

Vitamin-D and it's Health Effects Over Humans

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Vitamin' D and melatonin are pluripotent compounds. Some think of them as vitamins, but they are more convincingly classified as hormones. These two molecules interact with each other in an incredibly complex circadian dance [1], a dance that affects us profoundly. Due to modern lifestyles, more and more of us are out of step, and suffering ill health as a result.

'Vitamin' D is the hormone of sunlight, and melatonin is its dark twin. Both molecules appear very early in the evolutionary tree, and both play key roles in defending the cell's ability to generate biologically useful energy in the mitochondria, around the clock. This goes some way to explaining the importance of D and melatonin to our health, and their involvement in many diseases.

'Vitamin' D protects mitochondria in various ways. These include a possible direct antioxidant effect in mitochondrial membrane [2] and the up-regulation of antioxidant enzymes such as glutathione peroxidase [3]. D also up-regulates various anti-ageing and mito-protective proteins including Klotho [4,5], the sirtuins [6,7] and the Heat Shock Proteins (HSP's) [8,9].

The D receptor (VDR) occurs in mitochondrial outer membrane [10] where it regulates the permeability transition pore [11]. D is thus involved not only in mitochondrial survival but also the life and death of the cell housing those mitochondria [12-15].

The age-related decline in Klotho, sirtuin and HSP synthesis drives symptoms of ageing such as loss of muscle volume and function [16-19] and the age-related decline in mitochondrial function exerts multiple adverse effects in many tissues [20]. Against this background, 'Vitamin' D can legitimately be regarded as a gero-suppressant.

While the effects of D supplements on mitochondrial function are subtle and complex and vary depending on dose and duration [21], they are generally protective. Overall, D deficiency impairs mitochondrial function and D repletion restores it [22-25], in muscle and probably other tissues. 'Vitamin' D will not build and maintain muscle and other tissues on its own, but is a necessary element in that process.

Unlike D, which is formed exclusively in skin, melatonin is synthesized in the mitochondria of all animal, plant, fungal and bacterial cells, and in the chloroplasts of plants [26-30].

Melatonin's ubiquity is unsurprising. Chloroplasts and mitochondria were originally prokaryotes which needed antioxidant defenses against free radicals produced by photosynthesis and oxidative phosphorylation respectively. The original free-living prokaryote species (cyanobacteria and purple non-sulphur bacteria) still produce melatonin in a clockwise manner [31,32] and our eukaryotic cells have learned to capitalize on it [33-36].

Melatonin and its metabolites are highly effective in scavenging reactive oxygen and reactive nitrogen species and modulate a large number of antioxidative and pro-oxidative enzymes, leading to a reduction in oxidative damage. Like D, melatonin up-regulates Klotho [34], the sirtuins [35] and the HSP's [36], creating a powerful mito-protective effect; and like D, melatonin is a gerosuppressant [37].

This translates into protective effects against neurodegeneration [38,39], myocardial damage [40,41], renal fibrosis [42] and various cancers [43]; especially when combined with vitamin D and pre-transitional nutrition.

Unfortunately, our indoors lifestyles and lack of exposure to daylight has created wide-spread hypovitaminosis D, even in the subtropics [44]. Hypomelatoninism, which is induced by the widely used beta blocker metoprolol [45], non-steroidal anti-inflammatory drugs such as aspirin and ibuprofen [46], alcohol [47] and even the dim light emitted by LED screens at night [48], must be equally common.

Our D and melatonin rhythms are out of sync too.

Most human activities display circadian rhythms. We are generally more active during daylight hours and require higher levels of mitochondrial function - one reason why our mitochondria have maintained circadian rhythms similar to those of their prokaryote ancestors [49,50]. This creates circadian rhythms in insulin sensitivity and is the key to time-restricted eating (See below).

Once those prokaryotic bacteria had infected eukaryotes and then higher life forms with their circadian clocks, our timing machinery required daily re-setting in order to take circannual changes into account. In humans, light sets a master clock in the supra-chiasmatic nucleus which entrains cellular clocks in other tissues, linking inner requirements to external cues and resources. The opposing light/dark rhythms in D and melatonin are an important part of this.

Getting out of sync - i.e. shift working, eating at night, staying up very late - disrupts these links and is another way in which the modern lifestyle contributes to today's appalling public health. Animal studies show that the equivalent of night work and recurrent jet lag trigger weight gain and metabolic syndrome.

'Wrong' meal timing pushes nutrients into the blood when the mitochondria are in resting phase, and less able to deal with them. This dysrhythmia is made worse by a high-fat (i.e. ultra-processed) diet. and these factors help to explain why urbanization and particularly shift working increases the risks of obesity, diabetes and cardiovascular disease.

It also explains why clinical trials show that time-restricted eating, which brings food intake and mitochondrial function back into sync, provides weight-loss and major metabolic benefits even without calorie restriction.

In the real world, however, the problems of dysrhythmia are further exacerbated by sleep-deprivation which leaves our tired brains over-responsive to food stimuli, making us eat more. In a final twist of the screw today's ultra-processed diet, rich in sugars and fats but low in fruit and vegetables, creates a negative feedback loop which damages sleep further. Polyphenol depletion is implicated.

Back to the lifestyle-related problems of hypovitaminosis D and hypomelatoninism.

The evolutionary process has built so many buffering systems into us that on their own, they would probably not cause serious harm. But these endocrine abnormalities are super-imposed on a population already experiencing chronic inflammatory stress, glycativ stress, Type B Malnutrition and, critically, dysbiosis.

The microbiome is also on the clock and displays bacterial and chemical shifts which affect host rhythms and are affected by them. Dysbiosis likely worsens the impact of circadian disruption, increasing the risk of inflammation, insomnia, depression, diabetes, cancer, infections, auto-immunity and other problems.

D and melatonin supplements are therefore a potentially good idea, if used appropriately. Sadly, hypovitaminosis D is generally not alleviated by the arbitrarily tiny doses of D permitted in the EU. Nor is hypomelatoninism helped by melatonin supplements, which have negligible bioavailability due to low absorption and first pass metabolism.

Sub-lingual tablets avoid first pass but are, simply, awkward. Trans-mucosal delivery systems such as bio-adhesive gel strips make perfect delivery systems, and their low payload is not a problem with the doses relevant to D and melatonin.

Day and night strips containing D and melatonin respectively make sense to me. Apart from any health benefits they would help many to sleep better at night, feel more awake the next day, improve their memory and even lose a little weight. And here, I will stop the clock.

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