

DOHERTY, JEANNE L., M.S. Associations among Diet, Inflammation and Iron Status in Young Adults (2019)
Directed by Dr. Seth Armah 69 pp

Obesity is a risk factor for poor iron status due to the chronic, low-grade inflammation of adipose tissue hypertrophy. Among other positive acute phase proteins, the hepatic peptide hormone hepcidin is secreted during inflammation, inhibiting systemic iron efflux from enterocytes and downregulating systemic iron recycling by suppressing iron release from the mononuclear phagocyte system. Conversely, production and secretion of the iron transport protein transferrin by the liver is reduced during inflammation. In addition to increasing adiposity, certain foods are also known to promote inflammatory states and may contribute to these same effects in concert with, or independent of obesity. In this study, we evaluated how inflammatory diets are related to inflammatory and iron status biomarkers among 98 young adults with normal weight, overweight and obesity. Three-day dietary records and biomarker data for iron status and inflammation from two cross-sectional studies of similar design (Diet and Inflammation Study, n= 39 and the Selenium and Inflammation Study, n= 59) were used in this study. Dietary Inflammatory Index (DII) scores were calculated for each subject using nutrients and other dietary components from the dietary records, and subjects were further classified into two DII categories using cluster analysis. Using ANOVA we compared iron status and inflammatory markers among subjects with normal weight, overweight and obesity. We determined the association between DII scores or DII category and C-reactive protein (CRP), hepcidin, serum iron and total iron binding capacity (TIBC). Statistical significance was set at $P \leq 0.05$. Mean \pm SEM were reported for continuous

variables except for skewed variables in which case geometric means (geometric mean \pm 1SEM interval) were reported. CRP concentration differed significantly by BMI category ($p < 0.05$ for all comparisons) and serum iron (SI) was lower in the obese category compared to normal weight ($p=0.014$). Results from the regression analysis showed that high DII scores were associated with increased CRP concentration and decreasing TIBC. Similarly, subjects in the anti-inflammatory diet group showed higher TIBC compared to those in the inflammatory diet group. In conclusion, our study showed that inflammatory diets may impair iron status by reducing the capacity of the iron transport protein transferrin to transport iron in the blood.

ASSOCIATIONS AMONG DIET, INFLAMMATION AND IRON STATUS IN
YOUNG ADULTS

by

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A Thesis Submitted to
the Faculty of The Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Greensboro
2019

Approved by

Committee Chair

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I dedicate this thesis to the spirit of Pro Humanitate so that the health, well-being and vitality of others may be improved, and the risk for diet driven chronic diseases will be reduced.

APPROVAL PAGE

This thesis written by JEANNE L DOHERTY has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro

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ACKNOWLEDGEMENTS

Foremost I would like to thank my faculty mentor Seth Armah for giving me the opportunity to work as a graduate assistant on his Diet and Inflammation Study. I learned so much about conducting research with human subjects and I am very grateful for his patience and unwavering support. Dr. Armah's knowledge, attention to detail and statistical prowess were invaluable to this thesis project.

I would also like to thank Lauren Haldeman and Steven Fordahl for serving on my thesis committee. Dr. Fordahl's wisdom and guidance kept me motivated throughout the project. I am especially grateful for Dr. Haldeman who was the first to encourage me to earn a Master of Science degree in Nutrition. Her leadership will always inspire me.

Additionally, I am thankful for my early science professors Bruce Banks, PhD and Maulik Trivedi, PhD for dispelling my fears of chemistry through their inspiring and fascinating lectures and for every instructor in the Nutrition department for the expertise and knowledge they share daily. I would also like to recognize the ongoing support of Paula Cooney, the departmental research coordinator, and Sherry Ritter, the department's administrative assistant who makes everything possible in the Department of Nutrition.

Lastly, I would like to express my deepest appreciation for my husband, Timothy and children, Jack and Katy, my parents and my sister for encouraging me in every way while I pursued learning about food and nutrition. Their love, care and support are truly boundless.

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CHAPTER I

INTRODUCTION

Beyond providing nutrients, certain foods offer other health benefits through unique properties such as their antioxidant and their anti-inflammatory properties. The effects of foods and their components on inflammation have been investigated in both observational and experimental studies (1–4). In conjunction with epigenetic research, an understanding of how exposure to certain foods influences genetic expression and post translational modification of proteins is becoming well established (5–10). The upregulation of inflammatory cytokines by food components is an important concept that continues to be widely studied as the mechanism by which phenotypic changes toward a chronic disease phenotype are born.

Inflammatory cytokines are small proteins that play a primary role in local and systemic signaling that initiate the immune response to infection and injury. Namely, an increase in interleukin 6 (IL-6), interleukin one beta (IL-1 β), and tumor necrosis factor alpha (TNF α) are associated with an increase in the hepatic protein, C-Reactive protein (CRP) which binds to the surface of the affected cells to augment various immunological processes of the innate immune system (11,12). In addition to stimulating release of CRP, the hepatic peptide hormone, hepcidin is also released and its job is to keep a tight homeostatic regulation of iron. Circulating hepcidin causes sequestration of circulating

iron into the liver and macrophages, reduces iron absorption in the intestines and decreases iron efflux from enterocytes into the bloodstream.

During the acute phase response, the immune system resolves pathophysiological threats and normal iron physiology can be restored. However, individuals who are overweight or obese have been found to have chronically elevated levels of hepcidin and other markers of inflammation even in the absence of infection or injury resulting in poor iron status (13–19). It is suspected that the increases in hepcidin and other inflammatory markers in the overweight and obese may be attributed to an accumulation of activated macrophages in adipose tissue that secrete adipocytokines including IL-6, and TNF α which activates transcription of the iron storage protein ferritin (20,21). Atypical adaptations to iron metabolism during obesity related chronic inflammatory states are thus being observed and current studies suggest that obesity may be a risk factor for poor iron status (13–15,22,23).

Coupled with activated macrophage initiation of IL-6, dietary sources can also stimulate IL-6 production and begin the inflammatory cascade (24–26). Food related mechanisms that have been implicated in the promotion of the inflammatory phenotype center around increased expression of the protein complex, nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) which is responsible for producing IL-6 (27,28). For example, certain free fatty acids in the diet that act as non-immune ligands to activate toll-like receptor 4 (TLR4) have been shown to decrease the expression of peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC1) which will

upregulate the expression of NFκB (29). Other dietary sources of inflammation are the advanced glycation end products of highly processed foods which have been found to increase oxidative stress and overexpression of the Receptor for Advanced Glycation End Products (RAGE) in enterocytes (30,31). These may all contribute to sustaining chronic inflammation and impairing iron status.

However, individuals who regularly consume dietary antioxidants and anti-inflammatory dietary components such as omega 3 fatty acids and certain flavonoids may demonstrate improved biomarkers of inflammation, reducing their future risk of chronic disease (32–34). Proposed mechanisms of action for anti-inflammatory effects of bioactive food components include improved composition of cell membranes, support during oxidative stress and through cell signaling pathways that can alter gene expression (35–37). Although the exact mechanisms are still being actively investigated, qualitative studies and data from experiments in cell and animal models offer convincing evidence on the health benefits of including anti-inflammatory foods regularly in the diet (38–44).

In order to most effectively evaluate the contribution of diet to inflammation, various dietary patterns and indexes have been developed. Among them is the Dietary Inflammatory Index (DII) which was designed to consider both proinflammatory and anti-inflammatory foods (45). The DII is a validated predictive model for inflammatory markers and can be used with a variety of dietary assessment tools including 24h recalls, food frequency questionnaires, and dietary records. In observational studies, higher DII

scores have been associated with higher IL-6 and higher CRP concentrations. However, no study has investigated its relationship with hepcidin and iron status.

Main objective: The aim of this study was to determine the association between dietary intake and inflammation and how that influences circulating iron biomarkers in young adults. Circulating iron was assessed using serum iron and total iron binding capacity (TIBC).

Specific Objectives

1. To compare circulating iron (serum iron and TIBC) and inflammatory biomarkers among study participants with normal weight, overweight and obesity.

Hypothesis: *Subjects with higher BMI will have poorer circulating iron status biomarkers and higher CRP concentration*

2. To determine the association between the DII score and inflammation among study participants.

Hypothesis: *DII scores will be positively associated with CRP concentration among study participants.*

3. To determine the association between the DII score and circulating iron biomarkers among study participants

Hypothesis: *Higher DII scores will be associated with poorer circulating iron biomarkers (serum iron and TIBC).*

CHAPTER II

LITERATURE REVIEW

The prevailing obesity epidemic in developed countries and that which is emerging in developing countries due to nutrition transition is alarming. While obesity is a well-known risk factor for various chronic diseases, recent studies have implicated obesity as a risk factor for poor micronutrient status (46). Particularly for iron, low-grade, chronic inflammation associated with obesity may increase concentrations of the iron regulatory protein hepcidin which may negatively influence levels of circulating and functional iron (47). Considering that diet may play a role in reducing inflammation, there is a need to investigate how dietary changes may indirectly influence iron status through its effect on inflammation among individuals with overweight and obesity. This review focuses on the importance of iron to human health, factors that influence iron status and the relationships between diet and inflammation, and methods for assessing the inflammatory effects of foods.

Iron and Human Health

Iron is required for sustaining human life and in maintaining healthful physiological functions. Iron participates as a catalyst and promoter in enzymes and is a component of several globular proteins such as hemoglobin and myoglobin. Primarily the human body uses iron for the transport of oxygen by red blood cells and thus, a

majority of body iron is contained in the heme protein, hemoglobin. After hemoglobin ferritin, which stores iron as Fe²⁺, accounts for the next largest supply of the body's iron and is followed by myoglobin, with transferrin containing the least amount of iron, as ferric iron, (Fe³⁺) (48). In addition to the globin proteins, heme is a part of peroxidases and redox cytochrome enzymes. Iron functions in ribonucleotide reductase and is a part of several iron sulfur proteins including aconitase of the TCA cycle and nucleotide binding protein (49). In general, proper iron homeostasis is required for cognition, immunity and physical performance.

Cognitive Development and Functioning

Progress in iron research continues to support and further clarify how iron is a key factor for proper cognitive development and functioning, effective immunological responses, and sustaining physical competencies. A novel study comparing the effects of iron deficiency (ID) on both white and gray matter in developing rats supports that even mild iron deficiencies may affect hypomyelination in hippocampal and cortical tissues. Greminger et al. observed proximal shifts in apical dendrite branching and significant decreases in basal dendrite length and branching with 50% fewer interactions in the Fe deplete diet group compared to the Fe diet group (50). In a prospective cohort study using cord blood, Amin et al. compared the auditory brainstem evoked response of infants born full term. Results of the study showed significantly prolonged interpeak latencies in the infants whose cord blood serum ferritin levels were between 11-75 ng/ml compared to infants with cord blood serum ferritin over 75µg/ml (51). There is an

increasing pace of studies on the associations of iron status and attention deficit disorders, pointing to the effects of iron deficiency (ID) on frontal lobe functioning(52). A study of women of reproductive age adds support to previous findings that even marginal declines in iron status of non-anemic women are correlated with reduced proficiency in completing executive functioning tasks such as sustained attention, learning and shifting, inhibitory control, working memory and problem solving (53). Results of this study are the first to suggest that even marginal increments in ferritin and total body iron are related to improvements in problem solving and planning tasks among non-anemic iron deficient women of reproductive age.

Immunity

Current research on the relationship between iron status and immunological response includes studies on asthma and lung function, improved immune function studies, and how iron deficiency may be protective against malaria (54–58). Using data from the 2007-2010 survey cycles of the National Health and Nutrition Examination Survey (NHANES), Brigham et al. found that among women 20-49 years of age, those with the highest ferritin values experienced an average reduced risk of lifetime asthma, and current asthma by 31% and 53% respectively (55). In addition to ferritin, the iron binding glycoprotein lactoferrin (LF) which is very similar in structure to transferrin, is another important iron-bound molecule that supports immunity (56). LF is expressed by epithelial tissue and can be taken in exogenously from human breast milk and other unpasteurized, raw mammalian milk sources. Its positive effect on immunity has been

shown in a number of in vivo and in vitro studies (54). The ability of LF to effect improvements in immune functioning in older adults was observed in an RCT of people ages 66-87 receiving lactoferrin supplementation. The experimental group in the study experienced significant increases in neutrophil phagocytic capacity, natural killer cell cytotoxicity and limited improvement in lymphocyte subset ratios (57).

Interventions with iron supplementation have also shown improvements in immune functioning. In a case control study on the effects of iron deficiency on the humoral and cell mediated immunity of children, lower CD4 lymphocyte levels as well as impaired CD4:CD8 ratios were improved following 3 months of iron supplementation (6mg/kg/day elemental iron) preceded by treatment for parasitic infections (59). However, supplementing with iron in cases of unresolved parasitic infections has been shown to negatively affect outcomes (58,60).

Optimizing Physical Performance and Aerobic Capacity

Optimal physical functioning and aerobic capacity are also known to rely on adequate functional iron supplies. While this is a well-established principle, current areas of research are expanding the breadth of the literature to include non-anemic iron deficiencies, effects of intense physical training on individuals with iron deficiencies, and the benefits of iron supplementation on aerobic and strength training performance among women, including athletes, women in the military and recreationally active women (61–65). Together these studies offer good evidence for monitoring and for iron

supplementation in men and women who may have non-anemic iron deficiencies or who engage in moderate to high intensity activities on a regular basis.

Factors Affecting Iron Status

Iron Intake and Absorption

Although the majority of body iron supplies are maintained by recycling during erythropoiesis, enough iron must be taken in by the diet to replenish the 1-2 mg lost daily (49). Recommended daily intakes for iron are 8 mg for adult men, 18 mg for adult women and 27 mg for pregnant and lactating women (66), however Armah et al. have suggested that these values may need to be adjusted upwards to be able to meet physiological iron requirements (67). Humans acquire iron through consumption of heme from myoglobin or hemoglobin in meats and inorganic iron of plant foods, synthetically fortified foods or of animal tissues. While a higher percentage of iron is absorbed from heme sources (68), most of the dietary iron consumed is from iron fortified cereals and breads due to the widespread consumption of both food products (69).

It is well known that iron from heme sources is taken up and utilized more efficiently than non-heme sources. This is based primarily on the consensus that heme moves into the enterocytes of the brush border membrane (BBM) intact, unencumbered by competition for transporters or through loss due to “anti-nutrient” activity of oxalates and phytates. Evidence continues to support this assertion and points to endocytosis or movement through the transmembrane protein heme carrier protein (HCP1) as probable

modes of absorption at the BBM (70,71). A study of piglets with iron deficiency anemia (IDA) showed a four-fold increased expression of Slc46a1, the gene coding for HCP1 in piglets given oral supplementation of bovine hemoglobin compared to both control piglets given parenteral Fe and to piglets receiving intramuscular injections of the conventional treatment of iron dextran. Results also showed that piglets receiving oral heme supplementation had more than a three-fold increase in Fpn mRNA expression on the basolateral membrane (BLM) of duodenal enterocytes compared to both control and to iron dextran injected piglets. Furthermore, hepcidin mRNA expression in the livers and plasma of the heme and control piglets remained consistently low throughout the study compared to increased hepcidin levels in iron dextran injected pigs, which began to increase significantly at day fourteen of the study and continued to do so until the study's conclusion (72).

Following digestion, iron from vegetable sources is transferred into the cellular environment from the intestinal lumen by a divalent metal transporter (DMT1). Control of iron absorption by enterocytes depends both on systemic factors, local transcription of HIF-2a, and by posttranscriptional mechanisms of the iron regulatory protein and iron response element systems (71). Since ferric iron (Fe³) must be reduced prior to transport by DMT1, its absorption can be increased by the presence of ascorbic acid which reduces it to ferrous iron (Fe²), allowing it to bypass the ferric reductase enzyme, duodenal cytochrome b (Dcytb) present in the lumen. Other dietary components that enhance non-heme iron absorption are amino acids, animal proteins and fermented products.

Alternatively, other digested compounds such as phytates and oxalates may bind with iron in the lumen causing it to pass unabsorbed and unutilized by the body. Similarly, other metals, like calcium, cadmium, cobalt, magnesium and zinc in excess, may compete with iron for DMT1, reducing the amount of iron absorbed and cause it to pass unutilized by the body (73,74). Recent ex vivo experiments have demonstrated that hepcidin too can reduce absorption of dietary iron by downregulating mRNA levels of DMT1 and Dcytb (75).

Because vegetarians do not include heme or animal protein in the diet, it is estimated that only between 5% and 12% of iron in their diet is absorbed (76). For this reason, the United States Institute of Medicine recommends that vegetarians consume 1.8 times more iron compared to those consuming a mixed Western diet (66). Proper meal planning that accommodates optimal iron absorption via nutrient to nutrient interactions are essential for maintaining proper iron status. Researchers Ghatpande et al. (77) studied the relationship between iron status, inflammation and the dietary data of 85 adolescent girls in India, a nation whose population relies heavily on non-heme iron from plant-based diets. Among the subjects, 28% were anemic and 66% were ID. Their primary goal was to examine the relationship between ferritin, serum iron, hepcidin, TNF α and B12. Overall the study reported that regular consumption of vitamin C rich fruits had significant effects on iron status and that B12 was negatively associated with TNF α . Amla, a fruit very rich in vitamin C, was regularly included in the diets of girls with higher serum iron, and a significant positive correlation between hepcidin and

ferritin was observed. Among the girls who ate guava regularly, B12 and ferritin associations were significant. An interesting finding involved consumption of fetid cassia, (fruits from a tree that grows in ruined buildings) which is a traditional treatment for ringworm. Subjects who did not eat fetid cassia were at a 3.9 times increased risk of low serum iron.

Additionally, sufficient intake of B12 either from supplements or fish sources must also be made available for effective erythropoiesis to protect against anemia. The benefits of a combined folic acid (FA), B12 and iron supplementation were shown in a supervised RCT among 446 IDA adolescent girls living in a very low socioeconomic section of New Delhi. In the study, Bensal et al. (78) showed that while both the FA and B12 +FA iron supplements reduced the prevalence of iron deficiency anemia (IDA) among the group, the B12 + FA iron supplement reduced IDA among the subjects more significantly as well as improved ferritin status compared to the FA+iron supplement.

Physiological Needs

The higher incidences of ID and IDA among pregnant women, premenopausal women, and children reflect the increased physiological demands for iron in these demographics (79–81). Pregnant women require more dietary iron for increases in blood volume and supplies to the fetus, premenopausal women with menorrhagia need more iron for replacing excessive blood losses and children require more iron for the changes in blood volume and hemoglobin concentrations (66). Also, hypoxia is a physiological state that cause changes to iron status. Subsequently, in these individuals, upregulation of

erythropoietin will enhance intestinal iron absorption and dietary iron intake will subsequently have a greater impact on iron status than in individuals without higher physiological needs (82).

High altitudes, severe blood loss, low erythrocyte production and adipose tissue hypoxia will limit oxygen supplies for red blood cell production. When these changes are sensed by baroreceptors in nephrons, EPO transcription is upregulated in the interstitial fibroblasts in the renal cortex via binding of hypoxia inducible factor (HIF) heterodimers to hypoxia responsive element (HRE) of the EPO gene (83). The increases in EPO suppresses hepcidin via upregulation of the erythroid, erythroferrone (ERFE) and ultimately causes increases in dietary absorption to correct the deficiency (84,85).

Infection

Intestinal parasites are another gastrointestinal disorder that can impair iron status. While most common in developing nations and among children, intestinal parasites continue to be a major cause of anemia globally. Parasitic infestations on their own, or in combination with an already poor diet quality can worsen iron status. An increased prevalence of the intestinal parasite *Giardia*, a major cause of diarrhea (86), is suspected of increasing IDA, especially among school children in both developed and developing countries (87). Hussein et al. (87) conducted an analysis of 650 stool samples from pre-school Egyptian children presenting with IDA to determine the association of *Giardia* infection types with IDA. While several intestinal parasites were discovered, 88 of the children were shown as having only giardiasis. Their results showed that *Giardia*

assemblages A were associated with 90.9% of the IDA cases and Giardia assemblage B with only 9.1% of the cases. Helicobacter pylori (H. pylori) which is also found in populations around the world is more prevalent in older people with recent studies showing that H.pylori may be impacting vitamin B12 status in addition to reduced blood iron (88,89). A case control study of younger hospitalized patients hospitalized with H.pylori showed that the decreases in B12 and iron levels were improved to near normal levels upon treatment for the infection (90). Lastly, studies on the effects of colonic microbiota are demonstrating a viable link between an organism's microbiome and expression of hepcidin (91).

Inflammation

Hepcidin, an antimicrobial peptide produced mainly by the liver, helps to maintain safe supplies of functional iron by facilitating the sequestration of circulating iron into storage as ferritin if liver iron stores are high or whenever inflammation is triggered by the innate immune system. This inflammation cascade is initiated at the site of infection or injury by neutrophils which secrete interleukin-1 (IL-1) to recruit macrophages that in turn secrete interleukin-6 (IL-6) that signals the liver to produce and release hepcidin (92,93). As hepcidin circulates in the body, it prevents iron from entering the bloodstream by binding to and disabling the transmembrane iron exporter protein, ferroportin (Fpn) which is found primarily on hepatocytes, macrophages and enterocytes. While this effectively limits the efflux of iron from these cells and into circulation, hepcidin's role in decreasing absorption in the duodenum is not as well

established. However, in a recent *ex vivo* study, it is reported that hepcidin exposure elicited changes in human duodenal mucosa that modulate several steps of the iron absorption process, including a reduction of dietary iron by Dcytb, its uptake by enterocytes through DMT1, the mucosal uptake of heme iron by HCP1, and enterocyte iron release to plasma by Fpn1 in conjunction with hephaestin through transcriptional change (89). Conversely, when iron is required for the formation of red blood cells, erythroferrone (ERFE) is produced and hepcidin is suppressed (94). The impact of inflammation on iron status is seen in conditions such as autoimmune disorders, and inflammatory bowel disease in which high hepcidin concentration may predispose patients to anemia of inflammation (12).

Foods and Inflammation

It is well recognized that foods can significantly impact inflammatory status through a variety of mechanisms. Some examples of foods and food components that have been linked to inflammation are discussed below.

Fatty Acids

Certain fatty acids have been shown to directly influence proinflammatory cytokines via the arachidonic pathway and polyphenols have been shown to indirectly affect inflammation by reducing conversion of arachidonic acid to eicosanoids, modulating nitric oxide production (NOS) and downregulating the expression of genes associated with inflammatory signaling pathways, scavenging of reactive oxygen species (ROS) and other free radicals of metabolic reactions, and chelating metal ions (26,95–

98). Both monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA)s are known to be healthful fats and are recommended over saturated fats which have been shown to have acute inflammatory effects (95–98).

The potential health benefits of MUFAs and PUFAs were highlighted in the large-scale intervention study, PREDIMED, which studied how three diets containing different fat profiles affected the risk for CVD among high risk patients. An extra virgin olive oil (EVOO; MUFA diet) diet, a PUFA rich diet with nuts (walnuts, almonds and hazelnuts), and a low-fat diet fashioned by the American Heart Association recommendations, were studied. All three diets included recommendations for high consumption of fruits and vegetables. A number of sub studies have emerged comparing these three different diets with plasma concentrations of inflammatory cytokines in the blood samples.

Casas et al. (38) investigated the anti-inflammatory effects of MUFA and PUFA diets in a subcohort of 164 PREDIMED participants with atherosclerosis over the course of 12 months. C-reactive protein and IL-6 were reduced by 45% and 35% and 95% and 90% in the MUFA and PUFA diet respectively ($P < 0.05$). In a long-term study of an elderly cohort, the same researchers found that at 3 and 5-year test points, both the MUFA and PUFA rich diet showed a significant reduction of IL-6, IL-8, MCP-1, and MIP-1 β ($P < 0.05$) compared to subjects following the low-fat diet recommendations. The MUFA rich diet stood out further in that it demonstrated improvements in TNF- α , as well as the other markers of CVD disease risk studied ($P < 0.05$).

The Canola Oil Multisite Intervention Trial (COMIT) compared the effects of three different Canola oils and two safflower blended oils on the biomarkers of CVD risk which included CRP and IL-6. The Canola oils were designed to have higher percentages of omega-3 fatty acids while containing the same amount of protein, carbohydrate, lipid, saturated fat, fiber and cholesterol percentages whereas the safflower blended oil diets contained higher omega 6 fatty acids than the Canola oils. A primary objective of the study was to better identify the effects of oils containing various amounts of alpha linolenic acid (ALA). Linoleic acid (LA) Oleic acid (OA) and docosahexaenoic acid DHA outside of the Mediterranean diet context (99). Since only endpoint differences were reported it is unknown how CRP levels changed from baseline among the subjects. However, endpoint data showed that CRP was significantly lower in the Canola oil diet compared to the corn/safflower blend control diet which had a disproportionately higher omega 6 to omega 3 ratio.

Another interventional study that included a comparison of the anti-inflammatory effects of an unprocessed oil with a processed oil demonstrated the anti-inflammatory benefits of EVOO compared to refined olive oil (ROO). In the study, HIV patients who consumed an EVOO diet had significantly lower average CRP levels compared to those patients consuming ROO diet, which contained no polyphenols (100). These observations were attributed to the presence of polyphenols in reducing the effects of lipid oxidation, thereby protecting the tissues (epithelia) from oxidative stress and injury which elicits and inflammatory response.

Polyphenols

Polyphenols are a group of plant-based chemicals that have at least one phenol group. They are divided into two main groups, phenolic acids of red fruits, black radishes, onions, coffees, cereals and spices and the spectrum of flavonoids, which are found in soy (isoflavones), in berries (anthocyanidins), in herbs (flavones), in broccoli, kale and tea (flavonols), flavanones found in citrus fruits and juices (flavanones). Cell studies, mouse studies and human studies all demonstrate the anti-inflammatory effect of a polyphenol rich diet (PPD) (101,102).

Examples of commonly consumed polyphenol rich foods include coffee and tea. Both beverages contain an array of polyphenols. Chlorogenic acid, 5-caffeoylquinic acid (5-CQA), which is contained in the coffee bean, is consequently one of the most commonly consumed phenolic acids in the world. Green tea is high in flavon-3-ols and black tea which is fermented, also contains oligimeric flavonoids. Both coffee and tea contain the flavonol, quercetin (103). A number of cell culture, animal and human studies have been performed and demonstrate the anti-inflammatory effects of their bioactive components (103–114). Studies have also shown anti-inflammatory benefits of isoflavones which are primarily consumed in beans (115–122) (116–123).

Influences of Western Style Diets

In contrast to the anti-inflammatory effects of monounsaturated fatty acids and polyphenols found in more traditional diets, injurious metabolic and bioactive byproducts of modern and western style diets are being shown to contribute to the inflammatory

response both acutely and in chronic fashion. These diets are characterized by being highly caloric, highly processed and high in manufactured, refined oils (123). Recently, Christ et al. (124) demonstrated how exposure to a Western diet both induces the systemic inflammatory response and evokes long term phenotypic changes of an enhanced immune response in myeloid cells regardless of dietary change. This research has revealed the nucleotide-binding oligomerization domain receptor protein 3 (NLRP3) inflammasome as the central mediator of diet induced systemic inflammation and how myeloid precursor reprogramming are involved in the long-term immunomodulatory effects of inflammatory diets. Both are important additions to the established body of research that describes more acute inflammatory responses (125–129) to components of food and may lead to a broader understanding of how food borne “sterile” inflammation may impose a persisting, heightened trained-immune response of metabolic pathways.

Added Sugars

The added sugars in Western diets include fructose, sucrose, and high fructose corn syrup. Ample evidence supports a role for added sugars in the promotion of chronic disease. (130–134) including a number of studies showing associations between biomarkers of inflammation and increased consumption of sugar sweetened beverages (SSB) (135–138).

In a cross-sectional observational study of 9678 participants in the population-based Fenland Study, O’Connor et al. (135) studied how free sugars from beverages, fruit juices and processed foods were associated with metabolic risk factors compared to

sugars from solids with naturally occurring sugars. The results of the analyses revealed that intakes of free sugars from liquids and from sugars added to liquids like coffee and tea but not sugars from foods, were significantly associated with increased CRP among subjects in the highest quintile compared to the lowest quintile of consumption (124).

In a mouse study, seven months of either 15% glucose or 15% fructose showed higher accumulations of triglycerides in gastrocnemius muscle of both groups compared to standard chow controls but higher intramyocellular lipids and associated IL-6 in fructose group compared to glucose group (139). More recently, Kovacevic et al. (140), studied female Wistar rats fed either standard chow with water (n=9) or standard chow with 10% fructose solution for 9w. Results showed NFK- β to be higher in the cytosols and nucleosols of VAT of fructose treated rats compared to water with chow treated rats and increased mRNA levels of both NFK- β and Il-1B by 25% and 40% respectively among fructose treated rats. Together these findings reveal how added sugars induce inflammatory signaling and cytokine production by way of increased oxidative stress in female rats.

A two-week crossover RCT by Raatz et al. (141), examined the metabolic effects of chronic intakes of three sources of sugars (honey, sucrose and high fructose corn syrup) in both glucose tolerant (GT) and glucose intolerant (IGT) subjects (n=60). While triglyceride concentrations were significantly increased in all subjects from baseline, only IGT subjects had significant associations of CRP and glycemic response with the added sugars. Since all three sweeteners had undergone thermal

processing similar results found in exposures to the different sweeteners may indicate that the heat treatment of the sugars may have caused these effects. Also, the treatment period of only two weeks, along with the relatively low amount (50g) of sweetener may not have been enough added sugar to evoke a metabolic inflammatory effect in normoglycemic individuals. Concentrations of CRP observed in the GT group were within the normal range (<3.0 mg/L). Higher body weight among the IGT group may have been the factor behind the status × treatment interaction found in the study results ($P= 0.03$).

The inflammatory effects of low to moderate intakes of SSB were first demonstrated by Aeberli et al.(142), in a clinical trial evaluating the effects of beverages containing different sweeteners on metabolic factors in healthy young men. In the study, six different SSB interventions of varying concentrations of fructose, glucose or sucrose were given to normal weight males (n=29) aged 19-25y that did not take regular medications or consume more than 60g SSB daily. Although differences were observed among the sugars on LDL size, all the sugars had a similar effect of increased fasting glucose and more than twice the CRP concentrations compared to baseline. However, a similar RCT in Hispanic adolescents with NAFLD that were exposed to either glucose or fructose beverages, reported that CRP was reduced by nearly half in glucose beverage group compared to fructose after 4 weeks of exposure (143).

Dietary Advanced Glycation End Products

In addition to being high in added sugars, western style diets are also high in advanced glycation end products that result from the non-enzymatic Maillard reaction, a common food preparation and processing technique that is widely used in the manufacturing of ultra-processed convenience foods that accommodate modern lifestyles. Dietary advanced glycation end products (dAGEs) are produced when carbonyl groups of non-reducing sugars interact with free amino acid groups of proteins. Intermediate aldehydes and dicarbonyls are first produced and then react with other biomolecules, to form a group of heterogeneous, “end product” compounds (144). Even as much as the cooking process enhances the flavor, aroma, and appearance of foods, these end products which are found to a great degree in French fries, potato chips, baked goods and pasteurized dairy are now believed to contribute to the inflammation associated with chronic and autoimmune diseases (89,145–147) . The most commonly studied dAGEs include carboxylethyl-L-lysine (CEL), carboxymethyl-L-lysine (CML), and hydro-methyl-imidazolone (MG-H1). Several observational studies have reported associations between dAGES with increased inflammation and human interventions have demonstrated that reduced inflammatory markers are associated with dAGEs restricted diets (27,148–151).

Researchers Di Pino et al., have conducted both observational and interventional studies investigating the health risks of dAGE exposures in subjects with type 2 diabetes mellitus (T2DM). In their 24w, RCT study, subjects on low dAGE diets had significant

reductions in CRP compared to standard dAGE diets (150). In their cross-sectional study (n=85), the researchers reported that subjects consuming diets containing more than 15,000 kU/dAGEs/day had significantly higher CRP than subjects whose diets were below 15,000 kU (149). Similar associations between dAGE consumption and serum AGEs (sAGEs) were found by Uribarri et al., (27) in an earlier prospective cohort study of subjects with obesity and risk for metabolic syndrome (MS).

While human studies are still limited, numerous animal models offer insights into dAGEs role in inflammation. The pro-inflammatory effects of CML, and associated renal damage were reported in a study of intrauterine growth retardation piglets (IUGR)(n=8) that were fed either low heated (LHF) or high heated infant formulas (HHF). In the study, Elmhiri et al. (152), observed that piglets receiving HHF had higher mRNA expression and protein activation of NF- κ B by 33% and 120% respectively. Recently, a mouse model expressing firefly luciferase under control of NF κ -B regulation was used to investigate systemic activation of the secondary messenger pathway, NF- κ B from AGE modified foods. In their experiments, NF κ -B luciferase activity was significantly higher in animals fed AGE treated bovine serum albumin (BSA) compared to both BSA fed animals and to positive controls with the highest luciferase activity found in the gut at 6-8h post feedings (153).

Increased intakes of dAGEs add to the pool of endogenous AGEs which are produced when proteins such as albumin or globulins react non-enzymatically with plasma glucose. Both dAGEs and endogenous AGEs contribute to an accumulation in

systemic AGEs which is commonly observed in diabetes, during aging and from diets high in added sugars (148). Circulating AGEs from either source (endogenous or diet derived) can be bound by the advanced glycation end receptor 1 (AGER1) or by the receptor for advanced glycation end products (RAGE). AGER1 binding of AGEs reduces their intracellular and extracellular presence and therefore reduces oxidative stress both intracellularly and among the tissues. RAGE binding of AGEs however, activates several signaling pathways including NF- κ B, resulting in a proinflammatory effect which mediates increases in both transmembrane and soluble RAGE which is found in the sera (14). Most importantly the link between RAGE and the NLRP3 inflammasome was established by Yeh et al., (154) in BALBc mice experiments, who demonstrated that dAGEs mediate activation of NLRP3 secretion of Il β -1 via conversion of pro-caspase to caspase.

Inflammatory Diet Indexes

Approaches that reflect the overall health potential of the diet are currently being used to describe population and individual diet patterns. Mediterranean Diet Patterns, Anti-Inflammatory Patterns and the USDA promoted, Healthy US Dietary Pattern are considered more useful in promoting healthful eating, capturing multiple dietary factors, and offering more comprehensive assessments of diet quality while accounting for the complex interactions of foods and nutrients. Researchers have also developed indexes that can be used to assess the inflammatory/anti-inflammatory potential of diets. The Empirical Dietary Inflammatory Index Pattern (EDIP) and a Dietary Inflammatory Index

(DII) are two examples of such indexes. Both tools were created to quantify the overall effects of the inflammatory foods in an individual's diet in mediating inflammation related diseases and can be used by researchers, public policy makers and clinicians helping patients reduce risk of inflammation related diseases.

Empirical Dietary Inflammatory Pattern Index

The development of the EDIP was driven by the hypothesis that reduced rank regression analysis (RRR) of dietary data from the Nurses' Health Study (NHS) would be predictive of inflammatory markers (155). The developers believed that an "a posteriori" statistical method would better portray the inflammatory effect of foods by using the response variables to derive the dietary patterns than would an indexed or an "a priori" pattern in which scores are derived from current scientific knowledge. Additionally, the EDII was construct validated in two independent samples of women and men in the NHS.

Instead of including single nutrients in inflammatory scoring methodology, the EDII score is based on 39 food groups previously defined in the 1986 and 1990 FFQs of the NHS. First, a mean daily intake of the food groups was calculated and then RRR was applied to derive a dietary pattern associated with CRP, IL-6 and TNF α R2. The researchers found 18 food groups as significantly contributing to the inflammatory markers. Intakes of white meat fish, tomatoes, processed meats, high and low energy beverages, vegetables (other than green leafy or yellow), red meat, refined grains and organ meats were positively associated with inflammatory markers. Curiously, pizza, and snacks which contain refined grains, processed meats and non-leafy vegetables as

well as fruit juices which are high energy beverages, were inversely associated with inflammatory markers. The relative validity of the EDIP score was evaluated in 2 independent cohorts of health professionals: the Nurses' Health Study (NHS)-II and Health Professionals Follow-up Study (HPFS) (156). Using data from the Women's Health Initiative (WHI) baseline FFQ, researchers confirmed the association of the EDIP score with markers of inflammation in a more racially diverse population of older women. While this tool may be useful in studies that rely on these same food groups and that do not have access to nutrient data analysis, it seems limited in its scope to accurately portray the inflammatory load in diets other than US diets.

The Dietary Inflammatory Index

The DII also quantifies the overall effects of the inflammatory foods in the diet. Originally, the index was developed from 929 research studies and validated in 2009 with subjects' data from the Seasonal Variation of Blood Cholesterol Study (SEASONS) (45). The DII was developed further by the Cancer Prevention and Control Program at the University of South Carolina in 2011-2012. The researchers enhanced the scoring algorithm of the original DII with the data of more recent and a much larger number (1,943) of articles. In addition to increasing the robustness of the data collected, the scoring system was improved to include differential inflammatory effects reported among various foods and is standardized based on human consumption. Data from eleven regional populations are also factored into the scoring to provide comparison consumption within the food parameters. Thus, the tool is more global and inter-

regionally reliable. Lastly, the DII can be used with a variety of dietary data. Scoring is reported as a percentile of maximum inflammatory effects of the data from each of the 45 food parameters which include macronutrients, micronutrients, flavonoids, and some herbs.

Since its redesign in 2012 the DII has been used to assess the inflammatory effect of foods in several studies, especially among populations afflicted with colon cancer (125). It has proven to be predictive of gastric and breast cancers, cardiovascular disease CVD, and poor diets (157–162). Its methodology was construct validated with data from NHANES, the SEASONS study and the WHI (163–166). It has also been validated among African Americans (167), post-menopausal women(166), and police officers(168). Recently the same researchers developed a children’s DII (C-DII). Up until now, no study has investigated the interrelationships among DII scores inflammation and iron status.

CHAPTER III
RESEARCH ARTICLE

Introduction

Poor iron status in obesity is reflected by an iron profile of which hypoferrremia is often, but not always paired with hyperferritinemia (22,169–172). These effects, which have been observed in iron studies among subjects with obesity are believed to be the result of increased hepcidin signaling. The hepatocyte response in obesity mirrors that which is seen during the acute phase response in which IL-6 signaling from tissues causes increased hepcidin release from the liver (93,160,173–176). However, in obesity and other chronic inflammatory diseases, the factors fueling the hepatic response remain uncorrected, obstructing hepcidin's original purpose, and subsequently healthy iron metabolism becomes impaired.

It is well established that the relationship between inflammation and obesity is rooted in a mechanism of persisting adipose plasticity that promotes an inflammatory cascade via increased IL-6 signaling. Several studies have described parallel cytokine messaging from both hypertrophic adipocytes and neighboring hypoxic tissues supporting adipocytokine and cytokine release and increased macrophage infiltration into omental fat depots (174,177,178). Overproduction of TNF- α , IL-1, IL-6, and MCP-1 results from upregulated hypoxia inducible factor (HIF-1a) in nearby tissues and from toll

like receptor-4 (TLR-4) due to the lipotoxic effects of chronically elevated free fatty acids (FFAs) in obesity. Together these create a positive feedback paracrine loop of deregulated TNF- α synthesis that promotes and supports persistent systemic inflammation.

Similarly, dietary sources can also stimulate IL-6 production via the immune system and therefore may also contribute to poor iron status by supporting increased release of hepcidin via the inflammatory cascade (124,125,179,180). Food components, such as free fatty acids, added sugars and advanced glycation end products act as non-immunity mediated ligands for TLR-4, NLRP-3 and other cell surface receptors that mediate induction of nuclear factor kappa B (NF κ B). Conversely, diets high in foods with antioxidant and anti-inflammatory properties including polyphenols, vitamin C and Omega 3 fatty acids for example have been associated with reduced risk of chronic inflammation (42,44,77). Thus, studying associations between diet mediated inflammation and iron status may offer insight into modifying the inflammatory cascade via food intake strategies.

In order to optimally assess the overall effect of dietary inflammation, the dietary inflammatory index (DII) was designed to consider both proinflammatory and anti-inflammatory foods. As a validated predictor of IL-6, and the well-known biomarker of systemic inflammation, CRP among a number of populations, the DII may be calculated using a variety of dietary assessment tools including 24h recalls, food frequency questionnaires and dietary records. In this study, we sought to investigate if

inflammatory diets impair iron status independent of BMI. We hypothesized that DII scores will be positively associated with CRP concentration, and that higher DII scores will be associated with poorer circulating iron biomarkers.

Methods

Study Population

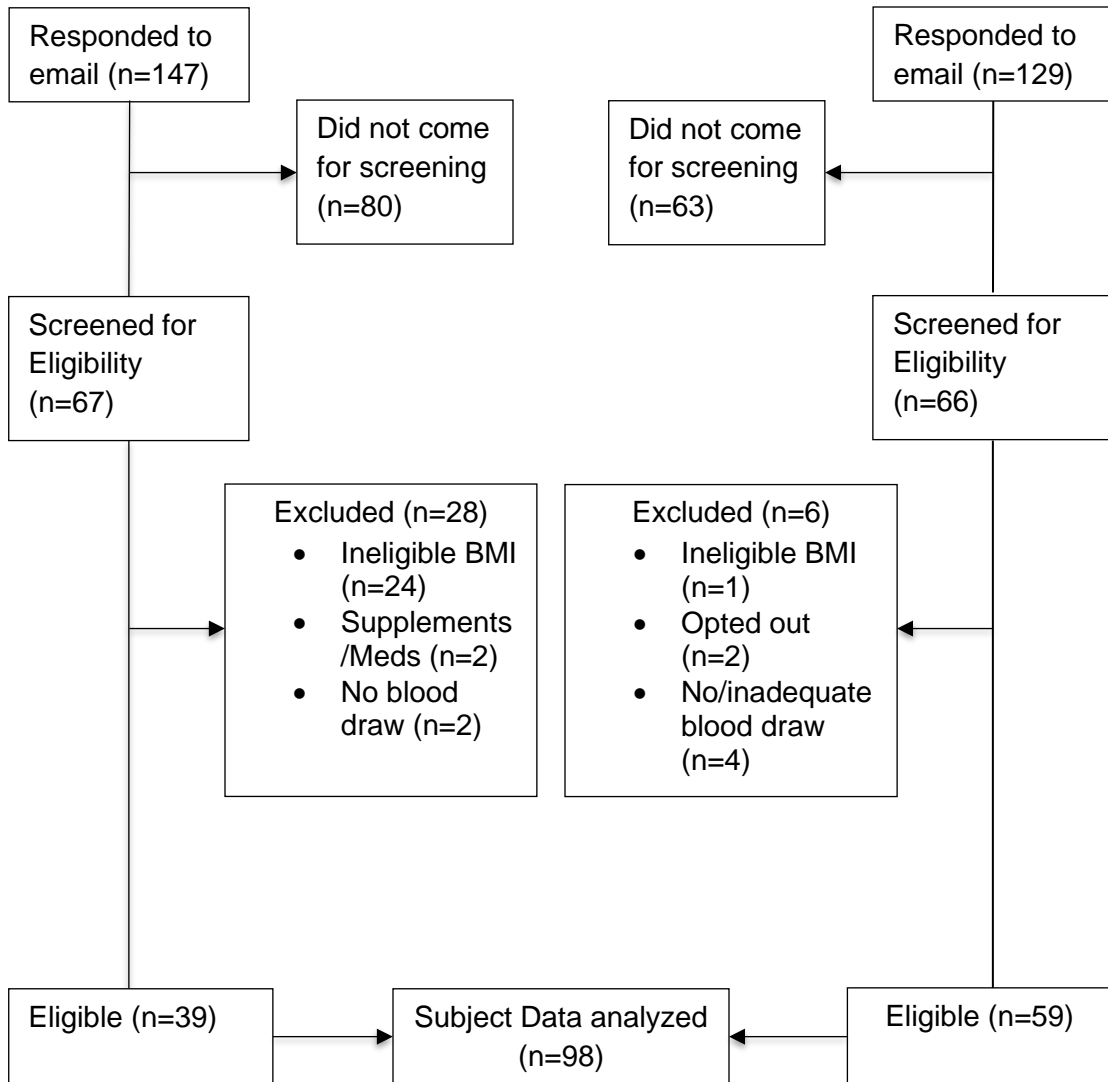
Data from two cross-sectional studies of the same design namely the Diet and Inflammation Study (DI study) and the Selenium and Inflammation Study (SI study) were used for this analysis(181,182). The DI study was conducted in Spring 2017 to investigate the relationships among diet, hepcidin and iron status. Subjects recruited for this study were those within the age range of 18 to 49 years who were non-pregnant, non-lactating, and non-smoking. Additionally, they were not to have donated blood in the past two months, must not be taking vitamin and mineral supplements, and must have a BMI within the range of 25.0 to 40 kg/m². A total of 147 subjects responded to the mass e-mail and 67 subjects were came for screening. Twenty-two participants were ineligible due to BMI, two were excluded due to supplements or medications, and two did not complete blood draw. In total, 39 participants completed the DI study. Dietary intake, and anthropometric (height and weight) measurements were conducted on each subject. Fasting venous blood samples were collected to measure concentrations of iron status and inflammatory markers. The SI study on the other hand was conducted in Spring 2018 to investigate the associations among selenium status, hepcidin concentration and iron status biomarkers in individuals with overweight or obesity compared to normal weight

controls. Similar to the DI study, subjects were included if they were non-pregnant, non-lactating, non-smoking, not using vitamin and mineral supplements and had not donated blood in the past two months. However, the BMI criteria for inclusion in the SI study was $\geq 18.5 \text{ kg/m}^2$. In addition to collecting dietary, anthropometric and biochemical markers, the SI study also collected additional anthropometric variables such as body fat, visceral fat, and muscle mass, and also measured plasma selenium concentration, and other biomarkers of selenium status among subjects. A total of 129 subjects responded to mass e-mail and 66 came for screening in the SI study of which two opted out for personal reasons, one did not meet BMI criteria, and one subject did not complete the blood draw. In total, 59 subjects were included in that study. Both studies were conducted at the Cemala Foundation Human Nutrition Research Laboratories at the Nutrition Department of The University of North Carolina at Greensboro (UNCG). The study protocols were approved by the Institutional Review Board of UNCG. Summary of subject recruitment and inclusion in the two studies is shown in **Figure 1**. In each of the studies, informed written consent was obtained at screening from every subject before recruitment. After signing the consent form, each participant was requested to complete a screening form requiring information such as demography, vitamin and mineral supplement use, medical history and pregnancy status. Height and weight measurements were also done at screening to assess BMI for inclusion.

Figure 1. Subject Recruitment

Diet and Inflammation study

Selenium and Inflammation study



Data Collection

For each of the two studies, qualified participants were provided with a dietary record form, food frequency questionnaire, and a weighing scale and were required to record all foods consumed on three non-consecutive days of which two were weekdays and one was a weekend day. At the follow-up study visit, anthropometric measurements were repeated, a 10h fasted venous blood (approximately 30 ml) was collected and participants submitted their completed three-day dietary records. The dietary records and food frequency questionnaires were reviewed with each participant by trained research assistants.

Dietary data from the three-day dietary records were analyzed into nutrients using the Nutrition Data System for Research (University of Minnesota, MN, USA) and used in calculating the DII scores. Up to 45 food components can be used for calculating DII scores. Thirty of these were available from the NDSR data and were used in the analyses of this study (**Table 1**). These included: fiber, vitamin B6, folic Acid, niacin, riboflavin, thiamin, beta carotene, vitamin A, vitamin D, vitamin E, vitamin C, caffeine, alcohol, selenium, magnesium, zinc, isoflavones, MUFA, Omega 3, Omega 6, PUFA, total fat, trans fat, saturated fat, iron, carbohydrate, protein, cholesterol, Energy, vitamin B12. The first twenty-one components were considered anti-inflammatory and the remaining considered inflammatory. The DII calculations were done at the Cancer Prevention and Control Program Center at the University of South Carolina as previously described (45).

For each participant, some of the fasted blood samples were sent to LabCorp (Burlington, NC) after processing for the measurement of hemoglobin, iron saturation, serum iron, total iron binding capacity (TIBC), serum ferritin and C-reactive protein concentration (CRP). The remaining were stored at -80 °C at UNCG for the measurement of hepcidin concentration at the end of each study. Hepcidin was analyzed using ELISA assay kit from Peninsula Laboratories International (San Carlos, CA, USA).

Table 1. Food Components of DII Scoring Algorithm

Anti-inflammatory		Pro inflammatory
Alcohol	Folic acid	Total fat
n-3-fatty acids	Selenium	Vitamin B ₁₂
Vitamin E	Flavonones	Carbohydrate
Vitamin B ₆	Garlic	Cholesterol
n-6 fatty acids	Thiamin	Energy
Zinc	Anthocyanidins	Iron
B-Carotene	Ginger	Protein
Onion	Turmeric	Saturated fat
Green/black tea	Isoflavones	Trans Fat
Caffeine	Magnesium	
PUFA	Vitamin A	
Flavan-3-ol	Pepper	
Eugenol	MUFA	
Riboflavin	Vitamin C	
Flavones	Thyme/oregano	
Fiber	Niacin	
Saffron	Vitamin D	
Flavonols	Rosemary	

Subjects were categorized as having normal weight (18.5-24.9 kg/m²), overweight (25-29.9kg/m²) or obesity (above 30kg/m²) according to established BMI criteria. To

categorize the DII scores into either pro inflammatory or anti-inflammatory diet group, we used cluster analysis.

Statistical Methods

Statistical analyses were done using the R statistical software (183).. DII scores were treated both as a continuous variable and as a categorical variable for the purpose of investigating all possible relationships between the DII and the primary outcome variables which were serum iron, TIBC, hepcidin concentration and CRP concentration. To categorize the DII score into either a pro inflammatory or anti-inflammatory diet group, we chose cluster analysis with only two groups to ensure adequate sample size for each group. Percentages were reported for categorical variables such as sex, ethnicity and BMI categories. Hepcidin, ferritin, and transferrin saturation values were used for post hoc analyses. The means and standard error of mean (SEM) were reported for the continuous variables such as age, BMI, serum iron, hemoglobin, TIBC, transferrin saturation and for the concentrations of ferritin, hepcidin, and CRP. Skewed variables were log transformed and the geometric means were reported. Fisher's exact test and ANOVA were used to compare background characteristics. Where ANOVAS showed statistical significance, Tukey's HSD was used for multiple comparison. Linear regression analysis was used to determine the association among the DII as an independent variable with CRP, hepcidin concentration, serum iron and TIBC. All regression models were adjusted for age, gender, and ethnicity. We also adjusted for

meat, fish and poultry intake where necessary since iron intake was considered pro-inflammatory in the DII calculations. Statistical significance was set at $P \leq 0.05$.

Results

Background Characteristics of Subjects

Participant background characteristics grouped by BMI category are displayed in (**Table 2**). The overall mean age was 21.0 ± 0.4 y and the majority of the subjects (72 of the 98) were female. Despite higher female representation, the distribution of both sexes among BMI categories was not significantly different. ($p=0.6$). Similarly, there was no significant association between BMI category and ethnicity ($p = 0.7$). BMI categories were also well represented with 29% of subjects having normal weight, 40% having overweight and 32% having obesity status (total percentage not equal to 100 due to rounding).

Table 2. Background Characteristics According to BMI

	BMI (kg/m ²) category				P-Value
	Normal 18.5-24.9 N= 28	Overweight 25-29.9 N= 39	Obese ≥ 30 N= 31	Total N=98	
Age (y)	21.2±0.4	21.4±0.7	21.8±0.6	21±0.4	0.8
Sex ¹					0.6
Male	8 (8.16%)	9 (9.18%)	10 (10.20%)	27 (27.55%)	
Female	20 (20.41%)	30 (30.61%)	21 (21.43%)	71 (72.44%)	

Ethnicity ¹					0.7
Hispanic	3 (3.06%)	4 (4.08%)	4 (4.08%)	11 (11.22%)	
NH White	14 (14.29%)	11 (11.22%)	13 (13.27%)	38 (38.78%)	
NH Black	6 (6.12%)	13 (12.27%)	16 (16.33%)	35 (35.71%)	
Other	5 (5.10%)	3 (3.06%)	6 (6.12%)	14 (14.29%)	
BMI ¹ , kg/m ²	22.5±0.3a	27.0±0.24b	34.9±0.50c	28.±0.5	<0.0001

Values are ¹means ± SEM · ² are n (%) or ³geometric means (geometric mean – SEM, geometric mean + SEM)

Nutrient Intakes and DII Scores among Subjects

DII scores and the median intakes of selected nutrients including iron, MFP (meat, fish, poultry), protein, fiber and fat by BMI category are reported in (**Table 3**). There were no significant differences among BMI categories for the nutrients reported. Among all participants, the DII scores ranged from a maximally anti-inflammatory score of -4.2 to a maximally proinflammatory score of 3.7. Cluster analysis of the scores grouped them into distinctly anti (-4.2 to 0.7) or pro inflammatory (0.8 to 3.7) groups for bivariate comparisons.

Table 3. Selected Nutrient Intakes and DII Scores According to BMI

Factor/Nutrient	Normal Weight	Overweight	Obese	P-value
Iron, mg	16.87 (9.37, 19.43)	12.25 (9.72, 14.79)	15.68 (9.70, 20.20)	0.166
MFP (ounces)	3.56 (2.20, 6.25)	5.92 (3.57, 7.99)	4.59 (3.02, 7.05)	0.06
Calories, kcals	1779 (1426, 2527)	1875 (1433, 2209)	2229 (1591, 2628)	0.43
Protein, g	74.45 (50.26, 96.49)	74.09 (51.91, 98.30)	74.87 (71.30, 97.42)	0.48
Fiber, g	17.28 (11.70, 21.73)	14.41 (11.76, 17.18)	16.68 (12.20, 22.16)	0.24
Fat, g	67.89 (56.50, 106.32)	74.75 (52.97, 97.27)	95.05 (63.93, 113.71)	0.31
DII Score	1.02 (1.19, 1.97)	0.97 (0.18, 2.04)	1.01 (0.47, 1.96)	0.8

Inflammatory and Iron Status Biomarkers

CRP concentration was highest among the subjects with obesity [3.63 (2.98, 4.43) mg/L], and lowest among subjects with normal weight [0.40 (0.32, 0.48) mg/L] (P< 0.05 for all comparisons) (**Table 4**). A trend toward poor iron status as BMI category increased was reflected in most iron status biomarkers (serum iron, Tsat and TIBC), however, only serum iron was significantly higher in normal weight ($103\pm 10\mu\text{g/d}$) compared to obesity ($72.6 \pm 6\mu\text{g/d}$) category (p=0.01). Hepcidin concentrations were nearly twice as high in subjects with obesity compared to those with normal weight but this was not significant (p =0.06).

Table 4. Inflammatory and Iron Status Biomarkers According to BMI

	BMI (kg/m ²) category				P-value
	18.5-24.9 N= 29	25-29.9 N= 39	≥ 30 N= 31	Total N=98	
CRP ¹ (mg/L)	0.4(0.3, 0.5) ^a	0.8(0.7, 1.0) ^b	3.6(3.0, 4.4) ^c	1.1(0.9, 1.2)	<0.0001
Ferritin ¹ (ng/ml)	37(31, 45)	33 (28,39)	51 (43,61)	39 (35,49)	0.2
Serum iron (µg/dL)	103±10 ^a	83±6 ^{a,b}	72±6 ^b	85±4	0.014
Transferrin saturation (%)	31.3±3.4	26.1±1.9	23.0±2.0	26.6±1.4	0.07
Hemoglobin (g/dL)	13.6±0.3	13.1±0.4	13.5±0.3	13.4±0.2	0.6
TIBC (µg/dL)	355±15	346±8	344±12	348±6	0.8
Hepcidin ¹ (ng/ml)	10.7 (8.7, 13.2)	12.2 (10.1, 14.8)	20.8 (16.9, 25.6)	13.9 (12.4, 15.7)	0.06

¹Data were log transformed. Values are geometric means (geometric mean -1SE, geometric mean +1SE)

Associations of DII with CRP and Hepcidin Concentrations

Using linear regression, we investigated the association between the DII scoring as a continuous variable and inflammation as assessed using CRP concentration (**Table 5**). We found that CRP concentration increased with increasing DII score ($\beta \pm SE = 0.23 \pm 0.07$, $p=0.002$) and that caloric intake also predicted CRP concentration ($\beta \pm SE =$

0.54±0.17, p=0.002). In this model, having overweight ($\beta \pm SE = 0.63 \pm 0.26$, p=0.020) or obesity ($\beta \pm SE = 2.17 \pm 0.28$, p < 0.001) was associated with higher CRP compared to subjects having normal weight.

We also determined the association between DII as a categorical variable and CRP concentration (**Table 6**). In this model, the relationship between DII category and CRP was not statistically significant ($\beta \pm SE = -0.45 \pm 0.25$, p=0.076). Also, although the anti-inflammatory diet category was associated with lower hepcidin concentration, this was not statistically significant ($\beta \pm SE = -0.29 \pm 0.17$; p = 0.095).

Table 5. Associations of DII Scores with CRP and Hecpidin

Predictors	CRP, mg/L (n=98)			Hepcidin, ng/mL (n=98)		
	β	SE	p	β	SE	p
DII ®	0.23	0.07	0.002	0.03	0.06	0.546
Energy, cal	0.54	0.17	0.002	0.06	0.1	0.63
BMI Category						
Obese	2.17	0.28	<0.001	0.30	0.27	0.269
Overweight	0.63	0.26	0.02	0.21	0.20	0.286
CRP ¹ (mg/L)				0.07	0.08	0.378
Ferritin ¹ (ng/mL)				0.85	0.09**	<0.001

Regression models were adjusted for age, sex and ethnicity.

DII = Dietary Inflammatory Index

¹Data were log transformed.

Table 6. Associations of DII Category with CRP and Hepcidin

Predictors	CRP (mg/L)			Hepcidin (ng/mL)		
	β	SE	p	β	SE	p
DII category						
Anti-inflammatory	-0.45	0.25	0.076	-0.29	0.17	0.095
Energy, cal	0.4	0.1	0.018	0.1	0.1	0.383
BMI category						
Obese	2.25	0.29	<0.001	0.33	0.26	0.214
Overweight	0.72	0.27	0.010	0.24	0.19	0.225
CRP ¹ (mg/L)				0.06	0.07	0.411
Ferritin ¹ (ng/dL)				0.85	0.09	<0.001

Regression models were adjusted for age, sex and ethnicity

DII = Dietary Inflammatory Index

¹Data were log transformed. Values are geometric means (geometric mean -1SE, geometric mean + 1SE)

Associations of Inflammatory Diets with Iron Status Biomarkers

DII score was an independent predictor of TIBC when analyzed as a continuous variable (($\beta \pm SE = -8.46 \pm 3.44$, $p = 0.016$) (**Table 7**). DII scores were not however related to serum iron. Only the obese category was predictive of lower serum iron while ferritin concentration predicted higher serum iron and lower TIBC. Anti-inflammatory diets

were associated with high TIBC ($\beta \pm SE = 29.87 \pm 10.75$, $p = 0.007$) (**Table 8**). This relationship was independent of other iron status biomarkers.

Table 7. Associations of DII Scores with Iron Status Biomarkers

Predictors	Serum iron, $\mu\text{g/dL}$ (n=97)			TIBC, $\mu\text{g/dL}$ (n=98)		
	β	SE	p	β	SE	p
DII ®	1.98	2.63	0.454	-8.46	3.44	0.016
Energy, Cal	0.00	0.01	0.720	0.00	0.01	0.809
BMI Category						
Obese	-27.11	12.31	0.030	-4.16	16.36	0.80
Overweight	-14.24	9.18	0.125	-12.43	12.05	0.305
CRP ¹ mg/L	-4.99	3.61	0.171	5.14	4.79	0.287
Ferritin ¹ ng/mL	14.55	4.30	0.001	-43.33	5.71	<0.001

Regression models were adjusted for age, sex, ethnicity and MFP.

¹CRP = C-Reactive Protein

DII= Dietary Inflammatory index

Table 8. Associations of DII Category with Iron Status Biomarkers

	Serum iron, $\mu\text{g/dL}$ (n=97)			TIBC, $\mu\text{g/dL}$ (n=98)		
	β	SE	p	β	SE	p
DII Category						
Anti-inflammatory	2.03	8.20	0.805	29.87	10.75	0.007
Energy, Cal	-0.00	0.01	0.867	0.00	0.01	0.552
BMI Category						
Obese	-29.03	12.28	0.020	-3.03	16.10	0.851
Overweight	-14.15	9.23	0.129	-15.23	11.98	0.207
CRP ¹ mg/L	-3.93	3.48	0.262	3.57	4.55	0.435
Ferritin ¹ ng/mL	15.33	4.24	<0.001	-44.58	5.57	<0.001

Regression models were adjusted for age, sex, ethnicity, and MFP intake.

¹CRP = C-Reactive Protein

DII= Dietary Inflammatory index

Data were log transformed.

Discussion

Systemic inflammation can be triggered by several factors including diet and obesity (44,177,184,185) and can lead to adverse health outcomes such as type 2 diabetes and cardiovascular diseases. Recent studies have shown that inflammation may also play a role in iron status regulation through the protein hepcidin. For example, low grade inflammation in obesity has been implicated in the poor iron status observed among individuals with obesity (23,169,179,186,187). While diets may play a role in iron status

through their heme and nonheme iron contents, it is not clear if their inflammatory and anti-inflammatory properties also influence iron status. In this study, we investigated the relationship between the inflammatory score of diets assessed using the DII and circulating iron biomarkers, namely serum iron and TIBC, adjusting for obesity status and other potential confounders. We chose the circulating iron biomarkers because elevated hepcidin concentration directly reduces circulating iron through poor iron absorption or iron sequestration (91,176,188).

Median nutrient intakes in our studies were not significantly different among the three BMI categories (normal weight, overweight and obese). Compared to other studies (189), we found a much higher median MFP intake in our study population (5.08 ounces or 142 g vs 91 g) despite similarities in age group. This is due to the fact that the dietary intakes of subjects in their study were modified in some cases. On the other hand, fiber intake data by BMI in our study is similar to those among US college students reported by Garcia-Meseguer (190) in a study of fiber patterns among college students in three different countries (Spain, USA and Tunisia). They observed median fiber intakes among USA students of 18.1g, 15.3g and 18.3g in normal weight, overweight, and obese participants respectively compared to 17.28, 14.41 and 16.68 among our study participants.

DII scores in our study ranged from -4.44 to 3.49 with median of 0.99. The lowest DII score in this study compares favorably to the -4.93 minimum DII score reported in another study among young adults (21-35y) living in southeastern US (South Carolina)

(191), although they reported DII scores much higher than our maximum value of 3.49. Median DII scores in our study did not differ significantly among the different BMI categories ($p=0.8$). In a study of associations between body weight and dietary inflammation, Muhammad et al. (192) also found no associations between BMI and DII as a continuous variable or with DII tertile. While these support our findings, the contrary was reported by Ruiz-Canela et al. (193) who found a positive association between the two variables in a population with high risk for CVD. In this study, the correlation was found only among women and all the study participants were at least 55y. In a college setting similar to our study, Kim et al.(194) compared DII scoring with HEI and glycemic index scores. In their study, DII was positively correlated with glycemic index (GI) and inversely correlated with HEI. Wirth et al., also reported negative correlations between the DII scores of young adults and the HEI-2010 ($r = -0.65, P < .01$), AHEI ($r = -0.55, P < .01$), as well as the DASH diet ($r = -0.52, P < .01$). Even though DII scores were also not associated with BMI, lower DII values were found in individuals with the lowest waist-to-hip ratios (WHR), a reliable indicator of central adiposity (195–198). However we did not have WHR measures for our analyses.

In our study, geometric mean of CRP was 1.1 mg/L (0.9, 1.2). In two recent studies of young adults, mean CRP was found to be 1.72 mg/L and 1.5 mg/L (199,200). Our lower value may be due to the fact that we reported the geometric mean, while these studies reported the arithmetic mean. Our findings showed that CRP concentration increased with BMI category, being highest in the obese category and

lowest in the normal weight category. This affirms what has been reported in several earlier studies (201,202).

We also found in a positive association between DII score and CRP concentration, which attests to the ability of the DII score to predict inflammation. Our results also corroborate the findings from several other studies (164,167,200,201). For example, Boden et al. (203) observed that DII predicted 1.7% of elevated CRP in a prospective case control study of 1,389 verified cases of first myocardial infarction (MI). Wirth et al. (167) reported positive associations between DII scores and CRP levels among African Americans in the fourth quartile of DII category in baseline data of the Healthy Eating and Active Living in the Spirit (HEALS) intervention study. In our regression analyses that included DII scores, both DII scores and overweight and obesity status categories were predictors of CRP suggesting that diet in addition to increased adiposity may contribute to the higher CRP among young adults. Dietary factors are shown to trigger inflammation via NF κ - β activation and subsequent induction of inflammatory cytokines through upregulated innate immune signaling of toll like receptors-4 (TLR-4) and via the NLRP3 complex (124,154,204). High fat diets, particularly those high in saturated and trans fatty acids are shown to increase inflammation in mouse models and human studies while diets low in animal products are known to be anti-inflammatory. In an early mouse model, Lumeng et al. (205) found that a high-fat diet increases the inflammatory properties of macrophages recruited by adipose tissue in obese compared to lean mice. In a later study, Kim et al. (206) reported

increased systemic inflammation and acceleration of adiposity via increased TLR4 signaling by high fat diet induced endotoxemia in the intestinal lumen of mice. In humans, a recent meta-analysis that controlled for weight loss reported that plant-based diets were independently associated with reductions in CRP in subjects with obesity (207).

We also compared iron status and inflammatory markers among the different BMI categories. While other iron status biomarkers did not differ significantly, serum iron was significantly lower among subjects with obesity compared to those with normal weight ($p=0.014$). It is well documented that obesity is a risk factor for poor iron status (19,170,172,208) and the impaired iron status in obesity has been attributed to factors such as inflammation and concomitant elevated hepcidin concentration. Citelli et al. (179) reported increased hepcidin gene expression and iron accumulation in spleen and liver tissues as well as reductions in ferroportin (FPN) gene expression in obese mice fed a high fat diet. In humans, a combined cross-sectional and longitudinal case control study by Moreno-Navarrete et al.,(188) reported increased serum hepcidin, ferritin and hepatic iron content (HIC) among patients with obesity along with subsequent improvement in these values after dietary weight loss interventions. Chang et al. (2014 REF) observed associations of fat to carbohydrate ratios with BMI among women with iron deficiency anemia (IDA) but not among healthy women. Their findings showed a positive relationship between BMI and fat consumption ($p = 0.035$) and an inverse relationship between BMI and CHO intake ($p = 0.045$) only in women with IDA. These

studies suggest that obesity alone is not responsible for the alterations of iron metabolism in obesity (15,209,210). Therefore, in the present study we investigated how dietary inflammation, assessed through the DII scoring methodology, influences iron status independent of obesity related inflammation.

During inflammation, the iron transport protein transferrin is a negative acute phase protein, and its production, therefore is downregulated, reducing its concentration (211–214). In a female rat model, Zeid et al. (215) observed reduced TIBC in obese Wistar rats fed a high fat diet compared to control non obese mice fed standard chow. The researches also reported lower serum iron and transferrin saturation in high fat diet. This same study reported increased hepcidin, IL-6, ferritin and plasma leptin in the obese rats compared to control. In the regression analyses of our study, higher DII scores predicted lower TIBC levels which suggests lower transferrin levels among subjects whose diets were estimated to have had higher inflammatory effects. TIBC is reduced in both iron replete and inflammatory states. Since our analyses controlled for meat, poultry, fish intake and as well as for other iron status biomarkers, it is more likely that the inflammatory effects of the diet predicted reduced TIBC rather than increased iron intake.

Limitations

While data from the present study were from mostly female subjects (72%) which could affect the value of the iron status biomarkers, we did not find a significant difference in sex distribution among the different BMI categories. Another consideration

of this study's results is that the current version of the DII which is weighted toward anti-inflammatory components does not score more recently studied food components such as added sugars, non-nutritive sweeteners and advanced glycation end products which were common among the dietary records of the study's sample. Future studies are needed to determine the effects of dietary inflammation on transferrin production by the liver, as well as longitudinal investigations into how added sugars, non-nutritive sweeteners and the cooking effects of manufactured edible oils may influence inflammatory and micronutrient status.

Conclusion

In conclusion, we are the first to use the DII to examine the inflammatory effects of diet on circulating iron biomarkers and to demonstrate a relationship between inflammatory diets and decreased TIBC. While it may be easy to presume that the effects of weight gain, including increased adiposity, alone account for poor health outcomes, lifestyle factors such as diet and activity patterns may play a key differentiating role. In this study we have demonstrated that diet, independent of body weight status, predicts inflammation among young adults. This implies that less inflammatory diets can be prescribed for reducing inflammation in all patients independent of weight status and for improving outcomes in chronic diseases.

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