THE CARB-APPROPRIATE REVIEW

A MONTHLY RESEARCH REVIEW BY

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ABOUT CLIFF

Cliff Harvey PhD is an author, clinician, and researcher. He was one of the first clinical nutritionists to begin working with ketogenic and low-carb diets, way back in the 1990s and is also considered a pioneer in the area of mind-body integrative healthcare.

Cliff's early post-graduate work was in mind-body healthcare, while his master's research focussed on the use of medium-chain triglycerides to mitigate 'keto-flu' and encourage faster induction of nutritional ketosis.

His doctoral thesis continued to investigate keto-flu and ketogenesis, and the effects of different types of low-carbohydrate diets along with the individualisation of dietary prescription and how 'carbohydrate tolerance' varies from person-to-person.

He is a former world champion strength athlete, submission grappler, and author of several best-selling books, including *The Carbohydrate Appropriate Diet*, *Carb-Appropriate 101*, and *The Credo.*

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THIS MONTH

ALL YOU NEED TO KNOW ABOUT TREATING CANDIDA *NATURALLY*

Key Findings:

- Candida can affect many areas of the body with symptoms ranging from innocuous, to mild, to severe
- At greatest risk are those with severe immune dysfunction
- Sugar, ultra-processed foods, and trans-fats are likely to worsen candidiasis
- Medium-chain triglycerides reduce candida
- Omega-3 fats are likely to aid the treatment of candidiasis
- Many herbs also exhibit some anti-candida activity
- Mushrooms such as Reishi may also be of benefit to candida treatment

Candida albicans is a pathogenic yeast that is found in the gastrointestinal tract and mouth of at least 25% of healthy adults.[1] It is the main Candida species responsible for *candidiasis*—symptoms caused by an overgrowth of these yeasts. Candida is present in many people and may cause symptoms and effects that are mild to moderate (yet often very uncomfortable) in most people, through to very severe, and candidiasis is especially dangerous for those with compromised immune systems (those with HIV or cancer in particular) who are unable to adequately launch immune responses to deal with the yeast. In severe cases of immune dysfunction, candidiasis can be fatal. Candidiasis is typically treated with antifungal drugs amphotericin B, echinocandin, or fluconazole but nutrition may play a valuable role in helping to treat candida overgrowth. Candidiasis is known as 'thrush' (especially in the mouth) or as vaginal thrush or 'yeast infection' when found in the vagina.

Signs and symptoms of candidiasis can be diffuse and can present in many ways.

Oral

- White-to-yellow patches on the tongue or other areas of the mouth and throat
- Mouth or throat soreness and problems swallowing

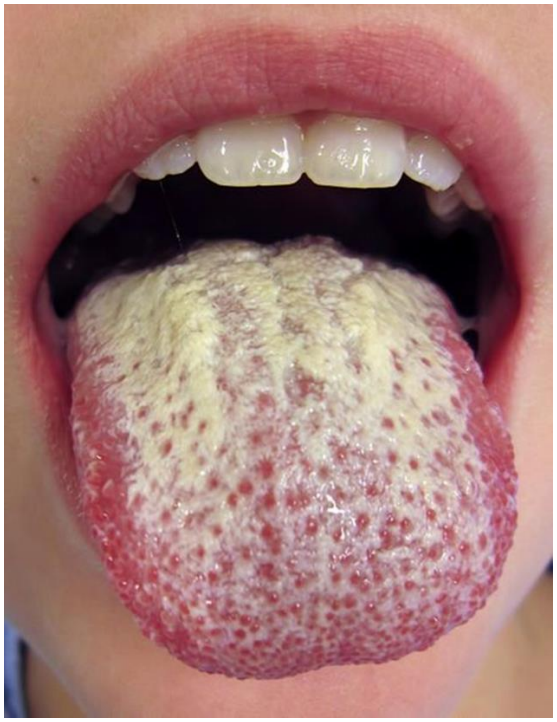


Figure 1. Human tongue exhibiting oral candidiasis. By James Heilman MD. https://commons.wikimedia.org/wiki/File:Human_tongue_infected_with_oral_candidiasis.jpg

Vaginal

- Genital itching or 'burning' sensation
- White "cottage cheese-like" discharge from the vagina

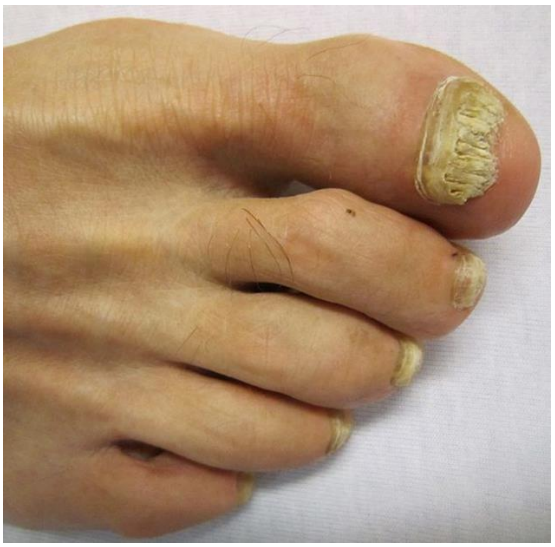
Penile

- Itchy rash

Invasive

- Itching skin
- Fever
- Fatigue
- Possibly many other symptoms

Candida is also one of the fungi known to be a cause of skin and nail infections known collectively as *tinea*.



Plausible mechanisms for diet therapy

Dietary sugars

It has been observed that the dietary sugars maltose and glucose encourage the adhesion of candida to epithelial cells taken from the gut and mouth, while lactose has no effect.[2] This adhesion or 'sticking' to the cells lining the mouth or other body cavities is considered to be a critical step in the development of candidiasis.

High concentrations of fructose, glucose, maltose, sucrose, and sorbitol

significantly promote the adhesion of *Candida albicans*, *tropicalis*, *glabrata*, and *parapsilosis*.[3, 4] While galactose, glucose, and sucrose elicit a maximal adhesion of candida albicans and tropicalis,[3, 4] *Candida krusei* adhesion was enhanced most when cultured in glucose. Maltose and fructose also promoted adherence of Candida albicans and tropicalis, but to a lesser extent than sucrose and glucose. The sweetener xylitol significantly reduced adherence of Candida albicans.[3] Lactose and trehalose do not appear to increase adhesion.[4]

> High concentrations of fructose, glucose, maltose, sucrose, and sorbitol significantly promote the adhesion of *Candida albicans*

Mice were exposed to candida albicans and allowed free access to water and food, with the drinking water supplemented with either glucose or xylitol or no carbohydrates (control). After 33 days, candida albicans growth on the mucosa of the intestinal wall and faecal cultures of candida were highest in the glucose group. 80% of mice in the glucose group showed extensive, invasive growth of candida in the GI tract compared to only 8% of the control and xylitol supplemented animals.[5]

Biofilm formation

Biofilms are defined as an *"aggregate of microorganisms in which cells that are frequently embedded within a self-produced matrix of extracellular polymeric substances (EPSs) adhere to each other and/or to a surface."* In other words they comprise of microbes (like yeasts, fungus, bacteria, protozoa) that clump together and adhere to a surface (in this case on tissue in the body) and become encased in a matrix of polysaccharides (long-chain carbohydrates), proteins, and other compounds that they produce, which support the structure of the biofilm and protect them against other microbes and, in the case of pathogenic microbes also protect against the immune system of the body.[6]

Biofilm of candida albicans showed pronounced growth when its growth surface was pre-treated with sugar.[7] Dietary sucrose might reduce the anticandidal activity of salivary lactoferrin.[8]

On denture surfaces, glucose, sucrose, and starch+glucose solutions increase the metabolic activity associated with biofilm formation and this differs depending on the type of carbohydrate

applied. The authors concluded that "dietary carbohydrates can modulate biofilm development on the denture surface by affecting virulence factors and structural features".[9] Candida varieties grown in glucose medium demonstrate more biofilm activity than galactose or control.[10]

Biofilm of candida albicans showed pronounced growth when its growth surface was pre-treated with sugar

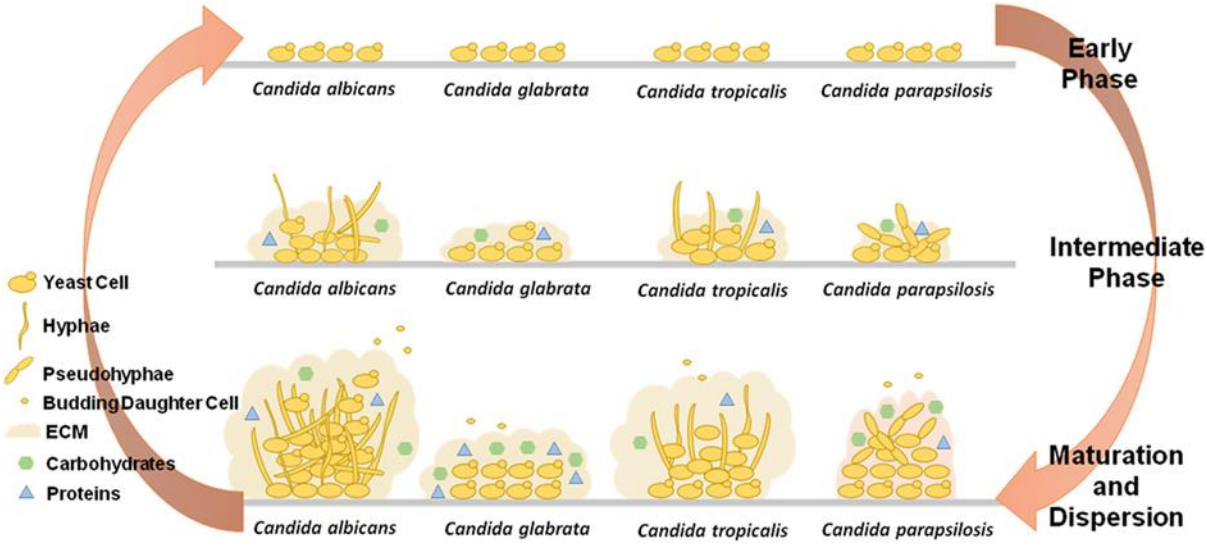


Figure 2. Progression of Candida species from yeast to hyphae to invasive infection with biofilm protecting the colony from the immune system. From https://www.frontiersin.org/articles/10.3389/fmed.2018.00028/full

Dietary carbohydrate

In an evaluation of the diet and health history of 373 women (< 50 years old) increased incidence of candida infection was associated with smoking, oral contraceptive use greater than 6 months, overweight/obesity, metabolic syndrome, and early sexual activity.[11]

Dietary analysis showed an increasing and significant trend for carbohydrate intake with the lowest carbohydrate intake associated with reduced risk and increased risk as carbohydrate content of the diet increased.[11]

analyses showed candida risk was lowest with the lowest carbohydrate intake

A strong association was also seen between overall energy intake and

incidence of candida infection (OR 2.44; 95% CI 1.36-4.37).

The addition of refined sugar to the diet has also been studied. In a 2-step study of 28 healthy volunteers, the habitual intake of refined carbohydrates was correlated with candida albicans concentration in the mouthwashes and faeces of subjects. Secondly, C. albicans counts were compared before, during, and after a high-sugar diet. No associations were found between candida counts and habitual intake of refined carbohydrate and a high-sugar diet didn't increase the frequency of candida-positive samples.

However, subjects with habitually high candida counts (pre-intervention) did have an increase in faecal candida counts in response to the high-sugar diet.[12]

In vulvovaginal candidiasis, urinary sugars are associated with infection. Reductions in milk, artificial sweeteners, and sugar resulted in ~90% of patients resolving infection for at least one year.[13]

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Is there evidence for an 'anti-candida' diet?

There are many diets that claim to combat candida but at this time there is limited evidence for the effectiveness of them and there are many misinformed claims made about both the severity of the illness and the methods that can be used to combat it. There is however some preliminary evidence that can help us to determine dietary strategies that might be of benefit to candidiasis.

In a pilot study, people with candida infection were treated with either *nystatin* (an anti-fungal medication) (n = 40) alone or in combination with an 'anti-candida diet' (n = 80). The diet consisted of the following food restrictions:

Avoid	Allowed
Honey, jam, candy, ice cream with sugar added and types of fruit with high sugar content such as grapes and watermelon. Foods containing a lot of starch, such as products made from white flour (white bread and rolls, cakes, biscuits, pasta), white rice, lentils, white beans and potatoes. Cured and 'fatty' meats; e.g. ham, bacon, salami, sausages, roasts, broil, red meat (pork, beef, mutton, chicken), entrails. Milk, yellow cheese, cheese spread and mouldy cheese. Alcohol, alcoholic vinegar.	Artificial sweeteners (including stevia). 1-2 fruit servings per day (excluding those with high sugar content). Food made from whole grain wheat flour (bread and pasta), potatoes, brown rice. Fish (e.g. mackerel, hake, tuna, salmon, sardines), seafood, low fat-white chicken meat. Yoghurt and acidophilus drinks (yoghurt with inulin and other probiotics). Dietary supplements: Omega-3 fatty acids (alone or with omega-6 and omega-9 fatty acids), linseed oil, evening primrose oil (1 teaspoon or 3 capsules) twice a day, propolis drops, multivitamin complex with selenium, zinc (one effervescent tablet daily), *Lactobacilli acidophilus* or probiotic *Bifidus* capsules or any other probiotic, herbal teas traditionally used against fungal diseases.

After ten days there were similar rates of remission (control of the fungal infection) between the drug or diet-drug combination therapy. However, after three months, there was a significantly higher percentage of people classified as 'cured' in the diet group (85%) compared to the non-diet group (42.5%).[14]

there was a significantly higher percentage of people classified as 'cured' in the diet group

While this is promising, it is highly preliminary, and there were some conflicting guidelines (potatoes both allowed and disallowed), and many supplements and herbs also allowed which could have influenced the results.

Other methods that might aid the treatment of candida

Breast-feeding

A study was carried out to determine the impact of formula or breast milk on candidiasis. In this study, the prevalence and intensity of Candida species were evaluated in 300 healthy Turkish children aged between 0 and 12 years. The prevalence of candida in children who

were fed with both breast milk and formula or other fluids was 18.5%, while in children fed only breast milk there were no cases of candida.[15]

Medium-chain triglycerides

Coconut oil and its constituent fatty acids like lauric acid have demonstrable antifungal activity.[16] In mice fed a coconut oil-rich diet, colonisation of the gastrointestinal tract by candida was lower than that for diets rich in either beef tallow or soybean oil. Interestingly, coconut oil reduced colonisation when the diet also contained beef tallow, and dietary coconut oil also altered the metabolic program of colonising *C. albicans* cells.[17]

MCTs, like capric and caprylic acid, may be effective interventions for treating Candida

Lauric acid (the main medium-chain fatty acid in coconut oil) is unlikely to be the only medium-chain triglyceride (MCT) that inhibits yeast and fungal growth. Capric acid (C:10) and caprylic acid (C:8) can also reduce the virulence of candida by reducing activity, adhesion, and biofilm formation of the yeast. Research has shown that capric acid and caprylic acid affect the yeast-to-hyphal (the development of yeast into a more virulent mycelium) signal transduction pathways of candida and reduce expression of key genes (Cdc35, Hwp1, Hst7, Ece1, and Cph1) that regulate the development of these yeasts. Other genes (Nrg1 and Tup1) that reduce hyphae formation are expressed more in the presence of capric or caprylic acid. This research suggests that other (non-lauric) MCTs, like capric and caprylic acid, may be effective interventions for treating Candida yeast infections.[18]

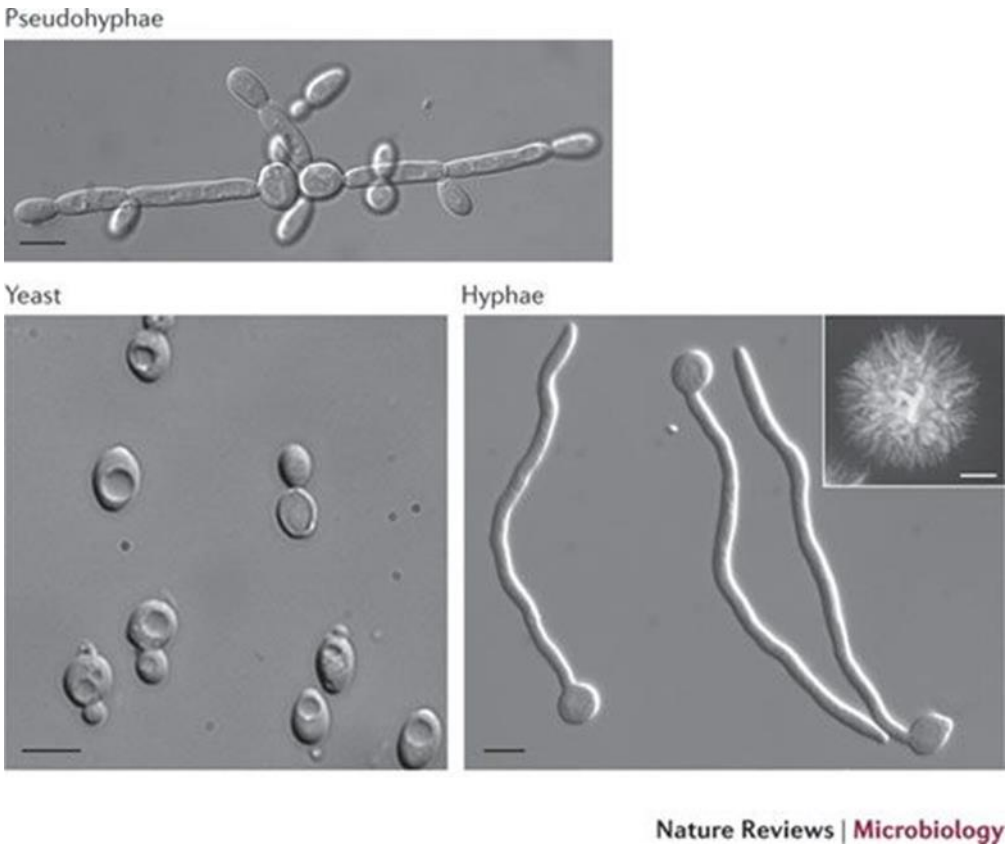

Figure 3. Yeast, hyphae, and pseudohyphae of Candida albicans.19 From https://www.nature.com/articles/nrmicro2636

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In human in vivo research, preterm infants supplemented with MCT oil experienced a significant reduction in candida load over a 3-week study (rate ratio, 0.15; P = 0.02) and the candida significantly increase after supplementation was stopped. (rate ratio, 61; P < 0.001).

infants supplemented with MCT oil experienced a significant reduction in candida load

Thus, supplementation with MCT may be an effective method to reduce candida colonisation.[20]

Herbal medicine

While research is only emerging, black cumin, garlic, several varieties of ginger, sage, calendula, mint, pomegranate, black pepper-tree, and thyme have reported some positive effects for reducing candida growth,[21-23] while turmeric, Eucalyptus, wormwood, and cinnamon, had greater antifungal effects.[24] Propolis extract also appears to exhibit greater anti-candida activity than thyme or garlic.[25] Antifungal activity against various Candida species has also

been demonstrated in vitro by goldenseal, guacatonga, calendula, and cranberry, with the exception of cranberry and *C. krusei* in which cranberry exposure appeared to increase growth.[26] Berberine may also be effective against candida by inhibiting its growth and also making it more susceptible to antifungal drugs.[27] Henna and common purslane have shown significant anti-Candida activity also inhibiting the growth phase and reducing biofilm formation.[28]

Clove has also been studied in animal subjects. When clove (*Syzygium aromaticum*) was administered into the oral cavity of *Candida*-infected mice, their oral symptoms were improved and the number of viable *Candida* cells in the cavity was reduced. In contrast, when the clove preparation was administered intragastrically, oral symptoms were not improved, but viable cell numbers of *Candida* in the stomach and faeces were decreased. These findings demonstrate that oral intake of clove may suppress the overgrowth of *C. albicans* in both the mouth and the gastrointestinal tract.[29]

Clove extracts reduce candida in the mouth and gut

Oil extraction of oregano has yielded promising results, with greater inhibition of fungal growth from oregano oil compared to the anti-fungal medication fluconazole.[30]

Carvacrol (a phenol from oregano oil, and also from thyme, pepperwort, and bergamot), epigallocatechin gallate (catechin found in green tea), curcumin and ginger have demonstrated the ability to enhance the activity of antifungals (voriconazole, caspofungin and amphotericin B) against Candida *in vitro*. This has led to the hypothesis that some herbal medicinal compounds might be used together with antifungals to reduce the dosage required and thereby reduce the potential for adverse effects,[31] especially resistance to antifungal medications appears to be rising.[23]

Essential oils

Geraniol, a monoterpenoid alcohol (found in rose oil, palmarosa oil, and citronella oil, and in small quantities in geranium, lemon, and other essential oils) reduces the integrity of the fungal cell wall, reduces virulence and hyphal and biofilm formation of candida.[32] Other essential oils such as fennel, summer savoury, cumin, and zataria, have also been studied in vitro for their anti-candida potential. While all essential oils exhibited some anti-candida activity, this was strongest for zataria and weakest for cumin. All essential oils performed less effectively than antifungal medications, amphotricin B and ketoconazole.[33]

Three Thai herbal essential oils used in aromatherapy; lemongrass (*Cymbopogon citratus DC*), holy basil (*Ocimum sanctum L.*) and kaffir lime (*Citrus hystrix DC*), were compared for their action against Candida biofilms. The strongest antifungal action was seen for kaffir lime oil, followed by lemongrass oil and holy basil oil.[34]

Traditional Chinese medicine

In vitro studies have demonstrated that goldthread (*Coptis chinensis/Coptidis Rhizoma*) extract exhibits antifungal activity against Candida tropicalis and glabrata.[35]

Other research has compared the anti-candida effects in vitro of goldthread, cork tree (*Phellodendron*) bark, giant knotweed (*Reynoutria sachalinensis*) rhizome, clove, pomegranate rind, Chinese sumac (*Rhus chinensis*), pulsatilla root, hairy vein agrimony (*Agrimonia Pilosa*), forsythia root, honeysuckle flower, flavescent sophora root (*Sophora flavescens*), cnidium fruit (*Cnidium monnieri),* and chebula (*Terminalia chebula*) fruit. Coptis root was found to have the strongest antifungal action, at a concentration of 6.25 mg/ml, followed by Phellodendron bark and giant knotweed (25 mg/ml), and clove, pomegranate rind, and Chinese sumac (~50 mg/ml).[36]

Medicinal mushrooms

A water-based extract from Reishi mushroom (*Ganoderma lucidum*) has demonstrated significant anti-candida action *in vitro*.[37]

> Reishi mushroom has demonstrated significant anti-candida action

Evidence-based recommendations for the treatment of candida

Increase/Use	Reduce/Avoid
Culinary herbs and spices: Garlic, ginger, sage, mint, thyme turmeric, cinnamon, clove, oregano, bergamot, fennel, cumin, lemongrass, kaffir lime Protein Omega-3 fatty acids (fish oil) Coconut oil MCT oil Reishi and other mushrooms	All added sugars Refined and processed carbohydrate foods (made with any refined flour) Wheat Trans-fats (found in refined and processed foods)

SUMMARY

The key and overarching consideration for the nutritional treatment of candidiasis is to eliminate or drastically reduce the intake of sugars and limit all processed and refined foods, especially those containing any type of flour.

Culinary herbs, while not 'medicine' (as they would be if given as concentrated medicinal herbal preparations), could also help and there is demonstrable evidence that many of these exhibit antifungal activity. Much (but not all) of this research has been performed *in vitro* (in test tube or petri dish) and so, antifungal compounds in these herbs are not assured to reach target tissue, but some evidence exists that in vivo herbs or spices (such as clove) are effective antifungals when in contact with infected tissue (such as in the oral cavity and the gut). There are other nutritional benefits from increased consumption of herbs and spices as they are incredibly nutrient-dense foods and when eaten with variety and as part of mixed meals, they are considered safe and with little chance of reaching toxic levels. For these reasons, increasing herbs and spices in the diet is prudent.

Increased protein might also be of benefit. Increased intake of protein is known to increase satiety, and although the effect of protein on sugar craving shows some conflicting results,[38, 39] there is some evidence that it might help to reduce sugar/sweet cravings.[40, 41]

Due to the impact of increased sugar, carbohydrate, and perhaps most importantly, total energy consumed on the growth of candida, increased protein intake, leading to better 'autoregulation' of energy intake, is likely to help in the treatment of candidiasis.

Omega-3 fatty acids aid immune modulation and reduce inflammation (especially in the gut) and aid the health of the microbiome,[42, 43] possible enabling the body to better combat candidiasis.

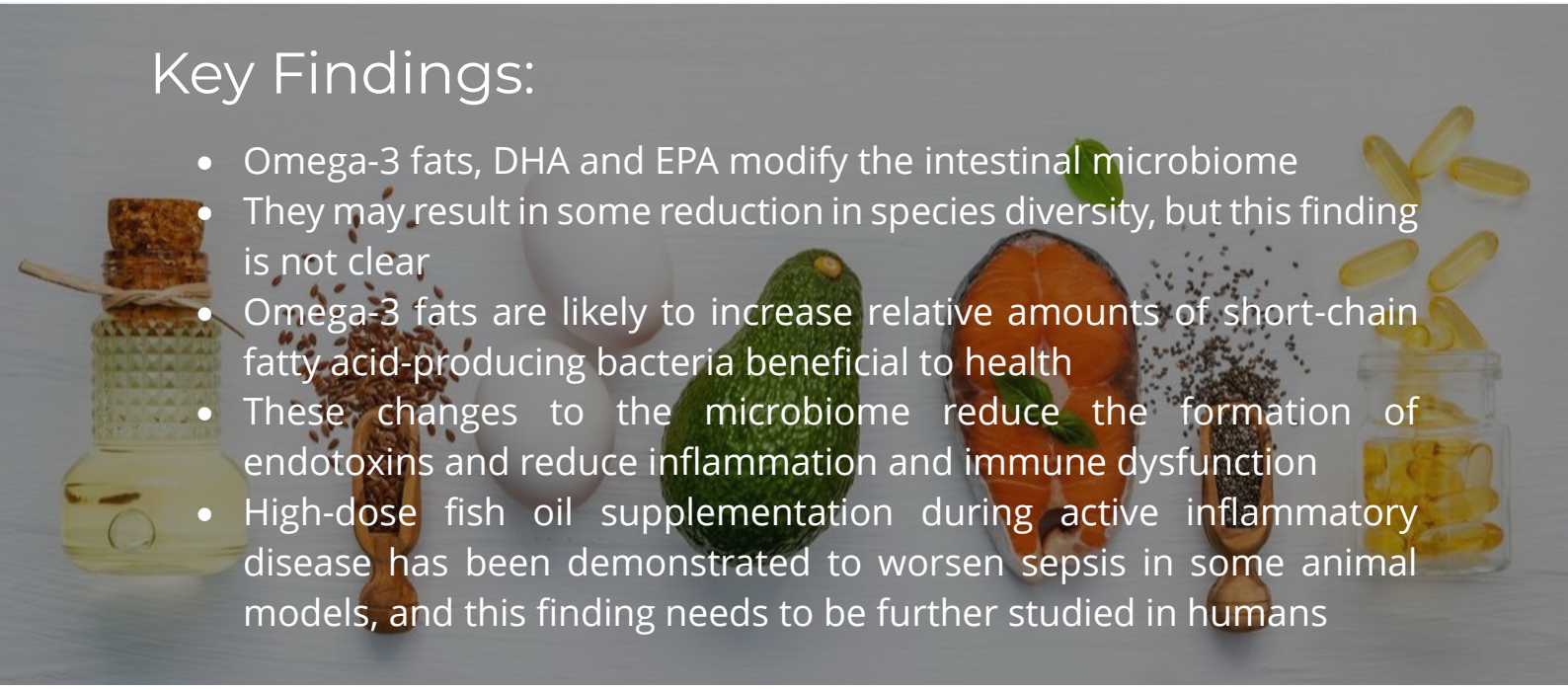
Both coconut oil and MCT oils are demonstrably antifungal and have demonstrated direct inhibitory effects against candida. These can be added as cooking oils or spreads (coconut oil) or added to smoothies, shakes, and other beverages (MCT oil).

The least amount of strong evidence probably exists for medicinal mushrooms such as Reishi (*Ganoderma lucidum*), also known as Lingzhi. However, the known health benefits of mushrooms of various types, added to the diet, or taken as traditional or modified beverages (such as 'mushroom coffee') are clear and so, it also seems prudent to use these as a generally regarded as safe, non-pharma option to aid health and the treatment of candidiasis.

Supplement recommendations for candida

Concentrated herbal medicines and mushroom extracts, and essential oils all show promise for the treatment of candida. However, much of this research has been performance in vitro and so, the transfer to humans cannot be guaranteed and there might be significant safety issues (especially with the use of some essential oils). Specific supplementation of these should only be prescribed by a qualified and registered health practitioner. This means that you should get nutrition and supplement advice from a registered dietician, nutritionist, or clinical nutritionist, and herbal medicine advice (including the internal use of essential oils) from a registered naturopath/medical herbalist. Essential oils are highly concentrated medicines that should only ever be prescribed for internal use by a qualified and registered practitioner. DO NOT use essential oils internally for the treatment of any disease or disorder without proper guidance and certainly do not use them on the advice of promoters of multi-level marketing essential oil brands.

CAN OMEGA-3 FATS TREAT DYSBIOSIS?



Key Findings:

- Omega-3 fats, DHA and EPA modify the intestinal microbiome
- They may result in some reduction in species diversity, but this finding is not clear
- Omega-3 fats are likely to increase relative amounts of short-chain fatty acid-producing bacteria beneficial to health
- These changes to the microbiome reduce the formation of endotoxins and reduce inflammation and immune dysfunction
- High-dose fish oil supplementation during active inflammatory disease has been demonstrated to worsen sepsis in some animal models, and this finding needs to be further studied in humans

Various studies have found that the omega-3 polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) found in fish oil, can reverse intestinal dysbiosis (distortion of the natural balance of microbes in the gut) by increasing beneficial bacteria species, including *Lactobacillus*, *Bifidobacterium*, and butyrate-producing bacteria, such as *Roseburia* and *Coprococcus*. In addition, omega-3 fatty acids decrease the proportions of lipopolysaccharide and mucous producing bacteria in the gut, along with reducing inflammation and oxidative stress,[44] and obesity.[45]

What are 'lipopolysaccharides'?

Lipopolysaccharides (LPS) are 'endotoxins' (toxins originating within the body) that are found in the outer membrane of various bacteria, which can be released into the body of the host. They are linked to sepsis, inflammation, auto-immune diseases, and even obesity in humans.

Animal Research

Systemic and chronic inflammation can be related to 'metabolic endotoxemia', or toxicity resulting from gut dysbiosis and increased levels of LPS (see above). Mice fed a diet high in omega-6 fats exhibit higher levels of metabolic endotoxemia and systemic inflammation. When mice are modified to be able to convert omega-6 fats

to omega-3s, both endotoxaemia and inflammation are drastically reduced. Increased omega-3 fats enhance the production of intestinal alkaline phosphatase (IAP), which induces changes in the gut bacteria composition resulting in decreased LPS production and reduced gut permeability (i.e. less 'leaky gut'), and ultimately, this reduces metabolic endotoxemia and inflammation.[46]

Animal research (in mice) has also suggested that elevated tissue levels of omega 3 fatty acids reduce body weight gain and the severity of insulin resistance, and these effects were associated with reversal of antibiotic-induced dysbiosis in the gut.[47]

> omega 3 fatty acids reduce body weight gain and the severity of insulin resistance

Further research has shown that both endogenous (created within the body) and supplemental omega-3 fats (fish oil) improve diet-induced microbiome changes (along with improvements in lipid profiles and fatty-liver disease), with supplementation having a bigger effect to reshape the intestinal microbiome and increase short-chain fatty acid production, which is both beneficial to health and also indicative of positive changes to the microbiome.[48]

Reduced maternal n-3 PUFA exposure has also led to significantly depleted *Epsilonproteobacteria*, *Bacteroides*, and *Akkermansia* and higher relative abundance of *Clostridia*.[49]

Mice supplemented with omega-3 fats had reduced expression of genes associated with *de novo* lipogenesis (creation of fats within the body) and these mice also had a higher abundance of *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*, which are negatively correlated with the genes associated with lipid and triglyceride synthesis.[50]

What are 'short-chain fatty acids'?

Short-chain fatty acids (SCFAs) have carbon chains between two and five in length. These fatty acids include acetic acid (C:2), propionic acid (C:3), butyric acid (C:4), and valeric acid (C:5). Short-chain fatty acids, especially butyric acid, are used extensively as a fuel substrate by intestinal epithelial cells. [51] Butyric acid is mostly produced by microbial intestinal fermentation of dietary fibre and resistant starch. Most of the butyric acid produced by this fermentation of starches is absorbed and used directly by cells of the intestinal wall, with the remainder absorbed into the hepatic portal vein and transported to the liver where it can be converted to ketone bodies.[52, 53] A small amount is also absorbed directly from the large colon and enters systemic circulation, to be used directly by peripheral tissue.[52] Butyrate reduces inflammation and cancer formation in the colon, and decreases oxidative stress, and promotes of satiety.[54, 55] Thus, it serves an important role in preserving the health of the colon, the microbiota, and has other beneficial effects on overall health.

Other research in rodents has shown positive from omega-3 fats in models of ulcerative colitis, an inflammatory bowel disorder. In research related to this, omega-6 fats have been shown to increase inflammation-causing bacteria such as Enterobacteriaceae, segmented filamentous bacteria, and *Clostridia* spp,[56] and *Helicobacter, Clostridiales bacterium, Sphingomonadales bacterium and Pseudomonas* species *Firmicutes*,[57] and mice with infection-induced colitis had greater intestinal damage, immune distortion and infiltration of pathogenic bacteria from the intestine when given omega-6 fats. In comparison, the addition of omega-3 fats to the diet, reverses the growth of these inflammatory microbial blooms and increases beneficial microbes like *Lactobacillus* and *Bifidobacteria*,[56, 58] and improves immune markers.[56]

> the addition of omega-3 fats to the diet reverses the growth of these inflammatory microbial blooms and increases beneficial microbes like *Lactobacillus* and *Bifidobacteria*

However, there was some suggestion that the prevention of systemic inflammation resulted in greater sepsis and mortality amongst omega-3 supplemented mice.[56]

Similarly, omega-3 supplemented mouse pups displayed positive changes to the microbiome and reduced inflammation, along with protection against oral peanut allergy, but also a tendency toward worsened responses during *E. coli* sepsis and had significantly worse outcomes during *Staphylococcus* skin infection.[59]

> liver damage and leaky gut were significantly improved in rats treated with fish oil

In rats treated with ethanol to mimic alcohol consumption in humans, ethanol increased intestinal permeability ('leaky gut') and decreased numbers of faecal Bifidobacterium. However, liver damage (as indicated by liver enzymes AST and ALT and inflammatory markers in the liver) and leaky-gut were significantly improved in rats treated with fish oil. [60]

Human Research

While it seems apparent that omega-3 fatty acids affect the microbiome in humans, the impact of these fats in the gut biome is less defined in human *in vivo* research than in the many emerging animal and *in vitro* studies. The few studies thus far completed in omega-3 supplementation in humans

show some consistency of changes in the gut microbiota, particularly, a decrease in *Faecalibacterium* and an increase in the *Bacteroidetes* and (butyrate-producing) bacteria belonging to the *Lachnospiraceae* family. Dysbiosis of these bacteria are commonly seen in inflammatory bowel diseases and omega-3 fats might exert beneficial effects to the microbiome in these diseases.[61]

In a recent case study, a 45-year-old male who consumed 600 mg of omega-3 daily for 14 days was observed to have decreased microbiome species diversity but increases in several butyrate-producing bacteria. There was a decrease in *Faecalibacterium prausnitzii* and *Akkermansia spp*. After the intervention and ceasing omega-3 supplementation, the gut microbiota reverted to pre-study levels (after a 14-day washout).[62]

Total omega-3 and DHA levels in serum were associated with microbiome diversity in a study of 876 twins. (DHA Beta (SE) = 0.13 (0.04), $p = 0.0006$; total omega-3: 0.13 (0.04), $p = 0.001$). Even stronger associations were found between DHA and certain bacteria such as *Lachnospiraceae* family (Beta (SE) = 0.13 (0.03), $p = 8 \times 10^{-7}$).[43]

In an open-label trial of 22 healthy volunteers, a mixed DHA/EPA formulation (4 g per day) did not result in significant changes in overall bacterial diversity but there were reversible changes in several butyrogenic bacteria; *Bifidobacterium*, *Roseburia* and *Lactobacillus*.[42]

Maternal fish oil supplementation increases the omega-3 fatty acid content of breast milk and this has been demonstrated to both affect the microbiome,[63, 64] and reduce inflammatory markers in breast-fed infants.[64]

CONCLUSION

From the evidence, it appears that omega-3 supplements, especially those containing the active omega-3 metabolites DHA and EPA can modulate intestinal bacteria, and in particular increase bacteria producing beneficial short-chain fatty acids and reducing inflammation. This is likely to be of benefit to both gut and overall health. However, there is some suggestion from the animal research that the use of very high doses of these fats during active bowel disease may have some effects on increasing the risk of sepsis due to over-suppression of innate immune and inflammatory responses, although this has not been observed in humans and there is relative abundance of use of fish oil in IBD patients.

> omega-3 supplements improve dysbiosis, increase short-chain fatty acid production and reduce inflammation

Overall, the use of fish oil in particular seems prudent for health and particularly for the health of the microbiome.

DOES PROTEIN REDUCE SUGAR CRAVINGS?

Key Findings:

- Increased protein intake increases satiety
- Protein has the greatest impact on satiety of any of the macronutrients
- This satiating effect reduces desire (and craving) for food overall (i.e. all macronutrients)
- Higher protein meals reduce the subsequent craving for both sweet and savoury and reduce energy intake
- Cravings and our desire for particular foods are not just based on physiology and macro intake but are complex and psychosocial, emotional, and behavioural factors need to also be considered

It is commonly stated by practitioners that protein enhances satiety (the satisfaction from meals) and reduces food intake (along with benefits to bone, systemic, and muscular health) and that it also reduces cravings for sugar. While the evidence convincingly demonstrates that increased protein intakes do increase thermogenesis and satiety compared to diets of lower protein content and that high-protein intakes reduce subsequent energy intake,[65] the evidence for an effect of protein on sugar cravings is less clear.

Mood is improved similarly in both 'carbohydrate cravers' and non-cravers after meals high in fat, carbohydrate, or protein,[66] suggesting that the intake of any form of energy practically eliminates cravings in the short-term, irrespective of whether you self-report as a sugar-craver or not. This is also suggested by research which shows that you crave what you restrict.[38] In other words, if you restrict protein or fat, you typically crave that, and if you restrict carbohydrate, you typically crave that. However, these restriction-enhanced cravings have no effect on subsequent food intake, so irrespective of what people crave due to avoiding it, they typically don't actually choose to eat foods high in the macronutrient they crave![38]

This finding though is further informed by our knowledge of human nutrition related

to anthropology. In a survival setting, we would be inclined to eat what we had available to supply necessary amino acids, even if those foods were not especially high in protein. *In other words, having a little is better than going without.*

> In a survival setting, we would be inclined to eat what we had available to supply necessary amino acids, even if those foods were not especially high in protein

Protein leverage theory is based on this idea, namely that we will continue to eat (what is readily available) until we have achieved amino acid sufficiency.[67] There are also considerable variations between what individuals themselves will crave and this is likely to be heavily influenced by behavioural 'types'[68] and psychosocial factors.

In contrast to the findings above, those following a low-carbohydrate, higher-protein, high-fibre diet had reduced sugar and sweet cravings.[40] And this is a common finding clinically. However in a comparison of a lower protein (21%) diet vs higher- (29%) in people with type 2 diabetes, no differences in cravings were observed between the groups,[39] notwithstanding that this is a very modest difference in protein intakes (i.e. would it have been the same if the protein intake was actually high?)

Finally, in one of the few studies directly looking at the effects of a high protein (vs low-protein) meal, a higher protein breakfast led to greater feelings of fullness and reduced cravings for both savoury and sweet.[41]

> a higher protein breakfast led to greater feelings of fullness and reduced cravings for both savoury and sweet

CONCLUSIONS

Protein does increase satiety and has the largest effect on satiety of any of the macronutrients. This could provide pronounced benefits to the 'autoregulation' of energy intake and thus, reduce the propensity to overeat. This satiety effect is likely to have some effect on cravings for food overall (irrespective of savoury or sweet). But the reasons we 'crave' any particular food, foods, or tastes is more complex than simply the physiological requirements for macronutrients or the metabolic status of an individual and psychosocial, behavioural, and emotional factors also deserve consideration.

IN THE MEDIA

High-fat diets change your brain, not just your body

Matt Davis

Stuff News | September 16, 2019

https://bigthink.com/mind-brain/brain-obesity

Article Summary

In this article, a mouse study from *Cell Metabolism* is referenced.[69] The key points listed were:

- Anyone who has tried to change their diet can tell you it's not as simple as simply waking up and deciding to eat differently.
- New research sheds light on a possible explanation for this; high-fat diets can cause inflammation in the hypothalamus, which regulates hunger.
- Mice fed high-fat diets tended to eat more and become obese due to this inflammation.

While the article headline and the key points focus heavily on the high-fat nature of the diet, the diet was, in fact, a high-fat AND high-carbohydrate diet, or in other words, a good model for the modern, ultra-refined 'American-style' diet that forms our food environment.

In mice fed this diet, the microglia of the brain and nervous system were activated, resulting in inflammation in the hypothalamus and this, in turn, resulted in increased food consumption and obesity. Additionally, the mitochondria (the energy-producing 'powerhouse' of the cell) of microglia shrunk due to increased production of 'uncoupling protein 2'.

The reason for this change is a survival one. Quite simply, in times of scarcity (i.e. most of our development as a human species!), it would have been beneficial for the body to encourage us to eat as much energy-dense (and both fat- and carb-dense) food as possible when it was available. However, in the modern food environment of abundance, and a McD's and Dunkin' on every corner, this adaptation is... somewhat less beneficial!

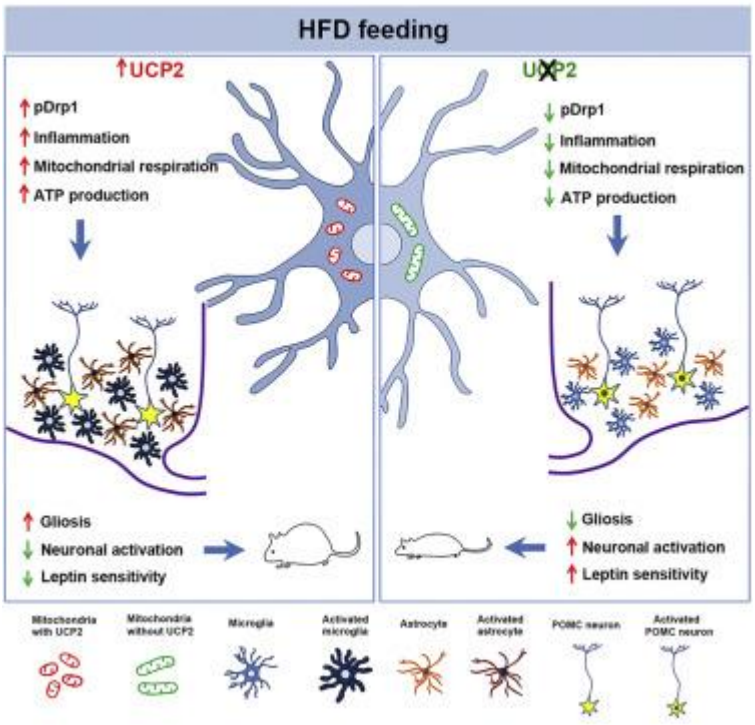


Figure 4. Graphical abstract from Microglial UCP2 Mediates Inflammation and Obesity Induced by High-Fat Feeding

Comment

Was the diet *actually* 'high fat'?

While the findings of the study are very interesting and incredibly valuable, the focus on the 'high-fat' nature of the diet is disappointing. This is a common and frustrating issue in the translation of studies to the mainstream audience, in which 'high-fat' diets are often also high in carbohydrate or sugar (especially in animal feeding studies) or in which 'low-carb' diets are actually moderate-carb, or mixed macronutrient models, or, in the case of observational studies, simply the lowest-carb consuming participants, who often are the lowest carb-consumers because they are choosing higher-fat and lower-carb junk foods...which are not low-carb per se.

'high-fat' diets in animal studies are often also high in total carbohydrate or sugar

Again, this speaks to a BIG problem in research, that macros are often blamed when in fact, the overall quality of the diet is the bigger factor by far as I have stated with evidence in previous issues of CARR.

What WERE the diets?!

I have noticed in various cell metabolism journals that there is little attention paid to the diets given to animal models. There are typically not 'methods' sections given, just a longer introduction than we would see in nutrition journals and results from the study. This is frustrating for a nutritional

scientist as what constitutes a 'high-fat' or 'high-fat, high-carbohydrate' diet based on 'chow' (the standard animal feed which is given to laboratory animals) could differ by a wide margin and might not, as mentioned earlier, be in any way close to what we might consider high or low in particular macronutrients in translational nutrition science.

On that note...the problem with animal studies

Look...I'm not one of those guys who dismisses results that I don't like purely because they come from animal models. Hell, I don't even *dislike* these results. BUT we do need to always exercise caution when translating the results from animal studies to humans. In relation to human health, animal studies are meant to inform our understanding of underlying physiology and processes that *might* relate to humans. This is because, quite frankly, animals are easier to study, there are fewer ethical constraints, and the food and environment of the animals can be more finely controlled. However, animals such as mice can be quite poor models for some aspects of human physiology, especially as it relates to our responses to changes in macronutrients.

animals such as mice can be quite poor models for some aspects of human physiology

Mice, for example, can be quite poor models for fat-adaptation and ketosis and some strains of mice are particularly poor for this purpose, especially those that have been bred specifically with a higher genetic proclivity towards obesity and diabetes. Humans, on the other hand, are typically extremely 'flexible' metabolically and can enter and sustain ketosis and increase their relative usage of fats for fuel markedly.

Mice, for example, can be quite poor models for fat-adaptation and ketosis

Animal studies should help us to define hypotheses for further research in humans so that we can figure out what the true functional outcomes are for our health. Unfortunately, many science reporters attempt to immediately translate preliminary animal findings into 'for' or 'against' arguments for particular human diets and that is simply something that one cannot do based on animal evidence alone. Outcomes that can be translated to humans must result from a combination of plausibility (the physiological underpinnings of what might be happening, often based in part on *in vitro* and animal *in vivo* studies), and demonstrability in controlled trials (which show the 'true' effect vs a placebo, but which are often short-term) and longer-term observational evidence (which is uncontrolled and suffers from other potential flaws such as recording and memory bias) which is typically the only way to see likely very-long-term effects of different diet types or interventions.

Outcomes that can be translated to humans must result from a combination of plausibility and demonstrability

Did the negative changes last?

There was a clear effect of the diet on markers of inflammation at 3 and 7 days. However, at 8 weeks all markers had fallen to similar levels to those seen in the control (standard diet) group with some higher, and some lower.

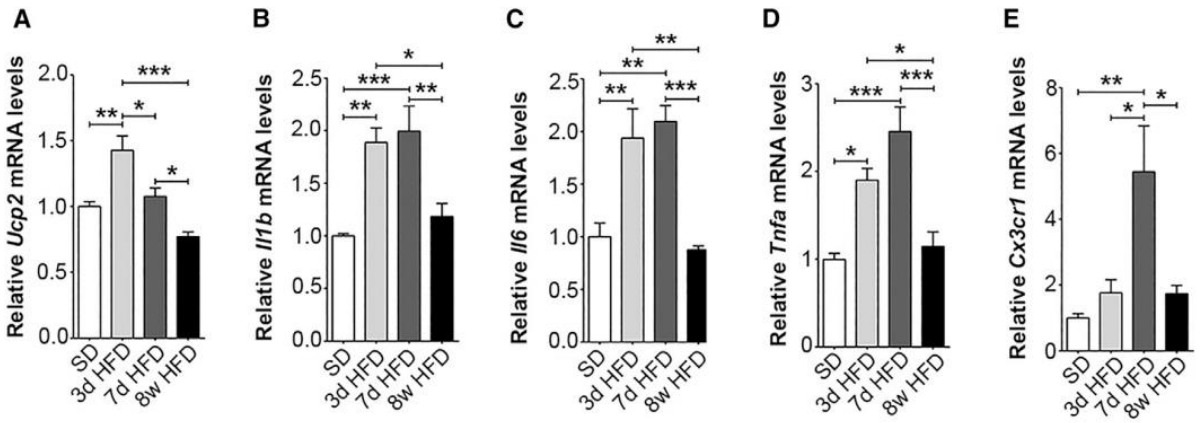


Figure 5. Markers for inflammation in standard vs 'high-fat' diet

Similarly, the area, number, and overall coverage of mitochondria over the different timepoints were somewhat equivocal with overall reduced area at 8-weeks on the diet vs control, but increased numbers of mitochondria and coverage.

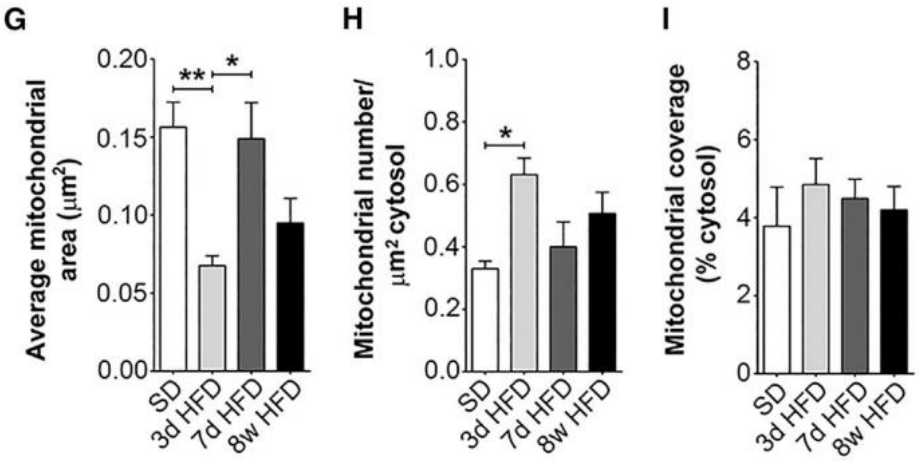


Figure 6. Mitochondria area, number, and coverage

Summary

The evidence is accumulating that an ultra-refined diet (which incidentally is typically high in both carbohydrate and fat) results in inflammation and negative changes to the structures and energy production of the brain and central nervous system.

Interestingly, in this study, these changes actually appeared to be limited in time and it will be interesting to see whether those results are mirrored in humans and what implications that might have for the treatment of 'diabesity'.

It is also unlikely that there would be negative, medium to longer-term effects on either glial structures or on inflammation or other risk factors from *truly* low-carbohydrate diets that are based on a compendium of unrefined foods (in other words, a 'good' diet) in humans. Indeed, existing research has demonstrated that gross physical health of the brain might be improved in several ways through the use of low-carb, ketogenic diets (as reported in a previous issue of CARR)

FOR NEW SUBSCRIBERS

Remember to check out our previous issues of The Carb-Appropriate Research Review

Previous topics have included:

Is Dairy Inflammatory?

Is a Keto Diet *Really* a 'Cure' for Cancer?

Can you be 'Heathy at Every Size'?

Do Low-Carb Diets Negatively Affect Female Hormone Balance?

And much more!

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