Comment to: Dual effect hypothesis of insulin analogs on diabetic retinopathy

Sir,

I read the current review article titled "Does tight control of systemic factors help in the management of diabetic retinopathy?" by Rajalakshmi *et al*. with great interest.[1] Authors present the impact of tight control of systemic factors on progression of diabetic retinopathy (DRP). I congratulate the authors for this lightening review and want to make a contribution.

One of the systemic factors discussed in the article is the glycemic control. Authors stated intensive glycemic control to reduce development and progression of DRP. They also stated that tight glycemic control is most effective when initiated early, but it may at times have adverse effects, including worsening of DRP. According to this statement, tight glycemic control seems to have "dual effect" on progression of DRP that associate with the duration of treatment. We previously hypothesized a mechanism as "dual effect of insulin analogs on progression of DRP" that may explain this phenomenon.[2] As authors addressed in the article, upregulation of insulin-like growth factor-1 (IGF-1) may be the reason of early worsening of DRP. Insulin and its analogs stimulate IGF-1 receptors. Especially some insulin analogs, being developed by changing amino acid chain, are more potent than human insulin. Insulin glargine was reported to be 10 times more potent than human insulin to stimulate IGF-1 receptor.[3] IGF-1 signaling may cause the progression of DRP. IGF-1 is a receptor of growth hormone (GH). An association between GH and DRP has being known for a long time. DRP regresses after spontaneous infarction or surgical ablation of pituitary gland.[4] In dwarfs, GH deficiency is a protective factor for the development of DRP.[5] Despite the same glycemic control, development of DRP is significantly higher in pubertal subjects than prepubertal subjects.[6] GH acts on IGF-1 receptor. Insulin analogs also stimulate IGF-1 receptor and may cause progression of DRP through GH-like effect. Insulin analogs may change cellular composition of retina through stimulation of IGF-1 receptors.

IGF-1 has been reported to stimulate and proliferate a type of glial cell named nonastrocytic inner retinal glia-like.[7] Traction force in retinal pigment epithelium and Mullerian cells generates by IGF-1 signaling.[8]

Gadkari *et al*. recently reported insulin usage as a risk factor for progression of DRP in Indian population.[9] Insulin analogs may deteriorate DRP through IGF-1. However, analogs should pass into the retinal tissue to show this effect. Inner blood retinal barrier (IRB) may prevent analogs to pass retinal tissue. When IRB is intact, analogs may not deteriorate DRP through IGF-1 signaling, also protect retina by lowering blood glucose, and prevent harmful effect of hyperglycemia. After impairment of IRB, analogs may pass into the retina and cause progression of DRP by stimulating IGF-1 receptor. We named this mechanism as "dual effect hypothesis of insulin analogs on DRP" that associate with impairment degree of IRB.

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Conflicts of interest

There are no conflicts of interest.

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