THE FATIGUE SUPER CONFERENCE

Case Study:

How stress hormones impact sleep

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Kirsty Cullen - [00:00:15]

Welcome to the Fatigue Super Conference, I'm Kirsty Cullen, CEO at the Optimum Health Clinic, and today I am joined by Sanna Anderson, one of our registered nutritional therapists here at the clinic.

Welcome, Sanna.

Sanna

Thank you.

Kirsty Cullen

So for today's session, we thought it would be really interesting to talk about the topic of hormone balance and its relation to sleep, so we're looking at the hormones involved in circadian rhythm, how we might assess those with functional testing and then considering some of the strategies that we might utilize to support the pattern of optimal cortisol and melatonin production and obviously ultimately improved sleep.

So let's start by explaining what the HPA axis is and why it is so important when we're considering good sleep patterns?

Sanna, over to you for this explanation.

Sanna

Thanks, Kirsty. So HPA axis stands for Hypothalamus Pituitary Adrenal, so HP and A and it's essentially a feedback loop, which is quite typical of lots of hormonal functions in our body. It's, I would describe it a little bit as a thermostat where hypothalamus first gets activated by a stressor, sends a message to pituitary, which in turn activates then the stress response mainly in the adrenal glands.

I think it's also useful to bear in mind that we often think that the adrenals only get activated or involved in a stressful situation, a short lived, maybe one off situation, but adrenals play also a very important part in our daily lives, and especially in our sleep and awake cycle or circadian rhythm, as we call it.

So because HPA axis it's a little bit like a thermostat, also HPA axis function and sleep is a two way relationship. So sleep is initiated when cortisol production and HPA activity are at their lowest, usually somewhere between sort of 9 and 11 o'clock at night. And then cortisol should start rising from around midnight onwards and peak around 9am the following morning.

So a lot of the sleep issues can be tracked back, or at least be contributed to by HPA axis dysregulation. First of all, if you just listen to the sort of the timings of the cortisol production, of course, it's incredibly important to look at the sleep hygiene of every individual, especially because we know that cortisol starts rising again after midnight. It would be very useful to finish off your day

before that and be ready for sleep before.

When you activate the HPA axis and the cortisol production is perhaps disrupted then the sleep cycle is often suffering as well, it can result in insomnia, fragmented sleep, shorter sleep periods overall. And when you're not sleeping well, when you are not getting enough continuous, deep sleep, you're also going to be struggling to replenish your cortisol stores overnight. And then, of course, you're more tired the following day, which is in and of itself quite stressful, which will probably initiate a bit of HPA feedback loop again, puts a further strain on the whole axis and you'll end up with further sleep disruption.

So it is really useful and important to understand what is happening with each individual, with their cortisol production. We can then guide them much better and support better sleep the more we understand about the daily patterns, individual differences in the cortisol production.

Kirsty Cullen - [00:04:31]

The research backs it up, doesn't it? There was a study in 2018 that showed that sleep deprived participants showed higher levels of baseline cortisol and also higher levels of subjective stress, interestingly enough. And then sort of additional research that considered that sleep disruption, as you've mentioned there, may be staying, trouble staying asleep or trouble waking early might also be associated with increased hs-CRP levels, which is a marker for inflammation. And what's so important about that is that that inflammation will then elicit more pressure through the HPA axis. So it kind of demonstrates that reciprocal relationship between the axis and disrupted sleep and how that can self-perpetuating in a sense.

Sanna can you introduce us to the functional tests that we might use to examine the HPA axis?

Sanna

Yes, great. So today, the samples that we are going to be showing you in the next half an hour or so are going to be from a test called the DUTCH test, which stands for Dried Urine Test for Comprehensive Hormones. As the name says it is, it does cover quite a comprehensive range of hormones, not just the cortisol. We'll talk a little bit about that but, of course, for today's purposes, mainly, we're sort of going to be looking at that part of the test.

It requires a urine and saliva sample or samples. They are very easy to collect at home. Saliva is collected into small little vials and urine collection actually only requires sort of collecting urine on these sort of strips, basically a little bit like a larger version of a pH strip, I would describe it, hence the name dried urine. Where historically often you would have had to perhaps collect, sometimes even a whole day's worth of urine. But with this test, it's only those dried urine strips.

And basically what we get is a really nice deep dive into hormone balance, not just cortisol production in isolation, which gives us lots more guidance in terms of how to individually support our clients.

Kirsty Cullen

So it's useful to look at some example test results so that we can see how the nuances and complexities of hormone balance work.

Sanna, do you want to talk us through this first set of test results and explain what they show?

Sanna

Yes, great. So, first of all, I think, I like pictures, so we've got in the top left hand corner, you've got that picture of the head and you can see what I was talking about with that hypothalamus pituitary adrenal axis. So you've got the stressor entering the brain, actually I think should probably just remind very briefly stressors, of course, they can be physiological or emotional as far as your HPA axis is

concerned it won't really make a great deal of difference. That same chain reaction will get initiated.

When we then look at the cortisol output out of the adrenal gland, which is that little bean shaped gland in that picture. First of all, you can see that metabolized cortisol or total cortisol production, which is exactly that, how much cortisol is made by the glands. Often we call it your total fuel in the tank for the day.

If you look below that, you can see those two graphs. You've got the saliva free cortisol pattern and cortisone pattern. And we'll talk about those differences in a little while. The free cortisol is how much cortisol is free and available to bind to receptors and be active. And then, of course, you can also see the pattern of the cortisol throughout the day. So those are the sort of main aspects that will be looking at.

Traditionally, many saliva based functional tests have only been measuring the free cortisol pattern. So in this example, perhaps if we were to just look at that pattern, that would look OK. It falls within the shaded sort of guidelines, the shaded area, which basically indicates the optimal levels.

But if we look at that total fuel in the tank figure of 2579, you can see that little yellow beak almost it's pointing right below the minimum optimal amount. So definitely we would be classing this as adrenal insufficiency.

Kirsty Cullen - [00:09:32]

And that shows the importance of having both of those markers there, doesn't it? And actually, just briefly, we'll talk about this more maybe in the next set of test results, but this also showcases the saliva free cortisone pattern, which should, in theory, sit very much in a similar pattern to the saliva free cortisol pattern. And if we look at that dial above those two charts, you'll see that that red dial is smack bang in the middle, which demonstrates really good balance between the two. And that's not always the case. And that's important because cortisone is in fact inactive cortisol. So it tells us not only what we've got available, but how much is actually active. And that can be incredibly important in the overall picture of what's going on.

Moving on to the second sample, Sanna, do you want to show us what we can see going on here?

Sanna

Yes. So, again, this is great because actually when I was choosing these samples, another thing, I think is useful, important, interesting to say, is that on the outset, both of these individuals were actually presenting with fairly similar symptoms of tiredness, poor stress, tolerance, various different issues. But really, I think traditionally, often we have immediately, especially if there has been a history of stress, we would look to suspecting adrenal insufficiency. But with this sort of deeper testing, we can definitely differentiate a lot more, which can then drive much, much better clinical decision making as well.

So if we look at this one and the total fuel in the tank, instead of the sort of dial pointing right towards the lower end, we can now see the dial is reaching the upper optimal limit. If we look at the pattern of the cortisol, you can see that again, that's the figure, sorry, the figure after waking is quite high. The other figures, yes, they sort of fall into the roughly optimal category again. But the nuance we see is the very much accelerated output for the day.

The other thing to look at is that balance exactly as you mentioned, Kirsty, between the free cortisol and the free cortisone, so the inactive one. And if we look at that little dial, it is pointing more towards cortisone. So, how I would describe this would be, you know, you've got a huge amount of fuel in the tank, you've got one foot on the accelerator because you're using it quite fast, there's a fast rise of cortisol as soon as you get up, but then your body is desperately trying to balance things out a little bit by also slamming on the brakes and trying to start moving the cortisol into the inactive cortisone format.

Kirsty Cullen - [00:12:51]

It's a really good explanation. It really clarifies. And of course, with this type of adrenal picture, then we might also want to consider another marker, which is the VMA marker. You want to talk us through this on the same set of test results?

Sanna

Yes. So on this picture, what you see is a snapshot from some further data that we get, we always get with this test. We've got something called Vanillylmandelic or VMA, which is a metabolic end product of adrenalin. Adrenaline, as we know, is another hormone produced by the adrenal glands. I think adrenaline sort of already means something for most of us anyway, we know adrenaline rush. We know it is that sort of very fast acting, immediate fight or flight type stress hormone.

When we look at this picture, not only is this person producing a lot of cortisol every day, but if we look at how much adrenaline end product there is, this figure is also above the reference range. So there's more cortisol. There's more adrenaline. They are very likely living in this perpetual high stress state, which would be incredibly draining on anyone's resources.

Kirsty Cullen

So given that these test results that are displaying different things but similar symptoms, how might you approach these two cases differently?

Sanna

Right. So obviously, first of all, I think it's always important to remember that when we look at test results, we look at those together with the individual behind it. Another thing maybe I just thought, if you don't mind, worth saying, often people ask about, well, you know, does it matter how I was feeling on the day when the test samples were collected, especially when you get results like this second set?

If your tank is empty. If your adrenals have reached a level of insufficiency, no amount of stress around collecting your samples or getting it right will give us a picture like this. So, it's OK, usually what we do say is collect samples on your typical day, not on your sort of calmest day as such. Actually, I'd rather see a little bit of stress going on so that we can actually see how the adrenals are capable of responding. But as I said, if the fuel isn't there, it's not going to show up in these results either.

But as we are talking about stress response in both cases, of course, we want to understand how have we ended up here? Perhaps a little bit of a different timeline in some ways when you're looking at the insufficiency one that we saw first, it is very likely that we are looking into the past, trying to understand what has led us to this point.

With the high cortisol and adrenaline output, we are probably looking more, what's going on right now? How can we improve stress management? How can we improve responses in stressful situations or just generally reduce stressors? And again, that's both psychological and physiological. Obviously, in my remit and in my toolbox, we'll be looking more at the physiological stressors. So we would be potentially looking at inflammatory pressure coming from imbalanced digestive system, chronic infections could also initiate the HPA axis activity.

So, again, it's important not to just look at these results, but very much keep asking the question why? Why are we here? What can we obviously do immediately, perhaps to alleviate some of these symptoms and almost in the second result, help calm things down? But what else do we need to do to prevent this from perpetuating?

With the lower results, obviously, what we are really looking at is trying to nourish and feed the struggling adrenal gland and those would be more, I guess, what I'd call stimulating supplements. With the overproduction we can immediately start supporting the situation by increasing breakdown a little bit, using more calming type supplements.

Both cases, sleep. Incredibly important to ensure that both of these individuals get as good a quality sleep as possible so that there can be some restoration rebuilding taking place overnight.

Kirsty Cullen - [00:18:10]

And in the second set of results you noticed quite an early peak in cortisol quite early on, so it seems an appropriate time to talk about the cortisol awakening response. And let's showcase that in the next set of results. And can you explain exactly what that is and how we can measure it quite effectively?

Sanna

Yes. So I think that's the sort of slightly newer addition, again, to this type of testing are looking at those changes within the first hour of waking up. So if you look at that free cortisol pattern, again, the chart on the right, we've got the waking sample, which is collected pretty much as soon as you wake up and open your eyes. And then what we ask the individuals, our clients to do, is to get up, face the world, and we then measure what happens in the body in those first 30 minutes as you're waking up. What then happens in the next 30 minutes? So the third sample is waking plus 60 minutes.

And basically there should be a rise because we are getting up. We are becoming active. We're opening our eyes. We're getting light into our retina. And so therefore, the cortisol production should also mimic that or mirror that, I suppose would be a better word. But like most things in life, it shouldn't be too high and it shouldn't be too low.

In this case, as you can see, first of all, this individual is starting with suboptimal cortisol levels. So the waking example is below where it should be. But then as we look at the difference between waking plus 30, that rise should be somewhere between 50 and 160 percent. So the difference between those two samples, here it is, 870 percent.

So what this is telling us is this individual is opening their eyes getting up. And for whatever reason, the HPA axis is telling the adrenals, we're under threat. The world is a dangerous place. Let's initiate quite an aggressive stress response, basically.

And so this is what we call a high cortisol awakening response. It can be quite typical of long term anxiety and depression. It's good to have, as I said, good to have a cortisol awakening response. There needs to be that rise. But certainly this sort of level of rise is incredibly draining on the system. You're, as I said, immediately feeling like you're under threat. Your stress hormones are coursing through your veins. It's not going to be a particularly helpful start for the day.

Kirsty Cullen

And in what kind of situation might we see a blunted cortisol awakening response?

Sanna

So the blunted cortisol awakening response, certainly there's been some research around, PTSD seems to be typical of that. Seasonal affective disorder is also linked to a blunted CAR. So one of the things we often say, CAR, as in cortisol awakening response. Sorry, all these different acronyms. We do say when we see an awakening response not high enough, one thing that can be really helpful is to use either SAD lamps or make sure that you open your curtains as soon as you wake up. As I said, in the winter when the sunlight and daylight isn't there yet as you're waking up using that sort of light that mimics natural daylight. Sleep apnea type problems which are linked to brain oxygenation, can also create a blunted cortisol awakening response.

Kirsty Cullen

So moving on to the other end of the day then, and obviously the impact on sleep with this next set of results, how might we see those adrenal hormones starting to impact on sleep patterns here?

Sanna - [00:22:36]

So here we've got, let's have a look. So we definitely have not enough fuel in the tank, again, as you can see. The dial is pointing way too much far to the left.

If we look at the cortisol awakening response, there isn't much of that. So, again, that could be already giving us some hints around sleep issues overnight. So the cortisol response during the day isn't quite where it should be.

And if we look at the further bits of information about adrenaline, metabolites and melatonin levels, those two are really helpful in this instance as well. So we can see that the adrenaline output seems to be above average, or at least the adrenaline metabolite is above average. Also, the melatonin level is lower end of the range. It's not quite suboptimal, but it's certainly creeping down a bit.

So, what do we get when we put all of this together? What I often see, first of all, is when you don't have enough cortisol fuel in the tank throughout the day to get you comfortably through, get you completing whatever you want to complete, oftentimes we end up trying to do more than we have capacity for. And you can often push through by compensating the lack of cortisol with a little bit of extra adrenaline, which looks to be the pattern in this case. So you don't necessarily have enough cortisol, but as you have to do what you have to do to get through the day, you will compensate that via the adrenaline pathway. Which, of course, by the time you get to the evening, you don't really want to have that adrenaline coursing through your veins because that would be quite disruptive for sleep.

And if you do have that adrenaline, you get the disrupted sleep. And the melatonin is not on your side either because it's a little bit on the low side. You don't replenish your cortisol stores well enough. So the next day, again, you don't have enough energy, you may help, you may use the adrenaline to help you push through. Sleep is suboptimal and on that cycle goes. So, again, a really, really useful example of getting the nuances right in terms of how to approach this clinically.

Also really useful in terms of managing expectations when we start working on this, someone who perhaps is used to getting through the day by running on a little bit of extra adrenaline, if we start taking that away, what you are left with is that underlying sort of, what I'd call, the real energy which isn't currently there.

So, it is a very good exercise in listening to your body, it can feel a little bit scary that actually the first step is that you lose energy rather than gain, because we take away the rocket fuel and then we'll start rebuilding the much steadier fuel in the form of replenishing the cortisol output.

Kirsty Cullen

And as you say, those nuances are so important because if we saw sleep disruption with this set of test results here, just because we're not seeing elevated nighttime cortisol and desperately low levels of melatonin doesn't necessarily mean that there isn't sleep disruption there. It's about the balance here that we have got suboptimal or insufficient adrenal capacity through the day. We've got adrenaline coming in to sort of try and perk that system up. And actually, because we've got lower end melatonin, those things are still coming together in a concert to maybe contribute towards somebody who can't sleep as well as they might be able to. Is that essentially the picture?

Sanna

Yeah, that's absolutely right.

Kirsty Cullen

On the subject of adrenaline, then, obviously hormone synthesis is hugely important, but actually hormone clearance is just as important, isn't it? So perhaps you could talk us through the next set of results and talk about how and why it's so important that we clear hormones from the body.

Sanna - [00:27:17]

Absolutely. So, yeah, exactly as you said, again, if we just look at the absolute levels of hormones, we are only getting sort of a one slice of that bigger picture. Already we can see how important seeing that balance between cortisol and cortisone was in those previous ones.

But if we look at really any hormones in the body, very much it's about the balance between production and breakdown. And of course, imbalances can develop anywhere along that continuum. You know, we can have problems in terms of raw materials to produce enough hormone, but we may also have, or we may be producing too much as we've seen already, but we also may have an issue with the breakdown. The production levels might be looking perfectly OK, but if we break down very sluggishly, then even smaller amounts are going to have a physiologically very, very different effect on that individual.

And the beauty of this test is that we can assess both the output as well as some of the breakdown pathways. And again, of course, in this picture, as you can see, what we are looking at is breakdown of oestrogen, but it's very representative of how the body works anyway. Most of the substrates that we clear are cleared by this two step process in the liver, phase one and phase two or step one, step two. And those two need to work in harmony together otherwise they struggle.

Somebody I think once described it, the first step is sort of your house spring clean where you put the rubbish out, ready for the bin collectors. And then the step two is the bin collectors coming to pick those up. You don't want to spring clean unless you've got the collection booked and ready. And also, if the collectors have nothing to collect, if the spring cleaning is not happening, then not ideal either.

But going back to this example, the key root here that we are looking at is that first green pathway from estrone E1. So if you go down, that's the enzyme CYP 1A1. Basically Cytochrome 1A1. That's your step one or phase one.

And then as you turn to the left, you've got the COMT methylation there. So catechol-O-methyltransferase enzyme that takes care of that second step. As you can see there is that word methylation, which I think a lot of us keep hearing a lot about. And of course, methylation is something that happens, you know, in a huge variety of biochemical processes in the body, in every cell, every second of the day. It's used for energy production as well. But for today's purposes, we're going to be looking at clearance.

The nice thing is, of course, that when we see indications for perhaps issues with this enzyme and methylation, we can potentially sort of extrapolate that a little bit further as well in terms of looking at the client and the individual and how they present. And perhaps raising questions of where else methylation problems might be hindering their health.

So, back to this one, so as I said, we're looking at estrogen clearance. Right at the end of that inverted L shape, you see that fan shape again showing preference or showing level of function in this case, it's very low. So the second step is very slow. And you can even see it when you start looking at those pictures. There is a lot coming down the CYP 1A1 pathway down to the two hydroxy oestrogen. So that's the 2OHE1 that you see at the bottom. There's a lot of it that's outside of the reference range.

And then when that substrate is trying to be processed through that COMT pathway, the quantity drops dramatically. So there is a very tight bottleneck there, basically how I would describe it.

So, woman with this sort of presentation, very much would be struggling to clear oestrogen, but the useful thing when we come to look at it within the context of what we are talking about today, is adrenaline is also cleared, we need the COMT enzyme when we clear adrenaline to get to that VMA, Vanillylmandelic that we've been looking at, adrenalin needs to move via that COMT step, basically.

So, as I already said, you know, that oestrogen is driven through or is trying to push through a very, very narrow path almost. Same thing will happen with adrenaline. Even a little bit of adrenaline will hang around for longer. Often these individuals present as somebody who's very easily triggered, they find it hard to rest, they find it hard to come down from any stressors they are often very sensitive

to their environment because, again, adrenaline is that kind of fight or flight hormone. Brilliant when you're under threat, that you are very sensitive to your environment, your hearing, your vision, your smell, your senses are all heightened. If you are living like that on a day to day basis, it's going to get quite uncomfortable. And of course, it's really not particularly helpful for rest and sleep.

Kirsty Cullen - [00:33:35]

So what type of dietary cofactors then might we look at to support that COMT pathway?

Sanna

So what we need to do is obviously understand, first of all, what sort of nutrients we need to sort of utilize as cofactors for the enzyme. Magnesium is one really key mineral, B vitamins I think for methylation we've all heard about the B12 and folic acid, but the rest of the B sorry, B vitamins as well are very important.

Diet wise, we want to keep the energy management as easy as possible. And what I mean by that is giving steady fuel through better dietary choices so that we don't have this sort of quick bursts of energy, which would be from fast releasing carbohydrates without sufficient amounts of fat or protein. It's much better to have a nice balanced diet where you have more complex carbohydrates, some protein to slow down the energy release. And that way at least your adrenals don't have to get involved in trying to smooth out those energy peaks and troughs throughout the day.

But really in a sluggish situation like this, I would very much also want to go in with some extra dietary supplements, as well as obviously optimizing what's on your plate.

Kirsty Cullen

And finally, Sanna, then it might be useful just to have a look at some suboptimal melatonin production, because obviously that's something else we can see within these test results if it's in existence. Shall we talk through this last slide?

Sanna

Yes. So this last slide, I think, is that, well should we say classic? I think we started off saying, well, melatonin is a hormone most people perhaps think of when we think about sleep, hopefully you've seen by now that there's a lot more to it. But again, I think it is incredibly helpful that within the remit of this test, we do also get that melatonin reading. And that way we can differentiate where we need to put our efforts into or how we can help gain that better sleep.

And yet, as you can see in this instance, for this individual, it really probably, very likely is the melatonin production being so low that is driving the sleep problems. Again, it's a very much, it will often give you a lighter sleep. And when you have lighter sleep, you will, clearly, not rest as well. But it will have a detrimental effect on your HPA axis as well. We haven't pulled that data into this one. But again, you could expect easily that if we looked at the cortisol output, very likely that would be on the low side.

There could also, of course, be some extra adrenaline, all sorts of other issues. But in this instance, yes, we'd be looking at how can we get the melatonin higher. And again, it's not just supporting the melatonin pathway and perhaps giving nutrients that feed that pathway, it is looking at the overall, what we call sleep hygiene, making sure that you get daylight before midday, which will then start stimulating better melatonin production. Making sure that your room is dark at night, again which feeds that better circadian rhythm, better balance, better melatonin production.

Kirsty Cullen

Sanna, that's been really helpful. Thank you so much for sharing all of that information with us today. Really appreciate it.

Sanna - [00:37:45]

Thank you.