed, the expression of the suppressor of cytokine signaling-3 (SOCS-3) increases significantly after the intake of an HFHC meal (Ghanim *et al*., 2009). SOCS-3 is known to interfere with insulin signal transduction at the insulin receptor substrate 1 (IRS-1) level by enhancing the ubiquitination of IRS-1 and by decreasing the association of IRS-1 and phosphoinositide 3-kinase (PI3-kinase) essential for the downstream activation of AKT/PKB (Emanuelli *et al*., 2001; Rui *et al*., 2002). Since SOCS-3 also interferes with leptin signal transduction, the induction of this molecule post prandially would also account for leptin resistance (Bjorbaek *et al*., 1999). Thus, post prandial oxidative and inflammatory stress is not only responsible for a potentially atherogenic milieu but also for insulin and leptin resistance. A cumulative action of such meals may lead to persistent increases in the molecules which interfere with insulin and leptin signal transduction. These observations may also explain to some

extent how excessive and persistent intake of pro-inflammatory meals may lead to concomitant insulin and leptin resistance. It is of interest in this context that a meal rich in fruit and fiber does not induce either oxidative stress or inflammation or an induction of SOCS-3 (Ghanim *et al*., 2009). In an attempt to evaluate which component of the HFHC meal is responsible for the induction of oxidative stress, endotoxemia, inflammation and an increase in the expression of SOCS-3 and toll-like receptor 4 (TLR-4), it has been shown that saturated fat taken as cream induces these all while glucose induces oxidative stress, inflammation and SOCS-3 but not endotoxemia or an increase in TLR-4 expression. In contrast, an equicaloric orange juice does not induce any of these changes (Deopurkar *et al*., 2010).

In order to further establish the link between macronutrient intake, inflammation and the pathogenesis of insulin resistance, we need to investigate several major kinases which have been incriminated as interfering factors in insulin signal transduction. These kinases cause serine phosphorylation of IRS-1 and insulin receptor substrate 2 (IRS-2) and thus block the downstream activation of the insulin signal transduction pathway (Gual, *et al*., 2005; Schenk *et al*., 2008). These kinases include PKC-β2, IKK, glycogen synthase kinase-3β (GSK-3β), ERK, ribosomal protein S6 kinase (S-6-K), JNK, mammalian target of rapamycin (mTOR). Whether their expression or activation increases following macronutrient intake needs to be investigated.

Since insulin exerts a potent anti-inflammatory action (Dandona *et al*., 2001b), any tendency towards interference with that effect is likely to result in a pro-inflammatory effect which may potentially promote insulin resistance further in parallel with increased atherogenesis. Indeed, our preliminary data show that insulin suppresses the expression of GSK-3β, PKC-β2, IKK, mTOR and JNK. This would suggest that insulin may be a potent insulin sensitizer and indeed, our data show that this actually occurs within a few hours of a low dose insulin infusion. Thus, for a given rate of insulin infusion, the amount of glucose that has to be infused increases by 50 to 75% to maintain euglycemia within 3 to 4 h of initiating the infusion.

Post prandial inflammation, chemokines and the homing of monocytes as macrophages in tissues

It has been shown that the chemokine, monocyte chemoattractant protein-1 (MCP-1) or CC chemokine ligand 2 (CCL-2), is secreted by the adipose tissue and that it is likely to be a major factor in attracting monocytes to the adipose tissue (Kanda *et al*., 2006). Its chemoattractant effect is mediated through its receptor on monocytes, CC chemokine receptor 2 (CCR-2) which also binds MCP-2 and eotaxin. Thus, it is important to determine the induction of chemokine and chemokine receptor patterns following the intake of macronutrients.

It is relevant that following the intake of cream, an increase in the expression of platelet endothelial cell adhesion molecule (PECAM) has been demonstrated (preliminary data). PECAM is an adhesion molecule which expressed both by the monocyte and the endothelial cell (Woodfin *et al*., 2007). It facilitates the trans-endothelial movement of the monocyte and other leucocytes. It thus facilitates the entry of these cells into extracellular spaces including the arterial intima and the adipose tissue.

On the basis of the above data, we can now consider whether diets based on the above principles have shown outcomes consistent with those data. These data have been obtained from observational studies and randomized controlled trials (RCTs).

Diets and their effects on cardiovascular outcomes

There is evidence of a causal link between dietary factors and coronary heart disease (CHD). A recent study reviewed 223 prospective cohort studies and 66 randomized controlled trials (RCT) conducted since 1950 to evaluate the effect of diet on CHD (Mente *et al*., 2009). Determination of an association between dietary factors and CHD in cohort studies was made by the Bradford-Hill criteria, which evaluates causality on the basis of strength, consistency, temporality and coherence for each dietary exposure. The evidence from cohort studies was examined for consistency with the findings of randomized trials.

In this comprehensive review, there was evidence to support a protective effect on CHD of intake of nuts (30% reduction), vegetables (23% reduction), monounsaturated fatty acids (20% reduction), fish (19% reduction), marine omega 3 fatty acids (14% reduction), folate (32% reduction), whole grains (19% reduction), dietary vitamins E and C (20-23% reduction), beta carotene (27% reduction), alcohol (29 to 31% reduction), fruits (20% reduction) and fiber (22% reduction). Among diets, the Mediterranean [37% reduction] (higher intake of vegetables, legumes, fruits, nuts, whole grain, cheese or yoghurt, fish and monounsaturated relative to saturated fatty acids) and "prudent"

[27% reduction] (high intake of vegetables, fruit, legumes, whole grains, fish and other seafood) diets had a beneficial effect on CHD. A harmful effect of trans-fatty acids (32% increase), foods with a high glycemic index or load (32% increase) and a western dietary pattern [55% increase] (high intake of processed meat, red meat, butter, high fat dairy products, eggs and refined grains) on CHD was also substantiated by this analysis. Intake of saturated, polyunsaturated fatty acids and total fat, alpha-linolenic acid, meat, eggs and milk were not associated with any significant effect on CHD.

The evidence of causality on the basis of cohort studies was supported by a significant beneficial effect on CHD outcome in RCTs for the Mediterranean diet, and intake of omega 3 fatty acids (see below). The benefits of supplementary folate, beta carotene, Vitamin E and C in cohort studies were not replicated in RCT's. Other diets or nutrients shown to have a benefit or harm in cohort studies have not been evaluated in RCTs.

Mediterranean diets

The Lyon Heart Study demonstrated that the intake of the Mediterranean diet led to a marked reduction in fatal and non-fatal myocardial infarction and the combined outcome of those two and unstable angina, stroke and pulmonary embolism (de Lorgeril *et al*., 1994). There was a reduction in these events by two thirds. Significant beneficial effect of the diet was observed as early as 27 months and was maintained at 44 months.

The intake of fish and fish oil

Intake of fish and fish oil has been shown to have beneficial effects on CHD. Fish and fish oil contain long chain omega 3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These omega 3 fatty acids lower VLDL triglycerides and reduce thrombotic risk by decreasing platelet adhesiveness and increasing bleeding time (Phillipson *et al*., 1985; Holub, 1988; Harris *et al*., 1991; Knapp, 1997). They have also been shown to reduce heart rate, blood pressure, and the vasoconstrictive response to angiotensin II (Kenny *et al*., 1992; Morris *et al*., 1993; Mozaffarian *et al*., 2005). EPA and DHA may also have anti-inflammatory effects as they counter the effect of eicosanoids produced from omega 6 polyunsaturated fatty acids (James *et al*., 2000). EPA and DHA reduce formation of arachidonic acid by inhibiting phopsholipase A2 (Martin, 1998). They also compete for lipoxygenase and cycloxygenase (COX), thereby decreasing pro-inflammatory type 2 eicosanoids and type -4 leukotrienes and increasing formation of prostaglandin E3 (PGE3), prostacyclin I3 (PGI3) and thrombxane A2 (Knapp, 1997; James *et al*., 2000). Oxygenated metabolites of EPA and DHA formed by cyclooxygenase-2 (COX-2) are called resolvins E and D and these oppose the effect of inflammatory prostaglandins (Serhan *et al*., 2008). EPA and DHA may also inhibit the activation of toll like receptors 2 and 4, which are involved in inducing inflammation by activating NFκB (Lee *et al*., 2004).

Fish consumption has been shown to be related inversely to cardiovascular events in the Nurses' Health Study in a most impressive fashion such that in the highest tertile of fish eaters the rate of cardiovascular events was approximately 45% lower largely due to a reduction in CHD deaths and the incidence of non fatal acute myocardial infarction (Hu *et al*., 2002). The intake of fish and ω-3 fatty acids leads to a reduction in thrombotic and thrombo-embolic stroke also shown in the Nurses' Health Study. Compared to subjects eating fish $<$ once/week, patients eating fish once /week had a reduction of relative risk (RR) for stroke to 0.76 and those eating fish between 2 to 4 times a week had a reduction of RR to 0.48. These rates of reduction are similar to those for acute myocardial infarction (AMI). These effects are consistent with the findings of other large cohort studies including the multiple risk factor intervention (MRFIT) trial, the Honolulu Heart Program and the US Physicians Health study (Dolecek, 1992; Rodriguez *et al*., 1996; Albert *et al*., 1998).

Randomized Controlled clinical trials have shown a beneficial effect of fish consumption twice a week or fish oil supplementation at doses of 0.85 grams/day to 5.4 grams/day in primary and secondary prevention of CHD (Jenkins *et al*., 2008). In the DART (Diet and Reinfarction Trial) study, fish intake or fish oil supplementation reduced mortality by 29% in subjects post myocardial infarction (MI) (Burr *et al*., 1989). In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) study consumption of 850-882 mg of EPA and DHA daily for 3.5 yr post MI was shown to reduce the incidence of AMI, reduce CVD mortality by 30% and decrease sudden cardiac death by 45%. (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, 1999) More recently, in the Japan EPA Lipid Intervention study (JELIS), 1,800 mg of EPA reduced major coronary events by 19% and incidence of unstable angina by 29% (Yokoyama *et al*., 2007). Fish oil has also been shown to have anti-arrhythmic effects through inhibition of sodium and L-type calcium channels. In prospective cohort studies and randomized

controlled trials fish oil consumption and supplementation has been shown to reduce atrial fibrillation, ventricular tachycardia and ventricular fibrillation (Jenkins *et al*., 2008). However, there is also a suggestion of harm in certain subgroups of cardiac patients, notably those with a history of ventricular tachycardia (VT) and heart failure who require implantable cardioverter-defibrillator (ICD) and are not on anti-arrhythmic drugs and caution is advised about recommending fish oil supplementation in these patients until further studies are completed (Brouwer *et al*., 2009).

EPA and DHA have also been shown to reduce insulin resistance in animal studies and in some human studies in normal weight and obese individuals (Fedor and Kelley, 2009). As inflammation is one of the major factors that lead to the development of insulin resistance, one of the mechanisms by which omega 3 fatty acids may reduce insulin resistance is through their anti-inflammatory effects. EPA and DHA have also been shown to increase leptin and adiponectin expression and secretion in animal studies. The omega 3 fatty acids are also known to regulate the expression of a number of transcription factors including peroxisome proliferator activated receptors (PPAR), sterol regulatory binding protein-1c (SREBP-1c), hepatic nuclear factors (HNF), retinoid X receptors (RXR) and liver X receptor (LXR) (Fedor and Kelley, 2009). Studies have shown that EPA and DHA may reduce in insulin resistance through the activation of peroxisome proliferator-activated receptor alpha (PPARα) and peroxisome proliferator-activated receptor gamma (PPARγ) and suppression of SREBP-1c.

The intake of fiber

Dietary fibers are classified as soluble, that are fermented in the colon and insoluble, that have bulking action but are fermented only to a limited extent in the colon. Major dietary fiber sources are whole-grain foods, vegetables, fruits, legumes and nuts. Average recommended dietary fiber intake is approximately 28 grams/day for adult women and 36 grams/day for adult men (Anderson *et al*., 2009).

Increased dietary fiber intake has been shown to reduce the risk of CHD by 29%, stroke by 26%, diabetes by 19% and obesity by 30% in cohort studies (Liu *et al*., 1999; Montonen *et al*., 2003; Steffen *et al*., 2003; Lairon *et al*., 2005). Fiber intake also improves lipid concentrations, lowers blood pressure, improves blood glucose in diabetes and helps with weight loss (Brown *et al*., 1999; Keenan *et al*., 2002; Anderson *et al*., 2004).

Soluble fibers have significant hypocholesterolemic effects and can reduce LDL cholesterol by 5.5% to 13% from baseline. They do not have any effect on HDL cholesterol or triglycerides (Brown *et al*., 1999). Proposed mechanisms for the hypocholestrolemic effects of fiber include the binding of bile acids in the small intestine, thus increasing their excretion in the feces (Kirby *et al*., 1981). Fermentation of fibers in the small intestine also promotes the growth of bifidobacteria which produce short chain fatty acids (SCFA) and this may inhibit cholesterol synthesis (Wright *et al*., 1990). Fiber intake has also been shown to reduce systolic blood pressure (BP) by 1.1 mm Hg and diastolic BP by 1.2 mm Hg (Streppel *et al*., 2005). These effects are greater in hypertensive subjects with a reduction of 6mm Hg in systolic and 4.2 mm Hg in diastolic BP (Whelton *et al*., 2005).

Intake of fiber is also associated with a reduction in the incidence of diabetes. In the Finnish Diabetes prevention study, subjects with the highest level of fiber consumption had a 62% reduction in progression from prediabetes to diabetes over a 4.1 yr period compared to those with the lowest fiber intake (Lindstrom *et al*., 2006). In this study, increase in fiber intake was associated with a reduction in C-reactive protein (CRP) and IL-6, even after adjustment for change in BMI. In non-diabetic subjects, increased fiber intake is associated with an improvement in fasting glucose, insulin and insulin sensitivity (Vuksan *et al*., 2000). In diabetic subjects, increasing fiber intake is associated with an improvement in fasting and post prandial glucose and overall glycemic control (Anderson *et al*., 1999). This may be secondary to the anti-inflammatory effects of fiber intake. In a recent study, low dietary fiber intake ($<$ 20 gram/day) was associated with a 47% increased risk of diabetes (Wannamethee *et al*., 2009). Dietary fiber was inversely associated with CRP, interleukin-6, tissue plasminogen activator (t-PA) and gamma-glutamyl transpeptidase (GGT) and adjustment for these markers attenuated the increased risk of diabetes with low fiber intake.

Fiber intake is inversely correlated with weight gain and obesity prevalence. Weight loss of 2% to 4.9% of baseline body weight have been seen in short term trials with fiber supplements (Anderson *et al*., 2009). Intake of fiber may increase satiety by delaying gastric emptying and by increasing gut hormones which increase satiety.

Conclusion

It is clear that macronutrient intake induces oxidative and inflammatory stress especially when it is

rich in saturated fat and refined carbohydrates. On the other hand, a meal rich in fiber and containing fruit does not induce either oxidative stress or inflammation. Associated with the induction of inflammation is the increase in the expression of SOCS-3, a mediator of insulin resistance through interference with insulin signal transduction at the IRS-1 level. Post-prandial inflammation following such meals is thus is a potential mediator of atherogenesis and insulin resistance. The fact that diets rich in fiber and fruit are associated with protection from diabetes and atherosclerotic complications in prospective trials is consistent with our observations that such meals do not cause oxidative stress or inflammation. Furthermore our most recent data show that orange juice may actually neutralize inflammation induced by the HFHC meal. This intriguing observation leads one to ask the question whether the combination of anti-inflammatory meals/foods would render the latter safer. These issues need further investigation and eventual incorporation into our life style and eating habits.

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