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What We Know, Think We Know, or Are Starting to Know

It is easy to get lulled into a 'fibre-centric' view of the importance of nutrient factors for the microbiome. However, we know that at the macronutrient level, the source of carbohydrates, proteins, and fats, appears to have modulating effects on the composition of bacterial populations in the gut, i.e., the microbiota [1].

The effects of dietary fat have generated recent interest from analyses that have indicated distinct changes in the gut relative to the fat content and composition of the diet [2-4]. The mechanism by which dietary fat may influence microbial composition and health effects appears to be through bile [1,3,4]. Dietary fat is consumed in the form of triglycerides, which are large structures that are difficult for digestive enzymes to break down. In order to facilitate this breakdown of a triglyceride into its component fatty acids [and glycerol backbone] for digestion, the gallbladder secretes bile in response to dietary fat ingestion. Fats entering the duodenum are then made soluble in bile acids as part of a process for the pancreatic lipase enzyme to break down triglycerides (5). A key point is that regardless of fat type, rendering triglycerides soluble in the duodenum involves secretion of bile acids.

Different bacterial species in the large intestine are specialised in the use of different dietary substrates to populate - be that fibre, proteins, or fats. There are certain bacterial species in the large intestine that specialise in the metabolism of bile acids that pass to the colon, generating what are known as 'secondary bile acid metabolites', which human intervention studies indicate may increase risk factors for colon cancer [3,4].

However, what is less clear is whether there is an effect of composition alone, independent of total content, or whether there may be an effect of the actual total fat intake in the diet. What is also unclear is whether there is a mediating effect of dietary carbohydrates and/or fibre, on these processes. The present study investigated the effects of three different levels of dietary fat and carbohydrate on the microbiota, inflammation, and blood lipids.

The Study

The study was a 6-month randomised and controlled feeding weight loss intervention conducted in healthy young adults participating in the Optimal Dietary Macronutrient Distribution in China trial.

The ODMDC trial was conducted across two study centres: the People's Liberation Army General Hospital in north China and Zhejiang University in South China. During the 6-month intervention, faecal samples were obtained from 217 participants at baseline and following the intervention to investigate the effects of the dietary intervention on the gut microbiota and relationship with cardiometabolic risk factors.

All foods and beverages were provided to participants for the duration of the intervention. Participants were requested to keep a daily food diary recording whether they had eaten all study foods, and any non-study foods consumed. All diets were isocaloric, matched for protein [14% total energy] and fibre [14g/d], and differing only in the ratio of carbohydrate to fat:

- Diet 1) Low-fat diet of 20% fat / 66% carbohydrate. This diet was designed to reflect macronutrient content of the traditional Chinese diet based on data from 30yrs ago.
- Diet 2) Moderate-fat diet of 30% fat / 56% carbohydrate. This diet was designed to reflect the current average macronutrient intake in China and the upper limit of fat recommended by the Chinese Nutrition Society.
- Diet 3) High-fat diet of 40% fat / 46% carbohydrate. This diet was designed to reflect the composition of Chinese diets in the megacities*.

Primary outcome measures included differences in the microbiota and inflammatory markers for diets with differing proportions of carbohydrates and fat.

*Geek Box: The 'Nutrition Transition'

'Nutrition transition' has become the term for the rapid changes in the food environment and dietary intakes in low-middle income or rising economic countries. This transition is driven by global transnational food and beverage corporations [TFBCs], who penetrate these emerging markets and alter the environment in retail and manufacturing, while expanding the fast food sector. This transition is possible, and in part explained, by rising incomes, increasing urbanisation, and a changing labour market. TFBCs have the capacity to dramatically alter the food supply and local food systems, and the dominant characteristic from a dietary perspective of this transition is a dramatic increase in the consumption of ultra-processed foods [UPFs] and sugar-sweetened beverages [SSBs]. Often, local cultural sensitivities are taken into account, to penetrate the market. For example, because chicken is a more popular meat than beef amongst consumers in China, KFC is more successful than McDonalds. Another characteristic of the nutrition transition is altering the food retail environment, by converting previous retail outlets into a food retail component. For example, in many Asian countries petrol stations are just that - petrol stations - but under TFBC partnerships are often turned into foodcourts that we would be accustomed to at any Shell station in the West. It is interesting to note that research has indicated a pattern to market penetration, beginning with SSBs, which are the easiest product to achieve rapidly rising sales with, before moving in with UFPs outlets. 'Glocalisation' - a process where global food products are given a local marketing spin and appeal, allows for UPF products to be adapted to local customs. The nutrition transition has profound consequences for global health, and planetary health, and the lack of appropriate regulatory frameworks in many of these countries means that TFBC are able to become well-established and precipitate dramatic shifts in the local food supply and dietary intake.

Results:

- ***Phylum:*** In the high-fat diet group, the relative abundance of *Firmicutes* decreased and *Bacteroidetes* increased, compared to the low-fat diet group. The ratio of *Firmicutes* to *Bacteroidetes* was significantly decreased in both the moderate-fat and higher-fat diet.
- ***Genus:*** In the low-fat diet group, the abundance of the *Blautia* and *Faecalibacterium* species, both of which are butyrate-producing genus' s, increased. Conversely, the high-fat diet led to reductions in *Faecalibacterium* and increase in *Bacteroides* [not to be confused with *Bacteroidetes*!], which are associated with lower SCFA levels and pro-inflammatory processes.
- ***Short-chain Fatty Acids:*** In the low-fat diet group, the abundance of the *Blautia* and *Faecalibacterium* species, both of which are butyrate-producing genus' s, increased. Conversely, the high-fat diet led to reductions in *Faecalibacterium* and increase in *Bacteroides* [not to be confused with *Bacteroidetes*!], which are associated with lower SCFA levels and pro-inflammatory processes.
- ***Inflammatory Markers:*** High-sensitivity C-reactive protein [hs-CRP] levels were significantly increased on the high-fat diet compared to the moderate and low-fat diets, and levels of pro-inflammatory mediators TXB and PGE2 were both significantly increased on the high-fat diet, compared to the low-fat diet. The increased levels of faecal AA on the high-fat diet positively correlated with higher hs-CRP, TXB, and PGE2.

The Critical Breakdown

Pros: Conducting the study across two centres allowed for inclusion of a regionally diverse representation of the population. The provision of all study foods and drinks for a full 6-months is impressive control of diet. The different diets was well-formulated, reflecting the nutrition transition which many emerging markets are experiencing.

Cons: No data is presented regarding dietary compliance, albeit the macronutrient levels suggest compliance with the diets. Weight loss occurred across all three groups, and differed between groups, which may influence the results; the role of weight and adiposity influencing the microbiota remains unclear. Assessments were only carried out at baseline and the end of intervention, which could have missed changes in the microbiota over time.

Key Characteristic

A characteristic of research in this area to date is the short-term responsiveness of the gut microbiota to dietary induced changes. In 3-day intervention investigating the effects of high animal fat, low fibre diets vs. high fibre diets on the gut microbiota, David et al. [3] found that diet rapidly shifted the microbiota to a profile implicated in inflammation and increased secondary bile acid metabolites, but these changes returned to baseline rapidly upon cessation of the diet. A similar study comparing the effects of a Western diet vs. a traditional high fibre African diet, while finding similar results regarding dietary fat and secondary bile acid metabolites, was a 2-week study in duration [4]. The 6-month duration is an important extension of this previous work, providing insight into the effects of more sustained dietary practices on the gut microbiota, and potentially related cardiometabolic health outcomes. However, per the 'Con' above, more interim measures would have been more informative to look at the time-course of changes in the microbiota over the intervention.

Interesting Finding

Despite the relatively low fibre intake across groups - 14g/d - the low-fat diet group exhibited increased levels of bacterial populations associated with short-chain fatty acid [SCFA] production. One explanation, which the authors highlight, may be that mainstay carbohydrate foods in the low-fat group - white rice and bread - contain resistant starch* [RS], which is often not included in the sum of dietary fibre. The human research on RS is still emerging, and there are challenges given the five different subtypes, however, the available data suggests that RS increase concentrations of faecal SCFAs, indicating increased SCFA production [6]. Given that meals were provided, it would be interesting to know if the rice was cooked and then cooled; this forms 'retrograde starch', or RS3, and emerging human research suggests this type of RS3 may results in improved post-prandial glucose and fat metabolism [6]. Nonetheless, the findings in the present study - with dietary fibre matched between groups - of increased SCFA-producing bacteria in the low-fat group, suggests that differences in RS content in the diets may explain this effect.

Another very interesting finding was that in the high-fat diet 24% energy was derived from polyunsaturated fats, soybean oil specifically, a commonly used oil in China, and while the benefits of polyunsaturated fats are well-established, most recommendations don't go over 15% energy. Increased levels of the omega-6 arachidonic acid [AA] in faecal samples was observed, and the researchers specifically tested the correlation between changes in fecal AA concentrations and changes in plasma pro-inflammatory markers, finding that plasma concentrations of PGE2 and hs-CRP all positively associated with changes in fecal concentrations of AA. This is an important question to tease out, as the overwhelming majority of research to date has found that even increasing PUFA significant amounts does not result in any changes in circulating AA levels (7). This is circulating AA vs. faecal content of AA observed in the present study. This is a relevant question for future research, as most of the studies showing negative effects of higher fat diets in the West have focused on high saturated fat content (2-4).

*Geek Box: Resistant Starch

Dietary fibre is considered the indigestible structures in edible plants, comprising both soluble and insoluble carbohydrates. Additional components to fibre include prebiotics, and resistant starches [RS], i.e., starches that are resistant to digestion and also pass to the colon, to undergo degradation by bacteria. RS is emerging as a particularly important part of overall fibre intake, and there are five types of RS. RS1 is physically inaccessible starch that is contained within whole grains, or legumes. RS2 is a starch found in raw potatoes, underripe [green] bananas or plantains, cereals, and other starchy tubers. RS3 is also known as 'retrograde starch', formed when foods like potatoes or rice are cooked, and then cooled [the stickiness on the cooled starch is RS3]. RS4 is chemically modified starch to resist digestion. Recently, a fifth type has been added, based on research showing that starch:lipid complexes form when amylose starch binds with a fat. Some interesting research is emerging to show that such complexes may reduce post-prandial glycaemia, and these complexes may have application in the food industry to make certain products, like oven chips, have less of a blood glucose impact. Overall, the research to date suggests an enhancement of production of the SCFA butyrate, providing health benefits to the host through the multiple protective benefits of butyrate in the colon. One thing to bear in mind: most nutrition softwares and databases do not have specific data added on resistant starch yet, so it is only dietary fibre that tends to be calculated.

Relevance

It should be noted that insofar as there may be population and regional differences in response to diet, that these results in a Chinese population may not necessarily hold true in other populations. We know that the microbiota is responsive to changes in diet in the short-term, but we also have evidence highlighting that geographic region - and associated dietary differences - may be important [8].

The increased ratio of *Bacteroidetes:Firmicutes* from the high-fat diet is consistent with research in both children and adults on the effects of high-fat Western diets, and is associated with increased pro-inflammatory processes [9,10], effects which were also observed in this study. The fact that these effects were observed in this study, in a different population group to previous research, and with a different fat composition to previous research, does implicate the total fat content of the diet as a relevant driver of these changes.

Or does it? In each of these populations, intakes of non-digestible, fermentable carbohydrates are low. The low-fat diet group in this study had increased levels of non-digestible carbohydrates, that were not accounted for in the quantified fibre intake [11]. What would the effect of higher - >35g/d - fibre be on these processes? We can only speculate. One gets the feeling the surface is still being scratched in this highly complex area, however, the present study does suggest an effect of the fat content and/or carbohydrate content of diet, but does not tell us whether the effects relate to the changes in dietary fat alone.

Application to Practice

It remains difficult to isolate the relevant variable - fat or fibre - but insofar as the two are intercorrelated, as the often are, then the interpretation becomes clearer: high-fat diets with lower fibre intake may precipitate changes in the microbiota associated with inflammation. For the practitioner, order of priority would still favour 'fibre first'. However, research is accumulating to suggest dietary fat is an important factor to consider for gut health.

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