slightly vary between 30-2 and 24-2 patterns, this is not the case for the pointwise-based methods. Regardless of the method that was used, all results pointed toward an acceleration of VF decay rates in the postoperative period.

Tuuminen and Grzybowski speculated that other nonglaucomatous phenomena, such as posterior capsule opacification (PCO), could explain the faster VF decay rates in our study population. We acknowledge that the postoperative degree of posterior capsule clarity (as well as the preoperative degree of cataract) were not included in our study. Although both these events reduce the VF sensitivity globally and may affect the mean deviation rate, we also found similar results with the VF index rate and glaucoma rate index (GRI), which are more robust against generalized VF depression (Rabiolo A et al, American Academy of Ophthalmology Annual Meeting; 2018; Chicago).[3] Also, mean visual acuity at postoperative month 3 did not significantly decrease over the follow-up up to postoperative year 5 ($P = .72$). Taken together, all these findings did not support a significant role for PCO in the postoperative VF decay.

Tuuminen and Grzybowski wondered why the number of medications decreased in the postoperative period despite the worsening of VF rates, and asked whether decisions were based solely on IOP readings. All the therapeutic decisions were made on an individual basis by the clinician treating the patients (J.C.), taking into account many factors, including glaucoma severity, VF decay rates, structural progression, status of the fellow eye, life expectancy, patient preferences and compliance, and presumed target IOP.

Tuuminen and Grzybowski suggested that "non-linear glaucoma progression should be incorporated in the statistical analysis to avoid the overestimation of VF decay postpseudophakia." They should note that 1 of the methods (GRI) used in this study to measure VF decay rates was based on pointwise exponential regression, which takes into account the nonlinear VF decay.[4]

Tuuminen and Grzybowski wondered whether quantitative optical coherence tomography (OCT) data confirmed the postoperative worsening found at the VF analysis. Due to the long-term follow-up of this study, patients were imaged with different OCT devices due to technological evolution. Inability to compare data acquired with different instruments (or even different releases of the same device) is a bothersome limitation of OCT imaging for long-term follow-up in glaucoma.[5] One would expect differences between structure and function because disagreement between structural and functional rates of progression were extensively demonstrated.[6] Further studies are warranted to investigate the effect of cataract surgery on rates of structural decay.

We appreciate the suggestion of the Tuuminen and Grzybowski to look at the effect of different intraocular lenses (IOLs) on the VF examination, but this is completely outside the scope of our study. Although different IOLs may have a slight effect on visual sensitivity, they are not likely to have an impact on rates of progression.

We appreciate the opportunity to further elaborate on the methodology and results of our study.

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Effects of Crocin on Diabetic Maculopathy: A Placebo-Controlled Randomized Clinical Trial

EDITOR:

I READ WITH GREAT INTEREST THE STUDY ENTITLED "EFFECTS of crocin on diabetic maculopathy: A placebo-controlled randomized clinical trial," by Sepahi and associates,[1] which evaluated the effects of crocin as a supplement on reducing inflammation in patients with diabetic maculopathy. The authors concluded that administration of 15 mg oral crocin could be effective on diabetic macular edema (DME) and significantly decrease central macular thickness and improved visual acuity compared to the placebo group. I would like to address several issues related to the aforementioned study by Sepahi and associates.

Although the pathogenesis of diabetic retinopathy (DR) has not been completely elucidated, accumulating evidence suggests that the inflammatory reactions may play a major role. Microglia are the primary innate resident immune cells in the retina that are involved in the inflammatory changes causing DR.[2] It has been reported that under diabetic conditions, microglia cells become activated, migrate near the perivascular areas, and upregulate the expression of several inflammatory cytokines, including

CCL2, TNFα, IL-6, and IL-8.[3] The implication of microglial activation in the pathogenesis of DR has led to the concept of microglial modulation as a therapeutic strategy. Recent clinical trials have investigated the inhibition of retinal microglia as a method to inhibit DR. As a result, several drugs including minocycline, doxycycline, and dextromethorphan, which are capable of inhibiting microglia activation, have been recently evaluated for the treatment of DME.[3,4]

In a previous study, our group investigated the effect of crocin on BV-2 retina microglial cells.[5] According to our findings, crocin significantly reduced gene expression of the proinflammatory markers IL-6, CCL2, and iNOS in lipopolysaccharide-challenged BV-2 microglial cells and potently blocked nitric oxide production in these microglia cells. Our findings support the anti-inflammatory and immunomodulatory effects of crocin on retinal microglial cells and indicated that its direct effects on microglia homeostasis could be mediated by its anti-inflammatory effects in animal models of neuronal degeneration.

As in line with this evidence, Sepahi's study results could also be attributed to the possible anti-inflammatory effect of the crocin on retinal microglia cells. However, all available studies aiming to determine the effects of crocin on microglial cells have been performed in the absence of a diabetic insult. In addition, as hyperreflective foci detected on spectral-domain optical coherence tomography (SDOCT) have been used as a surrogate inflammatory marker of DR and also may correspond to activated microglia,[6] the authors may also evaluate the change of hyperreflective foci on SDOCT in their study group.

Finally, while appreciating the initiatives aiming to evaluate the effects of herbal supplements as an adjunct to traditional treatment, further studies evaluating the exact role of these products on the pathophysiologic process of DME are needed.

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REPLY

WE THANK DR MÜCELLA ARıKAN YORGUN FOR HER ATTENtion and comments. As she mentioned in the letter, the pathogenesis of diabetic retinopathy (DR) has not been completely elucidated. The vascular endothelial growth factor (VEGF) causes leakage of neighboring capillaries; and it also stimulates the capillaries to grow ("new blood vessels"). The leakage causes the retina to swell up a little and become waterlogged, a bit like a sponge. This swelling then damages the retinal cells themselves. This is the main mechanism in "maculopathy" and "macular edema." Anti-VEGF treatment is only partially effective against diabetic macular edema.[1] Avastin injections are used to treat diabetic retinopathy. Avastin is an anti-VEGF drug. By blocking the effect of VEGF, Avastin stops the new vessels growing and reduces retinal leakage for a while.[2]

Reactive oxygen species (ROS) generated from mitochondria, NADPH oxidase, and other oxidases are known to play an essential role in the pathogenesis of DR. ROS modify redox-sensitive kinases and transcription factors such as NF-κB, signal transducers and activators of transcription proteins, and activator protein 1 and therefore induce inflammatory gene expression in DR.[3]

Increasing evidence indicates that inflammation is a key player in DR. Increases in vitreous inflammatory cytokines such as IL-6, VEGF, MCP-1, and IP-10 have been found to be positively associated with the progression of DR and the severity of macular edema. The concentrations of inflammatory cytokines such as IL-1β, IL-6, IL-8, MCP-1, IP-10, and VEGF are positively associated with macular edema, whereas levels of anti-inflammatory cytokines such as IL-10 and IL-12 are negatively associated with macular edema.[4]

In the pathogenesis of diabetic retinopathy, mitochondria are damaged and inflammatory mediators are elevated before the histopathology associated with the disease can be observed. Matrix metalloproteinases (MMPs) regulate a variety of cellular functions including apoptosis and angiogenesis. Diabetic environment stimulates the