DANNY LENNON: Okay, here we are. Welcome everyone to Episode 383 of Sigma Nutrition Radio. As always, my name is Danny Lennon, and I'm here with Mr. Alan Flanagan. Alan, how are you today?

ALAN FLANAGAN: I'm good, I'm free doing things...

DANNY LENNON: Yes, I was going to ask.

ALAN FLANAGAN: I'm free.

DANNY LENNON: You're presumably in better spirits now, we can do things.

ALAN FLANAGAN: Yeah. I had a haircut which was interesting, and the gyms reopened on Monday, so I'm sore. I'm looking forward to some newbie gains, I think. I'll be due after, what, four months, was it basically of no lifting, no proper lifting. So yeah, things have opened up a little bit, which is nice. I mean, there are still restrictions, and it's kind of good that somewhere, a lesson seems to have been learned from last summer when they just said, right, get back into the pubs and bars and restaurants now. So yeah, like, it's takeaway drinks, but you can't go in and stuff like that. So outdoor activity, and I think there's another

phase then of reopening soon. So yeah, so things are good.

DANNY LENNON: It definitely seems to have brought a wave of optimism over there, because there's definitely a lot of envy I think on this side of the water, where people are looking over and they have friends and family living in England who are being able to do, like you say, not like anything that crazy, just like a few extra normal things. But also, we're quite envious that yeah, it would be nice to have a gym open or nice to be able to go get a drink on a nice day...

ALAN FLANAGAN: We've been kind of slightly stifled a little bit by Mother Nature. It's been a bizarrely cold April, even though it's been quite nice, like blue skies and stuff, but bizarrely cold, temperature wise. So I think a lot of people's enthusiasm, and mine certainty, Monday, after my first training session, back in four months, and I was like, this is great, and I'm walking home, and blue sky, and get a pint and sit on the common and the next minute the sun goes behind the clouds and I'm miserable and freezing as if I was at Electric Picnic in the rain, you know, the next minute you're packing up and going home. So yeah, I think it's the enthusiasm will pick up as the weather gets better. But it is, like, it's so interesting how little things, tiny little openings in society and in life can make this massive difference after the past year.

DANNY LENNON: Yeah. So I think yeah, that's one of the good things that with each easing of the restrictions, there's going to be that bit of novelty for a while, where it's like, oh this is really nice. But then pretty soon, we will get used to that and be looking forward to the next one. In relation to some of our Sigma content, you recently published a statement on organic foods, and maybe you want to give a quick intro to that for people who haven't had a chance to read it.

ALAN FLANAGAN: Yeah, so hopefully, people do get a chance to read us. We looked at it really through the lens of the relationship between, well, defining

organic food and its regulation, and then thinking about organic food and actual health outcomes in humans, organic food and environmental exposures. We didn't focus on the environmental arguments for organic food, because that would have been a kind of separate rabbit hole, like, comparing the environmental impact of organic food. So by environmental pollutants, the focus was more on, for example, pesticide residues, and the difference between organic and conventional crops and whether indeed there is some risk to human health from pesticide residues that may be present, or things like antibiotic resistant bacteria. It's an interesting area – I think, what struck me was really for something that is an industry that's significantly growing, there's still a lot of gaps in the research, pretty big gaps as far as long term health outcomes. There's still a lot of consistencies in the research; and there's just not a huge amount of research overall, particularly, if we're talking about human cohort studies, many of which were set up not necessarily to look at organic foods specifically and have just had people report whether they buy organic food regularly or consume it.

So still a lot of research to come out. Ultimately, it is difficult to see how much of a benefit some individual might derive from consuming all organic foods relative to significantly increasing fruit and vegetable consumption overall. And I think there is a population health relevance that has to be factored into the discussion and cost implications within that as well. So, all in all, like, if someone had the ability to consume an entirely organic food diet, would they have a measurable benefit to their health? Possibly, but it might be relatively small compared to just simply consuming a diet rich in fruits and vegetables.

DANNY LENNON: Yeah, and for anyone that wants to get into some of those details and some of the kind of complexities of those questions that Alan just

outlined, you can go and read that statement now, it's over on the website. So just go to sigmanutrition.com, and then in the statements tab, you'll be able to find that latest one. And if you do have any questions or comments about it, just feel free to leave a comment under that article, and those will all be addressed. So with that, let's get into today's topic in focus.

We're going to be talking about irritable bowel syndrome, and particularly focusing in on the relationship with diet. And there's probably a few interesting avenues for us to explore, but just to kind of set the stage for some of this, with irritable bowel syndrome, this is something that is relatively prevalent – I mean, depending on what study you look at, we see different numbers reported and it also changes based on the countries. But we're looking somewhere around I think 10-12% of the world population that can range from five up to 20, depending on those studies. And irritable bowel syndrome itself tends to be where we have this, the main symptom being this recurrent abdominal pain gets associated with a change in bowel habits, and there's a certain set of criteria that we'll probably talk about a bit later that it needs to meet. So in addition to that abdominal pain that's associated with a change in bowel habits, there's four other symptoms that two of those need to be met. So one is an altered stool passage, here we'll be talking about things like straining or urgency or what's referred to as incomplete evacuation. The second symptom would be abdominal bloating. Third would be a distension or tension or kind of this hardness that tends to be made worse by eating. And then fourth, some sort of passage of mucus.

So two of those four symptoms, in addition to that abdominal pain that occurs – and typically that those have to be ongoing for multiple months, probably six months plus for this to be considered, it's not something that if you have some sort of abdominal pain in one-off

circumstances that we're talking about. In terms of the diagnosis, it's probably important to note that this is typically done also on a diagnosis by exclusion. So typically, you'll see someone having things like celiac disease, inflammatory bowel disorders, ulcerative colitis, Crohn's ruled out, so they're not the explanation for some of these symptoms. And it's also probably at this point important to note that we shouldn't have IBS and IBD confused, they're completely different things as we'll probably discuss.

So given that we're basing it on the set of symptoms, where we've excluded these other disorders, one of the really crucial things here is that we're not looking at something where there's clear structural damage per se, as there is in some of these other disorders, and stating that it's not based on this structural damage, but instead is on these reported symptoms that people are having. That is not the same thing as saying, oh it's all in your head, because sometimes that can be the implication people can get from it, that it's just kind of this idiopathic thing where, oh I've just been told all this is in my head. It's very much not in people's head, they're very much are those symptoms, it's just not related to structural damage per se.

The final thing I'll probably mention is that there are various different subtypes, and here where we're going to see different symptoms present and there's probably going to be possibly different interventions that may have more or less benefit, but you'll have diarrhea predominant IBS, you could have constipation predominant IBS, you can have a mixed type where both of those are present, or you could have IBS that's uncategorized essentially, where it's not either of those other three brackets. So that's kind of an overview of what we're talking about in some of the diagnosis. Is there anything that I've left out or anything that you think is worth adding to there, Alan?

ALAN FLANAGAN: No, I think the key point, I think within all of that is that those characteristics and diagnostic criteria for IBS occur in the absence of any identifiable structural or biochemical abnormalities. So this is important because IBS relates to the individual's subjective reporting and interpretation of the symptoms, and it's an experiential change from normal for them. And this is important because, as you said, within, for example, the bowel habit aspect of the criteria, you can have a spectrum from diarrhea to constipation, a mix of both, and periods with normal stools. So it's this characteristic of what they call a functional gastrointestinal disorder, which IBS is classified as, which is essentially a disorder of gut brain interaction, involving multiple factors, microbial dysbiosis, so disturbance to gut flora, gut microbiota; altered function of the intestinal mucosa, altered immune and potentially inflammatory function of the intestinal mucosa, this visceral hypersensitivity to distension, and potentially central nervous system dysregulation.

So all of these things factor into what ultimately is the kind of characteristics as you outlined, and so I think that's that crucial distinction that we make from other gastrointestinal conditions; and as you said, it's important to distinguish because of the similarity of the acronym, IBS and IBD are entirely distinct and so we're focusing on with IBD, obviously, the actual presence of identifiable biochemical structure and metabolic abnormalities at the level of the gut, whereas with IBS, these symptoms are occurring in the absence of those identifiable structural damage and biochemical damage. And that's reflecting the fact that it is a functional gastro disorder characterized by these kinds of various mechanisms that a lot of which are still just being kind of scratched at.

DANNY LENNON: Yeah, and I think the thing that makes this so complex to try and piece through is that it's only a minority of cases where the kind of known initial trigger is kind of known. So

what's referred to as post infectious IBS, I think, is like 5 to 15% of cases where the IBS has occurred after like a bout of gastroenteritis. And so, then in the majority of cases, it's what's known as sporadic or nonspecific IBS. So we have patients who have had symptoms for a long period of time, without any known associated event that kind of started that chain, so I think that's what's obviously a frustration. But interestingly, one of the papers I had read, Marshall 2010, it was a longitudinal follow-up study that looked at people that had post in infection IBS. A lot of those patients, I think maybe up to maybe 20% of them, were still symptomatic eight years later, despite their IBS being caused by an infection they previously had. So there's a lot of moving parts and interesting, and like I said, the frustration here is probably clear to anyone who either has suffered with IBS or has talked to someone who has. Interestingly, one of the statistics that I read that was absolutely shocking, and actually very saddening, was from a survey of people that suffered with IBS, would give up 25% of their remaining life years, if it meant that they would live the rest of their life symptom free. So the average for those people was 15 years was that 25% of the remaining life. So give up 15 years of life...

ALAN FLANAGAN: To be symptom free.

DANNY LENNON: That's incredible, yeah.

ALAN FLANAGAN: That's incredible, yeah. Particularly when you consider that IBS is like it doesn't affect life expectancy. So that's a sizable chunk.

DANNY LENNON: 14% of them would risk a one in 1000 chance of death, if it meant receiving a treatment that would mean they'd be symptom free.

ALAN FLANAGAN: Wow. And I think in terms of say the wider prevalence as well, and you mentioned, kind of a range of like five to 20% of the population, it is highly common. It affects all kinds of ethnicities and age, although there is evidence

of a general decrease in prevalence with increasing age; affects more women than men, I think the odds ratio of having IBS is like a 67% greater chance in women than in men, so there's a significant sex disparity in terms of prevalence; and even in terms of characterizing the actual definition and the symptoms, as we outlined at the start, it's a highly complex condition, there's multiple factors that seem to influence it. And, in particular, psychosocial factors seem to influence dysfunction, gut dysfunction in IBS, and this may be kind of quite central to the difference between an individual with IBS compared to, say, a healthy control or someone with no IBS symptoms that patients with IBS frequently present with accompanying psychological histories of psychological say, mood disruption or disorder, anxiety and depression.

There's a strong relationship between a history of kind of disordered eating or eating disorders, and it may be that these respective potential antecedents have modulated this bidirectional relationship between gut brain access communication or even modulated the actual composition of the microbiota itself such that IBS now occurs in response to nutritional compounds and food interacting with these parameters of gut function. So, in terms of the mechanisms, it’s very complex, and there doesn't seem to be any necessarily kind of unifying characteristic as far as something that would like linearly run through any individual group of individuals with IBS.

DANNY LENNON: Yeah, and that's it, I mean, one of the common questions, I think, for people who receive a diagnosis of IBS is, well, what caused IBS, what caused me to develop this, or do we know what these causes are. And like you outlined, the mechanisms is very difficult to work through, and it's obviously more ongoing research, but there's so many different aspects to this and various different hypotheses. You did mention one that we'll probably spend some degree of time on – I was looking at the gut brain access,

because I would say now it's pretty well established in most of literature that there's at least some degree of disordered communication between the gut and the brain in a number of these cases that has the secondary effects on whether we're talking about gut motility or hypersensitivity or whatever ends up being, but trying to piece that apart is quite difficult. There seems to be some genetic component or that doesn't really explain most of the cases, I don't think.

So there's a lot there, and I think probably the difficult thing is, there's a difference between what is that kind of mechanistic thing that's at the root of causing this versus what things just exacerbate symptoms. Right? So, like we know, I think like nine out of 10 people with IBS will say that food in some way generates some of their symptoms or at least causes a flare up, and that's quite common. But that doesn't necessarily mean that these certain foods are the kind of root cause, so to speak.

ALAN FLANAGAN: Yeah.

DANNY LENNON: It's difficult, right?

ALAN FLANAGAN: Right. And you see that, I mean, some of the studies, like one thing that I find quite interesting, some of the research is – the production of hydrogen, for example, from carbohydrate breakdown, fermentation occurs in both healthy individuals and individuals with IBS, clarifying using the term healthy individual, like, people with IBS are otherwise healthy, so I don't meet it in that sense of non-IBS control, so to speak. But the increase in gas production is the same, and the actual presence of hydrogen in the gut is the same. So it occurs in both non-IBS controls and people with IBS, but only in people with IBS would that prolonged hydrogen production correspond to an increase in pain and bloating. And similar observations have been noticed with visceral hypersensitivity, so distension occurs just as a normal physiological response to the digestion

of food and carbohydrates and the production of gas as a result of that. But subjects with IBS are going to or many may experience this hypersensitivity too to that distension, that a non-IBS control may not. So this comes back to the point we made in terms of defining IBS that there is an absence of kind of structural damage, biochemical abnormalities, even though there clearly are kind of underlying mechanisms at play.

And I think on that, one of the things that may relate to this, if we kind of... dig into the mechanisms a little more with the gut brain stuff, there seems to be that compared to healthy, in terms of differences, that individuals with IBS, compared to healthy controls, may have greater numbers of mast cells in their intestinal mucosa. And so, this mast cell activation, in response to food, has also been shown to correspond to visceral hypersensitivity. So that could be one aspect of kind of this altered mucosal function, and then obviously, the kind of communication of pain, the perception of visceral hypersensitivity, and the hypersensitivity to colonic distension may obviously relate to that. There's also the potential for inflammation to also be present, mucosal inflammation. So I think that potential mechanistic explanation for the hypersensitivity to distension is interesting because the gas production is relatively the same between healthy individuals or individuals with IBS.

DANNY LENNON: Really interesting. So maybe actually, let's work through some of the gut-brain axis and IBS stuff specifically, because this is a really fascinating area and many listeners will probably have heard at least something about it. Now there's been fantastic work done more broadly in the area of the gut-brain axis that goes beyond just IBS, particularly things like psychobiotics are now are an interesting avenue in research. Much of that is actually being done in Ireland down actually in UCC; they do a lot of great work there, looking at

how certain bacteria can have this impact on the brain. Now with the gut brain access more generally that communication, at least, from my understanding seems to be bidirectional, but not necessarily equal that it seems that most of it is from the gut up to the brain versus vice versa, at least from my understanding. And one of the review papers that I read, Holtmann was the lead author on it, was discussing that like based on at least epidemiologically what we know now that in a lot of IBS patients, the gastrointestinal symptoms tend to arise first; and then later do we see some of these incident mood disorders that you mentioned earlier, we have this overlap between.

ALAN FLANAGAN: Yeah, bidirectional, but the effect of, for example, like we just mentioned, potentially, mast cell activation, and also the presence of inflammatory cells in the intestinal mucosa as well, and the activation of those inflammatory cells and a combination of this immune inflammatory activation, creating these kind of neurological interactions which could provide a mechanistic explanation for the hypersensitivity. So in this case, we're talking about these immune and inflammatory factors present at the level of the gut, and the response feeding back to the brain, so that would be relatively, yeah, consistent with my understanding of how that bidirectional access actually works.

I think the kind of, the peripheral sensitization of these kinds of pain receptors in the gut and the proximity of those pain receptors is also interesting in terms of the pain aspect, but also the hypersensitivity aspect. So it would appear in terms of just like sequence of events, that a lot of these potential explanations for differences between the response of an individual with IBS to the process of digestion, gas production and otherwise, and maybe related to these kinds of pain, immune inflammatory receptors and cells at the level of the gut then feeding back to the brain.

DANNY LENNON: There's also then the kind of converse thing that we tend to see in relation to what may cause at least an exacerbation of symptoms, or at least some sort of flare up where it may be a psychological trigger that may not be anything to do with some of the dietary factors we're going to discuss, but in periods of, let's say, very high stress or anxiety or depressive episode, that that in itself can cause a flare up symptoms. And again, that kind of at least fits in under this bucket of, okay, there's this clear communication between the gut and the brain that is, in some way, inextricably tied, that we need to probably account for, that not everything is just dietary modulated, I guess.

ALAN FLANAGAN: Yeah, I think and given the overlap between IBS and, like we said, some of these conditions, experience of anxiety, depression or otherwise, that that overlap is, and like you get into a lot of chicken and egg, potentially. So I think it's just important to note that yes, the bidirectional nature of that means that it can be top down or potentially feedback from the gut with the potential for overlap obviously between the two, because of the related comorbidity. I think the prevalence is really high in terms of the relationship between histories of mood disorder and IBS concomitantly. I think the other, I'm sure, you may have come across this, because I know the UCC group have also produced some research in relation to this, I find this hypothesis quite fascinating – this potential role for disordered tryptophan metabolism, the tryptophan kynurenine pathway in response to the activation of an enzyme, I think it's called indoleamine dioxygenase.

And the hypothesis is that when that pathway is functioning, dietary tryptophan is diverted into serotonin production, which has a role in gastrointestinal function and motility, and this is the hypothesis is that the activation of this ideal enzyme diverts tryptophan down a pathway of kynurenine metabolism, and

elevated kynurenine levels may precipitate some of these kinds of inflammatory and immune responses at the level of the gut that may be associated with IBS. And that's another really interesting, and I stress hypothesis there, you know, there is research existing in relation to this potential pathway and the importance of it. But I think that's a really good example of the bidirectional gut-brain axis relationship and how it can relate to i.e., this kind of the creation of conditions that precipitates symptoms.

DANNY LENNON: It is fascinating, some of that stuff on those serotonin metabolism abnormalities, essentially, and trying to work out, okay, are we talking about primary factors here, secondary factors, but there's so many of these interesting hypotheses that we could probably spend a lot of time working through. But I think for the sake of our time today, we'll try and focus in on some of the dietary interventions that typically get used in IBS, and what level of evidence we have for various different interventions. I suppose, the first thing to make people aware of is that if we are talking about how this is dealt within dietetics, you have a first line treatment, these would be like first things to do when someone has a diagnosis that we would work through; and then only after that, if that doesn't lead to resolving of symptoms, there's then second line treatments. So in terms of those first line treatments, this from a diet standpoint, we're typically talking about healthy dietary pattern changes with some things that are probably specific here to IBS. So whether that's related to alcohol intake, caffeine intake, spicy foods for some people can cause those symptoms. We can maybe talk a bit about dairy. So there's all these different components that typically get discussed, that would be the first port of call to look at.

ALAN FLANAGAN: Yeah, it is important to clarify the clinical management has a very specific stepwise approach. And so, what we're assuming here is that an individual has had other potential

gastrointestinal disorders or conditions ruled out and, as you said, a diagnosis by exclusion of IBS arrived at. But the preliminary adjustment, the first line intervention, is, as you said, this kind of general healthy eating advice, restriction of say spicy and fatty food, alcohol, caffeine and general healthy eating advice. And if this first line intervention doesn't lead to any improvements, then the second line intervention is the low FODMAP diet, and that can be divided into three distinct phases that we can discuss as well.

But I think in terms of the general healthy diet, that's interesting in and of itself, because it may be that there are individuals who have some improvement, simply from following that advice. And one of the papers we were discussing was a paper from a few years ago, which was a comparison between a low FODMAP diet and kind of the general healthy eating diet, in about 30 odd patients in each group. And essentially, both of them had relatively equal improvements in symptoms at the end of four weeks on that intervention. So at that one level, we could say, okay, well, there's potentially little difference between the kind of low FODMAP diet and the traditional general healthy eating IBS diet.

Now, that said, there's also evidence, for example, there was a meta analysis a few years ago, Altobelli was the lead author – I think it was a 2018, maybe 2017 meta analysis – and that compared low FODMAP diets versus the general IBS diet, the first line recommendation, or low FODMAP diets versus high FODMAP diets, and also looked at kind of prospective studies, and comparing the low FODMAP diet to the general healthy eating first line IBS advice, the low FODMAP diet showed greater improvements in abdominal pain, as in lowering abdominal pain, and a decrease in boating and an improvement in stool frequency, although no improvement in stool consistency. So the greatest magnitude of effect was in relation to abdominal pain and bloating,

and that may be just because in people who are again, particularly sensitive to the effects of some of these short chain carbohydrates which we can talk about further, the general healthy eating advice does exclude common triggers of gastrointestinal symptoms in some individuals, but doesn't necessarily exclude some of these more targeted short chain carbohydrates that have the potential to ferment. So it's interesting that abdominal pain and bloating was the main symptom that was improved to a greater degree, or, in this analysis on a low FODMAP diet.

So this, I think, is an example of the significant heterogeneity in this area of research and perhaps reflecting that kind of subjective experiential nature of the changes that occur. It may just depend on the study, the response of the individuals within the study and other related factors.

DANNY LENNON: Sure, and we'll probably spend a bit more time looking at that low FODMAP diet intervention specifically, and some of those papers that you've just referenced. I think in relation to some of those healthy eating dietary recommendations. While a number of those we don't eat spend too much time on, I think there's a couple of interesting areas that maybe we can discuss. One is around dietary fiber, because again, here there's where we see some slight conflicting things, and then maybe we can talk about dairy foods, because I think typically, that's one of those most common ones that get tends to pull out the diet initially when someone is having symptoms. So in relation to fiber, I mean, based on those different subtypes of IBS, this is where we tend to see differential recommendations given. So whether it's constipation predominant or diarrhea predominant IBS, we may see either a recommendation to increase or decrease dietary fiber in an IBS patient with again, in this circumstance, it's going to be obviously a decrease for someone that has diarrhea predominant IBS, and then the opposite for

constipation predominant IBS. But there also seems to be then differences on where that increase in fiber comes from. So particularly, it seems to be advised to gradually over time increase soluble fiber intake when the recommendation is to increase fiber, because some of the interventions that have just used an insoluble fiber, like, I think there was one – there's a few papers actually on insoluble wheat bran that basically don't improve symptoms, whereas you see some improvements with other supplemental interventions that use linseeds I think.

ALAN FLANAGAN: Yeah, and that I think is important for that – seems to be important for that first line intervention in particular, because while you know exclusions of the kind of typical, well, fatty foods, spicy foods, coffee, etc., exclusion of those foods, I mean, it may be somewhat tedious if someone is a coffee lover, for example, but it's not necessarily going to have consequences for health effects; whereas exclusion of fiber obviously carries with it the risk of actual change in the gut. And indeed, this is something that is discussed generally in the weighing up of the pros and cons of IBS management ultimately is where someone to restrict certain types of carbohydrates including fiber, there is alterations in the composition of the microbiota that occur, and it's generally a reduction of species that we broadly associate with beneficial effects in the gut. So it is something to bear in mind.

I think that point you made about the type of fiber's quite important because, yes, you see no effect with wheat bran, and then some of the – and one of the interventions that looked at flax, it also had a psyllium husk group in which there was also no kind of significant difference in the psyllium group, but there was a significant difference in abdominal symptoms and improvement in constipation as well in the flaxseed or linseed supplemented group. So, it seems that, yes, the type of fiber is particularly important. One potential reason why there may

be a lack of effect for certain more kind of insoluble fibers could potentially be to do with the fact that there is an osmotic effect that is relevant in IBS symptoms. And by osmotic, we mean the drawing in of water, and into the small bowel, you know, there's the potential for an increase in distal bowel fluid to precipitate IBS symptoms, diarrhea, gas, pain, distension. So that could be another reason why people do experience symptoms with them, with certain short chain carbohydrates or certain fiber types, is this kind of drawing in of water into the small bowel, and this increase then distension, as a result of this osmotic effect of certain fibers.

DANNY LENNON: I think that we're making people aware that from an intervention standpoint, depending on the individual patient, there may be cases where the dietitian recommends for at least a short period of time a reduction in dietary fiber, and that low fiber intake may relieve some of the symptoms, particularly if the insoluble fiber is particularly aggravating to the gut as well, never mind causing some of these other symptoms. But again, that as a short term intervention, with the goal of over time, hopefully, that increasing, which is a theme we'll come back to, then in other cases, particularly that constipation predominant IBS, where an increase in fiber over time is recommended, there seems to be that that should be preferentially before soluble fiber. And we mentioned some of those supplementation interventions, for example, wheat bran doesn't seem to improve those symptoms.

And similarly, I think from some of, at least, I can't remember the specific trials but looking at increasing the fiber intake from cereals, or even some fruits didn't really improve symptoms. But where you may get a benefit from certain vegetables, probably because again they are soluble fiber intake, and increasing that gradually over time tends to be what's recommended. So there's just a bit of

interesting nuance for people to be aware of on the dietary fiber recommendations and what type of IBS subtype we're looking at in relation to dairy. This is just, I think, generally for a lot of things when it comes to elimination type diets, one that people tend to jump to, because a decent number of people tend to have some sort of issue with dairy produce in relation to IBS here specifically, probably from a first line perspective, it's looking at it from a lactose content of it, so particularly focusing on milk or yogurt. I don't know how many of the interventions that we need to go through on this, but again, quite mixed on how successful they tend to be to remove milk from the diet.

ALAN FLANAGAN: Right. Just as in the context of a standalone reduction or elimination as opposed to in the context of a wider low FODMAP diet intervention.

DANNY LENNON: Right.

ALAN FLANAGAN: And I think one of the interesting things like lactose, although there is a relationship potentially with the type of sugars in lactose and their composition, and how that relates to the overall picture of FODMAPs, there's no difference apparent in the population, in the general population in lactose malabsorption or diagnosed lactose intolerance. So it seems that the idea that there is somehow an increased sensitivity or an increased prevalence even of lactose intolerance in the general population – in people with IBS versus the general population doesn't actually seem to be the case, relatively similar levels. And I think as well, from a FODMAP perspective, lactose malabsorption doesn't necessarily mean lactose intolerance as a condition. And so, what is often observed with some of these structurally diverse carbohydrate types is the sensitivity to dose, and that’s part of the actual implementation. Obviously, the clinical management of the low FODMAP diet is a reintroduction phase that tries to assess thresholds for a tolerance. And it may be that

in certain populations, the sensitivity to lactose itself, or the sensitivity or perceived sensitivity to milk may actually relate to the total level in the diet, as opposed to a specific lactose intolerance or malabsorption.

DANNY LENNON: In terms of any of those other first line treatments, there are some other non-dietary things that we won't get into today, because we want to keep our focus here on some of the dietary interventions, but just to make people aware that typically there's recommendations around exercise, stress reduction, things like that, for reasons that should be obvious after our earlier discussion. But I think we should probably play some of our focus now specifically on those interventions related to the low FODMAP diet, broadly, would say most people within dietetics would have a positive view of this as an intervention and probably for a good reason as we'll explore. But maybe just to go way back to the start, just so everyone is on the same page, what is the, I suppose, reason for a low FODMAP diet? And maybe even before that, what are we talking about with FODMAPs, and why potentially, would their restriction play into hypothetically helping with IBS?

ALAN FLANAGAN: So the term is an acronym, so F-O-D-M-A-P, and it stands for fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols, so FODMAP. And it's a group of compounds, not any single constituent in the diet, and I think that's important, because it can often kind of – we tend to say FODMAPs, plural, but people can perhaps sometimes think that it's actually a specific thing that occurs just in different foods, the whey protein, for example, might be in a chicken breast as well as yogurt. So these are structurally diverse compounds. And they all slightly differ in terms of potentially slightly different terms of their relationship with IBS. So oligosaccharides, for example, humans lack the necessary enzymes to actually break down and degrade, and so they pass through to the colon, much in the

same way that say fibers would, and can undergo fermentation by bacteria in the gut, as a result producing hydrogen gas and are implicated then in symptoms like bloating, pain even, and flatulence.

So that's oligosaccharides, the first one. And then disaccharides that's the milk sugar, lactose. So it's a disaccharide compound, and we do have ethnic variations in terms of prevalence of lactase enzyme activity. And so, there is an overlap between the potential for a general lactose intolerance, which could be identified versus lactose in the context of IBS. And then with monosaccharides, that's a simple sugar, fructose, in particular, and it occurs naturally and as an artificial sweetener, and the effect that this appears to have is by exerting osmotic effects in the small bowel. So this idea of drawing water into the small bowel, causing distension and other related IBS symptoms. And then finally, polyols are also a form of simple sugar, and they're also found naturally, but they're commonly used as artificial sweeteners. And so you'll often see them in protein bars, for example, or mints, sugar free chewing gum, this kind of thing. And they, similarly to fructose, exert an osmotic effects, pulling water into the small bowel and potentially associated with distension.

So that's the group of FODMAPs. With the actual intervention itself, the implication, obviously, as we've just described, is that these compounds, may all individually have a particular effect that's related to IBS symptoms. Obviously, collectively, they would tend to occur in the diet, for example, oligosaccharides, average intake, because of the levels of kind of wheat and grains that we would typically consume in a Western diet, people could have an intake of a couple of grams a day of oligosaccharides. They may also have a couple of grams a day of lactose intake if they're consuming milks and yogurts and otherwise. So there’s the potential for multiple

of these compounds to be present in the daily diet.

And as we outlined, the process would have been that an individual would have had first line assessments and interventions, excluding gastrointestinal disorders and symptoms, how the diagnosis of IBS, and then would have gone through that first line intervention that we described. And then, in the absence of any symptom resolution or improvement with that first line intervention, they would then be advised to go to the next step, which will be the implementation of a dietitian led low FODMAP diet, and that's the second line intervention.

And an emphasis of this within dietetic management is that the low FODMAP diet is not a diet for life, and I think there is potentially some concern for the way that people kind of almost talk about the low FODMAP diet, as if it's kind of a general normal diet that you might do, it's a clinical nutrition intervention. And it's divided them into three phases. The first phase is the actual restriction phase. So they'll be guided to restrict all FODMAP rich foods, and this phase lasts, give or take, four to eight weeks. And they would obviously be canceled through the dietician to maintain nutritional adequacy for things like fiber, like you said, use of things like flax, potentially during that period, calcium.

And also the recommendation would be that if the individual did not have any symptom resolution during that four to eight week guided period, then they would discontinue the low FODMAP diet, they don't keep going with it in the hopes that at some point there will be symptom resolution. So it's deemed to have, to have not been effective for symptom resolution, if an individual does not respond to it. If they do improve, then they proceed to the next phase, which is the reintroduction phase, and they'll basically have again, a dietitian guided food challenge reintroduction with specific FODMAP subtypes. So there'll be a very

specific approach based on the various subtypes that we just described, and there'll be a particular focus on oligosaccharides, on fructans, and galactooligosaccharides. And this is because these are prebiotic compounds as well, and they feed beneficial bifidobacteria strains in the gut, which can decrease if someone just excludes all FODMAPs, and it's not very well guided.

And so the purpose of this reintroduction phase and these food challenges is to test individual tolerance to different foods and try and establish a personal threshold for tolerance to different FODMAP foods, and that's obviously again guided through by the individual's nutrition professionals. And then the aim is to obviously then transition to long term management, and that's the third phase, and final phase is the long term management. And this is, you know, the goal here is to find a balance between improving symptoms and managing and maintaining an improved and reduced symptom burden, while minimizing dietary restrictions overall. So patients then may find that they can actually consume foods that are labeled as a FODMAP food, but in varying amounts, depending on their personal tolerance threshold, and their personal tolerance threshold allows them to consume that food while minimizing any kind of negative symptoms as a result.

And so a lot of the research on this kind of final phase is retrospective, but we do have evidence that patients who do this successfully achieved this modified low FODMAP diet with individual foods consumed according to their kind of threshold levels, do actually have more successful long term symptom management. But as you highlighted, I think really importantly at the start of this, it's easy for me to lay out the stages of the low FODMAP diet and make it sound like, oh well, this is easy phase 1, 2, 3, and off you go, but that's not actually the case for everybody. And there obviously are many individuals who did not

necessarily even experience symptom resolution with that phase 1 restriction.

DANNY LENNON: And that's crucial, and we'll probably get to some of those interventions to discuss that, but I think the typical numbers are somewhere between like 50 to 70% of patients in some of these interventions may see a beneficial impact to some degree of a low FODMAP diet, but meaning 30 to 50% may not. And that might just be a function of it's just not, this is not the thing that's causing their symptoms. I wanted to recap over a number of the points you made because they're so crucial for people understanding this as an intervention. One was around the, I suppose, duration and goal of this diet, that this is a short term intervention, particularly that first restrictive phase where it's completely we're going to go low FODMAP across the board, that is for a short period of time that we're going to remove these from the diet. As you noted though, removing all foods that have a relatively high amount of these different types of FODMAPs removes foods that have important prebiotics that have therefore impacts on the balance of microbiota, and can have negative impacts longer term.

So the important thing to think about here is that the goal here is to return as many of those foods as possible over the long term, and as Alan said, these are not just one type of food, there's many different types, and for different individuals, they may have an issue with different types of foods in varying different doses, and the goal is to get as many of those back into the diet as possible, in the long term; it's not to stay on this restrictive elimination diet essentially, that's a short term period. And this is the problem with many of these more pseudoscientific versions of elimination diets that kind of hijack this to some degree where vertical in nature or not where you basically use a low FODMAP diet indefinitely, and people do see some degree of symptom resolution, but you're basically butchering an actual dietetic intervention. So we're trying to

reintroduce those as much as possible over time.

So with that, maybe we'll just mention a couple of interventions, because again, just for the sake of time, we probably won't work through in detail all of them, but it's probably worth noting that originally, a lot of this work would have originated from the group at Monash University, and we can maybe mention some of those trials, if there's any other in particular that you think you want to address, and then maybe we can talk about some of the implications of that Bond paper that you mentioned at the start, because I think, at least even within dietetics, there may be slight differences in how people interpret a study like that, because I've seen that some people will see, okay, this is – again, for a reminder for people, that particular paper that Alan referenced was looking at that kind of comparison between the low FODMAP diet versus that kind of, I suppose, standard of care in dietetics for people with IBS. And seeing that there wasn't really a noticeable difference at the end, now one person could read that and interpret that to mean, okay, we have both of these interventions led to an improvement in a number of these people. So now we have two good interventions that we can try with people, so kind of see in that positive light. Someone else might look at it and say, well, in terms of a low FODMAP diet, this is kind of a negative for me, because it doesn't do any better than that kind of standard of care, but it's a bit more restrictive, so there's different ways to view that. But with all that ramble, where's maybe a place you would like to start with any of the interventions – is there any in particular that you think we should bring up, or even if we just give a synopsis of?

ALAN FLANAGAN: Yeah, just even a synopsis, I mean, there's been a couple in terms of the, you know, there's a Halmos, I think if I'm pronouncing that lead author right, this was the Monash group I think, 2014 paper from Australia, and again, it

was low FODMAP diet versus usual diet, not just kind of typical Australia, you know, the general advice, three-week feeding study with people who I think were IBS-D, so diarrhea kind of predominant, and then mixed IBS types. And generally, overall low FODMAP diet kind of significant reduction, I think 70% in the intervention group had a significant reduction in abdominal pain, bloating, and diarrhea symptoms. So again, there's a hold over there, for not every individual in that intervention group had a benefit, but certainly a significant majority did I think out of 30 in the intervention group.

There's, I think, overall as well, there was another – there was a paper in Norway, I think Berg was the lead author, where it was IBS, specifically fructose reduced versus a kind of a general IBS diet, and again it's just a control. And with that restriction of fructose additional to the IBS diet, further restriction of fructose generally reduction in bloating, abdominal pain, and that was compared to the IBS diet alone. And then, yes, you have some findings that then are not entirely all positive in the direction of the low FODMAP diet. There is a Danish study that compared low FODMAP diet in different IBS types, and while there is an improvement noted in IBS-D and IBS-M and mixed type, the IBS constipation, IBS-C diagnosis or definition did not show any improvement from any treatment.

So I think there are obviously some nuances that may relate to the actual type of IBS, there are some nuances that may relate overall just to the nature of the intervention, and what's being compared to what I think is a really important aspect of this, like, is it just a general control, is it the first line IBS healthy eating advice, is it a comparison to healthy controls, or is it a comparison between different IBS types, and then what intervention are they put on. That may explain, I do think with the Bond study that you mentioned, I think it was four weeks low FODMAP diet versus traditional IBS diet,

and again, significant improvements in both groups. I think, the overall direction of effect for the literature, if we're considering totality of evidence, I think the overall direction of effect points to a benefit to the low FODMAP diet in reducing IBS symptoms, acknowledging that not all studies comparing a low FODMAP diet to first line dietary management have found differences between diets on symptom severity. But the overall direction of effect seems to suggest a greater magnitude of benefit, particularly potentially for pain and bloating, with the low FODMAP diet compared to other diets, including the kind of general first line management.

DANNY LENNON: I think that's correct, both in the research community and the dietetic community as well, you tend to see, in the majority of cases a favorable view of – overall, there tends to be a benefit from here relative to other potential interventions, at least for a significant enough number of people that this is an important intervention to have in the toolbox. I think, from just looking at some of the interventions and the trial design that might be interesting to discuss, because it relates to maybe some aspects we've discussed before, that can be a challenge with some of the trials on low FODMAP diets, is that in many cases, it's going to be difficult to have blinding and such of these trials, which we've talked about before in relation to nutrition. And especially depending on how the study is set up and how they enroll people, you could have people with IBS who obviously we've mentioned, there's a lot of frustration and really want to resolve this now have this potential treatment that you can't really be blinded to because of the restrictive nature of this diet really. And so, it's possible that such trials are going to be more prone to placebo and nocebo effects as well. And that's kind of one of the reasons why, regardless of the end outcomes of that Bond study, I think that was interesting to know of how they set that up, when they had those two diets, they were kind of – the patients were told ahead of

time that both of these diets had a good chance of helping them, but none of them was labeled as a low FODMAP diet as kind of one of those ways to try and get around these tricky issues that we have with such interventions.

ALAN FLANAGAN: Yeah, I think the expectation of benefits, I can't remember what the term for that bias is called, but the kind of expectation of benefit in going into an intervention and knowing that there is the potential or that you're being given a treatment that is supposedly beneficial, I think with the Bond study as well, if I remember, the participants were also consuming probiotics in both groups. Now, obviously, we've discussed and have a full statement on the use of probiotics, and the evidence is quite mixed, but there is still no evidence of benefit. So between the manner in which potentially they managed expectations equally in both groups and relating it to this idea of the kind of psychosocial component of FODMAP or well, IBS, sorry, not FODMAPs, and symptoms may go somewhat to explaining the relatively equal symptom improvements.

Yeah, I think overall, when you step back from isolated studies, it seems to me that the direction of effects supports the low FODMAP diet, again, acknowledging that not everyone, every individual will necessarily have a benefit. But it seems like certainly a majority, at least half will experience an improvement, and that the magnitude of that improvement may be greatest for things like abdominal pain and bloating.

DANNY LENNON: That's an accurate conclusion that this is going to have benefit in a significant number of cases. And I think this is why many of these different types of, let's say, non-evidence based diets or kind of pseudoscientific different ideas, ideas that people put forward to someone, and someone experiences a reduction of various symptoms, particularly if those are gastrointestinal, put it down to this magical nature of the diet, whereas it could be just

because this type of diet is accidentally low FODMAP, and that was the actual issue. So let's say, someone that is having symptoms of distension and abdominal pain and bloating, and now they're convinced to go on the carnivore diet. Well, the carnivore diet by nature is removing FODMAPs. So is it the magical healing properties of meat, or, is it the low FODMAP component?

I think a similar issue that often, where there's still much debate about is around the issue of gluten and gluten free diets. And again, a lot of people may remove gluten from their diet, and notice that it leads to some beneficial improvement in some of these types of symptoms, but then there's been this challenge then and say, well, when someone goes on a gluten free diet, there's probably going to be reduction in the total amount of FODMAP intake because of the foods they're now not consuming, and so, maybe it could be a FODMAP issue. And there was actually a double blind crossover trial, 2013 study that looked at this, and it kind of has circulated quite a bit, I will link to this in the show notes. But essentially, they had the participants randomly assigned to a two-week diet of reduced FODMAPs, and then were placed on a high gluten, low gluten or controlled diet for a week. Then there was a washout period, and they looked at different markers of intestinal inflammation and so on, and then a subset of those participants participate in the crossover to groups that were given a gluten, I think like 16 grams a day, whey protein at 16 grams a day, or a control where there was no additional protein, and they looked at various different symptoms. And in all of the participants in that study the gastrointestinal symptoms consistently and significantly improved with the reduced FODMAP intake, and so, the take-home was that the gluten specific effects were observed only about 8% of those participants, and all of those participants had people who had deemed themselves sensitive to gluten, and that's how they were enrolled in it. Whereas

really, that was only 8% of them, the rest it was a FODMAP issue. So I think that's interesting, that's not just gluten free, but things like carnivore or things that remove high FODMAP foods and people get less bloating and they think it's this magical diet.

ALAN FLANAGAN: Right. Yeah. And I think what I scratch the head at a little bit on that is it's a highly – it's basically determining the kind of health effects, so to speak, of that diet by reference to subjective symptoms. I think part of the problem is some normal physiological responses to food intake can be over pathologized. Someone who has IBS, it's a different story, but people often hear, well, oh, like, the experience of being full after a meal or distension or some degree of bloating, it can be completely normal to have those responses, depending on the type and quantity of food that has been eaten. And what I find, well, I guess, tragic is probably a better word than hilarious, when I hear about people, particularly saying, well, my old meat diet has improved, I don't get bloating anymore; or my restrictive – I exclude all of these fibrous foods and I don't get bloating anymore, therefore my symptoms have improved – they're not experiencing as a symptom what's going on under the hood in relation to those diets. And we have evidence from dietary interventions in humans of some of the quite quick and profoundly negative effects of those types of dietary practices, have in terms of secondary bile acid production, which are highly carcinogenic in the colon, the increase in potentially pathogenic bacteria and the complete alteration of the microbial, of the microbiota itself in terms of composition. So although they may not be experiencing the symptom of bloating, the idea that someone is benefiting their gut health or colorectal cancer risk, for example, by eating an all meat, no fiber diet, is really delusional, unfortunately.

DANNY LENNON: Yeah. And I think that's exactly this pathologizing of normal responses to eating

because, like you say, this is, in many cases, not an actual IBS diagnosis where this is prolonged abdominal pain that is very real, this could be someone now because of what they're hearing this person talking about, oh, do you get bloated after meals. And what is maybe a normal response in most cases, to eating a large meal, particularly if you're eating foods that have prebiotics which are actually good for you, people start seeing that as a negative. Exactly what he said, like, pathologizing normal issues, and then to try and rid themselves of these fake problems, go and follow something absurd, like a carnivore diet.

And you see that quite often with a number of things, right? It gets so often with carbohydrates, right? Do you eat a large meal of carbohydrates and feel tired, like, that's your brain fog, that's your brain shutting down. You need to stay sharp and alert at all times.

ALAN FLANAGAN: Yeah, that's the grain brain.

DANNY LENNON: Grain brain, spoiler alert. So we will speak more in a few moments.

ALAN FLANAGAN: Yeah.

DANNY LENNON: But let's maybe just wrap this up then and kind of conclude that this topic then. So just for like the main takeaway from what we've discussed here, in terms of diet's role within IBS, from a practical intervention standpoint, we're kind of saying that there are these, for clear, first line treatments that will happen within dietetics, around changes in the diet, there may be different recommendations around fiber intake, there may be some suggestions to remove things like alcohol or caffeine, etc., for a period of time to see if that leads to some degree of symptom resolution. If there's no improvement at all, we have the second line intervention where predominantly now within dietetics that's going to be a low FODMAP diet, where on the totality of the evidence available seems like a pretty efficacious intervention, and

for a significant number of people leads to a reduction in symptoms or, in some cases, a complete alleviation of that. Would that be a TLDR of this so far?

ALAN FLANAGAN: Yeah, I think that's a fairly good synopsis, I think, recalling the low FODMAP diet is a dietetic led clinical nutrition intervention. It's a second line intervention. If someone is really experiencing a lot of gastrointestinal discomfort or symptoms that look and sound or feel like IBS, then avoid the temptation to self-diagnose, because it's all too easy to do now, and really do avoid trying, as it seems a lot of people do, just to, I'm going on a low FODMAP diet as if they're announcing they're going vegan tomorrow. And that really shouldn't be done, because of some of the technicalities in the various phases that we talked about, like, guiding the reintroduction of specific foods, establishing tolerance thresholds for different individual FODMAPs in the foods that they come in, you know, really does – will benefit significantly by having an appropriately qualified nutrition professional to oversee that. And I think although we didn't touch on it too much because we're focused on the nutrition side, I think recognizing the psychosocial aspects of IBS, factors like stress, anxiety, depression, how that all might relate to gastrointestinal symptoms, and obviously, trying to bring that into the overall picture as well of kind of symptom management and health.

DANNY LENNON: And you do see that now, I think there's an increased recognition, from what I'm aware of, at least, of interventions like cognitive behavioral therapy, breathwork; even things like yoga and so on are now being kind of part of that mainstay of interventions along with some of these dietary components, because in many cases, it may not be a dietary factor, that's the main thing that moves the needle there for someone.

ALAN FLANAGAN: Yeah, I remember having a chat with a dietitian just about low FODMAP diet and kind of symptoms and stuff, and a really well put statement that I think is quite important for people to hear is just like, you know, they were stressing that in communicating with patients about the symptoms particularly if they are managing in the kind of long term management phase, they do experience symptom improvement, but they might have the odd, they're at a wedding or something, and the cheese cake dessert comes out, and the next minute they're experiencing some bloating or whatever.

The point was that to recognize, for the individual patient to recognize that there's no harm being done, what may be discomfort is not a representation of actual physical damage being done to the body. And I thought that was actually – it just stuck with me, because it was like – that's a really, I think, empowering way of communicating that, yeah, you might experience a transient flare-up and some symptoms in trying to kind of navigate the food landscape and all of that, but it's not, you know, you're not doing harm to yourself in experiencing that.

DANNY LENNON: Yeah, and that is, I mean, particularly for living this on an ongoing basis, the flexibility that allows of, yeah, in most cases, you obviously don't want those symptoms, but if they do occur at certain moments that you accept that tradeoff, you're not doing a clear harm, which is, again, like we said at the outset, what makes this different from something like celiac disease, where you have a ton of gluten, there is actual, say, destruction of gut tissue there in response to that. So one other thing that you mentioned that I wanted to go over again, just there is that whilst for someone that is experiencing these symptoms, or even has a diagnosis of this, or believes that they have IBS, right now, all this education is very empowering; but as Alan outlined, you, number one, certainly want to get an accurate

diagnosis from a registered healthcare professional, you don't want to self-diagnose because either, one, you don't want to give a diagnosis when maybe you actually have symptoms that are just normal, and you don't want to overthink it. But on the flip side, you also don't want to miss something more severe that you might miss out on because you've diagnosed that this is IBS, where it might be something different.

And then secondly, in terms of treatments, particularly with a low FODMAP diet, this is not something that you just venture into without doing some of the other changes, you do it in line with a dietitian, and you're certainly not going to take it just random bits of advice from some person on social media or some local trainer or something. This is a dietician you would work with on this to make sure it's done accurately because it is not a benign intervention, as we said, it's why it's done for a short period of time and managed appropriately. So just please keep all those things in mind.

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