# The Role of Nutrition in Retinal Health

A Clinical Conversation with Shalesh Kaushal, MD, PhD, and Robert Rountree, MD

*Shalesh Kaushal, MD, PhD, is a retina specialist and biochemist with a special interest in nutritional biochemistry, functional medicine, and disease prevention/treatment with nutrition. He completed his MD at The Johns Hopkins University School of Medicine and then went on to obtain a PhD in biochemistry at the Massachusetts Institute of Technology. Following that, Dr. Kaushal did his residency at the Doheny Eye Institute/University of Southern California in Los Angeles, and then a retina fellowship at Washington University, at the St. Louis Barnes Retina Institute. Following that, he spent one year at the Moorfields Eye Hospital in London. He became head of the retina division at the University of Florida School of Medicine before becoming chairman of Ophthalmology at the University of Massachusetts Medical School. Dr. Kaushal is now practicing in Orlando, Florida.*

**Robert Rountree: Please describe your background and tell us how you became interested in complementary and nutritional medicine.**

**Shalesh Kaushal:** Although I was originally interested in theoretical physics, I came to realize that there is not much interaction with people in that field. So, I went into medicine, and I was fortunate to go to the Johns Hopkins University School of Medicine. I originally thought of being a pediatric neurosurgeon, because of the inspiration of my mentor, Dr. Ben Carson [MD]. However, I felt that ophthalmology was my calling. I had wonderful mentors in the nationally and internationally known medical scholars, Drs. Ed and Irene Maumenee [MDs].

However, I was also very interested in biochemistry and research. So, after medical school, I made the decision to obtain a PhD at the Massachusetts Institute of Technology with Nobel Laureate, Dr. Gobind Khorana [PhD]. Dr. Khorana had originally discovered the genetic code but moved into retinal biochemistry. So, I had a phenomenal opportunity to work with someone who had expertise in photoreceptor biochemistry because of my interest in ophthalmology. After 5 years in the laboratory, which I enjoyed intensely, I missed taking care of patients. I decided at that time to pursue clinical training. Subsequently, I went on to do my residency in Los Angeles at Doheny Eye Institute and then a retina fellowship at Washington University at the St. Louis, Barnes Retina Institute.

I then trained for an additional 1 year at Moorfields Eye Hospital in London—considered possibly to be the premier eye hospital in the world. My mentor there was Dr. Alan Bird [MD], who is known to be one of the pre-eminent authorities on inherited retinal diseases and other medical retina problems. I learned from both Dr. Bird, as well as Dr. Shomi Bhattacharya [PhD], a world-renowned molecular biologist in vision biology.

Upon my return to the United States, I ended up at the University of Florida School of Medicine, where I was head of the retina division for many years before becoming Chairman of Ophthalmology at the University of Massachusetts Medical School.

It was during the tail end of my time at the University of Florida and the beginning of my time at the University of Massachusetts, that the genesis of my interest in nutraceuticals and nutritional biochemistry blossomed. I had a good-sized laboratory with postdoctoral scientists and graduate students who worked on projects wherein we were able to reconstruct some of the biochemical elements of what happens in macular degeneration and diabetes in cell culture. We modified cell-culture techniques so that we could screen hundreds of thousands of compounds that could potentially mitigate against those diseases and prevent oxidative stress and eventually cell death. These compounds were available free for research purposes and included nutraceuticals, Food and Drug Administration–approved drugs, and drugs that were also approved elsewhere in the world.

We developed an automated high-throughput screening process, so that we did not need to screen all of these compounds by hand. From this screening, we identified more than 60 compounds that caught my attention because of their dramatic effects in protecting retinal cells and protecting cells in diabetic models. Some of these compounds were nutraceuticals. I was skeptical at first because of my limited exposure to nutrition, but we had verifiable, reproducible results. This resulted in a whole new field for me. Although there was a lot of research in similar fields, none was in my own field—in retinal biology—and we were, in some sense, pioneers from that perspective.

I reached out to some excellent scientists and clinicians who had spent years, or their careers, studying in the field of nutritional biochemistry. I contacted them, read their articles, and

started attending meetings through the Institute of Functional Medicine, A4M, American College of Nutrition, and others. From these meetings with so many new people, I was able to think about medicine in a whole refreshingly new way. I realized that my own thinking was evolving and that this was perhaps the future of medicine. There is definitely a place for allopathic medicine. However, these other so-called "complementary" approaches are equally viable and are being tested in the same rigorous manner as Western medicine with placebo-controlled, double-blinded clinical trials. That was really the launching point of my own interest. I am still a retina specialist, and I love to see patients. However, now, I often find myself talking to patients about their diseases and about nutrition and the eye, and, specifically, the retina.

**Dr. Rountree: Was there something similar about the chemicals that had effects on the retinal cells? For example, did they all have something in common, such as being antioxidants, or was it a diverse set of mechanisms in which they were involved?**

**Dr. Kaushal:** On the surface, the tested compounds and drugs had diverse mechanisms. However, when we probed in our cell-culture models, it turned out that they basically fell into three major classes: (1) anti-inflammatories; (2) antioxidants; and (3) immune-modulators. We know that these three components are critical for addressing nearly every chronic condition, not only diseases of the retina. Obesity, high blood pressure, arthritis, coronary-artery disease [CAD], neurodegeneration, muscle wasting, type 2 diabetes, and even cancers all share common pathogenic events related to inflammation, oxidative stress, and a dysregulated immune system.

We tested these compounds in mouse or other animal models of retinal diseases and saw evidence of effectiveness. In collaboration with my brother Dr. Sunjay Kaushal [MD], my colleagues and I also examined these compounds in other models of heart disease, liver disease, and diabetes.[1] All of these diseases have those same major events—inflammation, oxidative stress, and a dysregulated immune system.

**Robert Rountree: Were there any compounds that stood out particularly for you because they had particularly remarkable effects?**

**Dr. Kaushal:** Yes, there were a few. For example, resveratrol caught my attention right away as a result of some work that came out at the time from the laboratory of Dr. David Sinclair [PhD], at Harvard Medical School, and a colleague.[2] Another was a known active ingredient in ashwagandha [*Withania somnifera*], withaferin-A. The curcuminoids, active ingredients found in turmeric [*Curcuma longa*] , were also of interest. The final one that I will mention is celastrol, which is found in a Chinese herbal preparation called *lei gong teng*, or thunder god vine [*Tripterygium wilfordii*] as we call it in the United States. My colleagues and I, including my brother, published a study on this compound last year.[1] These are just some examples—there were more.

**Dr. Rountree: Is it fair to say that you think all of these compounds have potential for use in the clinic?**

**Dr. Kaushal:** I believe so. We are still in the early processes of a lot of this research. The retina is a part of the brain that is easily accessible. In the clinic, we can look directly at all nine layers of the retina, including the blood vessels, the blood supply underneath the retina, and the nourishing cells. We can test these compounds, individually or in combination, using quantitative noninvasive diagnostic tests that have been developed over the last decade to measure structure and function.

**Dr. Rountree: Are you saying that these compounds do not just have the potential to treat eye diseases—that this high-throughput model with retinal cells could be used to determine if a wide range of compounds are useful for addressing any kind of chronic condition?**

**Dr. Kaushal:** That's right because they share a very similar underlying biology. That is one of the conclusions of this article that we published.[1] Because of its accessibility, the retina is a wonderful platform for the discovery of other drugs or nutraceuticals that would be useful for addressing chronic diseases. Also, with nutraceuticals, we often have large therapeutic windows. Curcumin, the main constituent of turmeric is used in published studies at doses of up to 12 g per day, suggesting safety at high doses.[3]

I have nicknamed these types of compounds *molecular rheostats*. With a thermostat, we do not adjust it wildly 10° either way; we tweak it a couple of degrees here or there to get comfortable in a room. By analogy, when a cell, tissue, or human being, is in a particular disease state, they are out of equilibrium and the goal is to try to reestablish equilibrium or biochemical balance. This allows for a clinical balance, or a mitigation or attenuation of the disease process. Normally, we discover drugs by finding a protein target that appears to be critical in the disease process, and we design or identify small molecules, that may be drugs or biologic agents, that bind at very high affinity to that protein. These agents can inhibit the function of the protein and are used at very high concentrations. Of course these agents can lead to significant side-effects in patients and have narrow therapeutic windows.

We can imagine that, in an average cell—and it doesn't matter where the cell comes from—there are about a dozen critical cellular pathways that control homeostasis. In a disease state, those pathways have been overtaxed and, like a seesaw at a playground, are out of balance. In order to return the cell back into balance, these small molecules can target multiple pathways. These pathways are all connected to each other in some way, and they act like a bundle of springs connecting to each other. If one presses on one of the springs, all of the other springs start moving. These compounds may have potential effects on one or two of those springs, but the whole system has a chance to reset and get back into balance or homeostasis.

In a way, these compounds are like adaptogens, although, in my thinking, they are distinct. I have realized how clever Nature is and that it was just a question of time for us to figure this out. These agents may be described as pleiotropic, but the

pharmaceutical industry calls them "dirty drugs"—agents that affect multiple cellular pathways. However, in reality, that is what we want to do. We want to reset the body's entire cellular biochemistry and cell biology. We want to be able to affect multiple cellular pathways that are communicating with each other. Only then are we allowing a cell to use its intrinsic intelligence, because the cell wants to return back to homeostasis. It wants to be in equilibrium. The agents we discovered facilitate the ability of the cell to return back to homeostasis.

**Dr. Rountree: Without getting too technical, please name some of the pathways involved?**

**Dr. Kaushal:** Some of these pathways include the oxidative-stress pathway (the Nrf2 pathway),[4] the unfolded-protein response,[5] the heat-shock response,[6] and calcium homeostasis.[7] There is the mitochondrial-energetics response, which determines how we produce energy in the cell, or the disposal responses, such as those involving proteosomes or lysosomes, which result in cellular-debris removal.[8,9] These are some of the major cellular pathways that control the day-to-day functioning and viability of any cell in the body. Each of these pathways has hundreds of proteins involved. Similar to getting a symphony sounding well, one cannot just fix the violinists. One has also got to deal with the people who are playing the flutes. One has got to let them know that they are all a little out of sync. The compounds we discovered communicate with multiple cellular pathways all at once.

The hormetic response means that exposure of a cell to a low, nontoxic dose of a compound primes the cellular pathways so that, when a higher dose is given, the cell can protect itself because of its learned memory. Some toxins also have beneficial effects when used at very low doses. An example of this is hydroquinone, an extremely toxic agent found in cigarette smoke. If we test hydroquinone in a cell culture of the retinal-pigment epithelial cells, at a low dose, the cell behaves as though it truly has not been insulted. At higher doses, similar to those found in a cigarette smoker, hydroquinone is a very toxic oxidant. During our high-throughput screens, we found that hydroquinone itself, at a low dose, protected the cells against higher dose hydroquinone-related toxicity or cell death.

**Dr. Rountree: I would like to ask you about treatments for macular degeneration. From what you are saying, there is inflammation, oxidative stress, and immune dysfunction involved in the pathogenesis, and yet we seem to have a narrow focus on treating this disorder with angiogenesis inhibitors.**

**Dr. Kaushal:** Yes, that is correct. We are treating with angiogenesis inhibitors, which are compounds that inhibit the production of new blood vessels growing underneath the retina.[10] These blood vessels leak both blood and fluid, leading to vision loss in patients with wet macular degeneration. Wet macular degeneration occurs in about 10%–15% of patients who have macular degeneration. Given that angiogenesis is part of the inflammatory response, we are treating the disease in a limited way.

Dry macular degeneration occurs in 80%–85% of patients with macular degeneration, resulting in distinct inflammatory oxidized yellowish debris deposits underneath the retina; these deposits are known as *drusen*.[11] These are greasy fat deposits, containing lipofuscin, oxidatively damaged proteins, microglial cells, cholesterol, and more. This is essentially the same biochemistry as what happens in CAD: It also happens underneath the retina. I refer to it as *atherosclerosis of the retina*. This means that, although these antiangiogenic agents are very effective for reducing the swelling in the retina, the underlying biology—which includes the inflammation and the oxidative stress—has not been treated. So we are postponing blindness, but we need to— and should be able to—stop or reverse it.

**Dr. Rountree: That is what they tried to do with the AREDS [Age-Related Eye Disease Study] studies. Please speak about that.**

**Dr. Kaushal:** As we know, the AREDS studies used vitamin A, E, and C, as well as zinc, and the AREDS2 included lutein/zeaxanthin and omega-3 fatty acids.[12] My take on the AREDS studies is a bit different. When we go back into the epidemiologic literature and look at the 40-or-so essential vitamins and minerals that we need for functioning, there are well-published articles that show that somewhere between 60% and 80% of Americans are deficient in a set of those nutrients.[13] So we look at the AREDS studies and wonder why there was not a bigger or more profound effect. However, if someone is already deficient in a set of these 40-or-so essential vitamins and minerals and a clinician just repletes a patient with four or five them—as in an AREDS preparation—then that is why it takes 5 years and thousands of patients to truly determine the effect. What if, instead of using an AREDS preparation, we use a balanced multivitamin with the full complement, including the B-complex vitamins? My prediction would be that we would see a more profound effect.

*We think in terms of a disease, a diagnosis, and a treatment, instead of the underpinnings of the disease.*

Yet, this is the way we learned medicine in the United States and in almost every other country. We think in terms of a disease, a diagnosis, and a treatment, instead of the underpinnings of the disease. We do not probe as deeply as we should. It is, of course, a challenge with all the information that is out there; however, we can distill it down to a biologic framework and ask if we can do better with more research. So, although I talk to my patients about the AREDS formula, I also talk to them about green and yellow vegetables in detail. I talk to them about goji berries and tomatoes as sources of lutein and zeaxanthin. I talk to them about the omega-3–containing fatty acids in fish oil because of the high concentration of omega-3 fats, especially docosahexaenoic acid, in the retina. So, these are things that I talk about, including AREDS, which has a small but reproducible "statistically significant," and possibly very small "clinically significant," effect.

## To Contact Dr. Shalesh Kaushal

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**Dr. Rountree: Do you recommend any of the other supplements, such as resveratrol or curcuminoids, for patients with macular degeneration?**

**Dr. Kaushal:** I mention some of these agents but do not use the word *recommend*. Resveratrol is available as a supplement, so I mention it. Celastrol, or *lei gong ten*, is not available in the United States. I do not think a lot of retina specialists talk about these compounds, and it was interesting and challenging for me to talk about them for years.

**Dr. Rountree: What do you think is the initiating event in macular degeneration? Why is it that some people get this disease and other people do not get it?**

**Dr. Kaushal:** That is a wonderful question. From my own perspective, there is clearly a genetic component. Some genetic single nucleotide polymorphisms are involved in the complement/inflammation pathway. As I mentioned before, the retina is the most metabolically active tissue per unit weight in the body and the macula, at the dead center of the retina, is important for central and color vision, and is the most active part of the entire retina itself. Like an engine, anything intrinsic or extrinsic to the engine that disturbs its function could have a profound effect. The intrinsic stressors could be genetic changes that all of us have. Extrinsic stressors could be the foods we eat, as well as the toxins and drugs we are exposed to in the environment.

Consider the photoreceptor cell: It is a cell primed to do one thing—to capture quanta of light. It is like an elite athlete, and if it is tweaked one way or another, the whole system can be thrown out of balance. This cell has only a certain degree of dynamic range to tolerate an internal or external stressor—not a lot of leeway. So, the biochemistry of the retina, coupled with the changes in a person's nutritional or environmental status affect the visual cells. Although, at this time, it is minimally understood, I would imagine the gut microbiome might play a role. The same biochemistry that occurs with gluten sensitivity, and overproduction of zonulin, and dehiscence of tight junctions in the gut enterocytes[14] is being repeated in the retina. There may even be a "leaky retina syndrome." We need to study this. At this point, it has not been established, but those experiments are not difficult. There has been research conducted recently on the role of the gut microbiome in an inflammatory disorder of the retina, uveitis.

**Dr. Rountree: How can someone get in touch with you to collaborate on these ideas, especially regarding the role of gluten in retinal inflammation?**

**Dr. Kaushal:** E-mails are welcome. [See box entitled To Contact Dr. Shalesh Kaushal.] I am planning a second conference next year similar to one we had earlier this year in Florida entitled "Can Chronic Diseases Be Reversed?" I and my colleagues brought together individuals who normally do not interact with each other—basic scientists and clinicians. They talked about their own fields of expertise. The conference was hugely successful, and we had the interest of about 2000 people without advertising. The program for next year will be finalized very soon. We will continue this work one step at a time. ■

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