

EDITORIAL

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Bilirubin in Diabetic Retinopathy: Too Little or Too Much?

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Abstract

Diabetic retinopathy (DR) is a significant diabetic complication that may result in loss of vision and blindness. The development of DR is intricate and encompasses numerous processes, such as oxidative stress. Bilirubin, a powerful antioxidant, has been proposed as a probable indicator for oxidative stress in DR. Bilirubin is a powerful antioxidant that helps to eliminate free radicals and other reactive oxygen species (ROS) in the body by being produced during the breakdown of heme. Additionally, it aids in the regulation of the expression of antioxidant genes, further bolstering its antioxidant properties. Therefore, bilirubin plays a crucial role in safeguarding cells from oxidative stress. Oxidative stress arises when there is an imbalance between ROS production and the body's ability to detoxify them. This can result in oxidative damage to cellular components like proteins, lipids, and DNA. Oxidative stress has been implicated in the development of various ailments, including Diabetic Retinopathy (DR).

Keywords: Bilirubin; Diabetic retinopathy; Oxidative stress

Introduction

Diabetic retinopathy (DR) is a serious complication of diabetes that can lead to vision loss and blindness. The pathogenesis of DR is complex and involves several mechanisms, including oxidative stress. Bilirubin, a potent antioxidant, has been suggested as a potential biomarker for oxidative stress in DR¹. In editorial, we will explore the effects of bilirubin as an oxidative stress marker in DR.

Bilirubin and Oxidative Stress

Bilirubin the yellow pigment produced during the breakdown of heme is a potent antioxidant that scavenges free radicals and other reactive oxygen species (ROS) in the body. Bilirubin also regulates the expression of antioxidant genes, further enhancing its antioxidant properties. Therefore, bilirubin plays an important role in protecting cells from oxidative stress.

Oxidative stress occurs when there is an imbalance between the production of ROS and the body's ability to detoxify them. This can lead to oxidative damage to cellular components such as lipids, proteins, and DNA. Oxidative stress has been implicated in the pathogenesis of several diseases, including Diabetic Retinopathy (DR)¹.

Bilirubin and Diabetic Retinopathy

Several studies have investigated the role of bilirubin as an oxidative stress marker in DR. Study by Liu Y et al., found that serum bilirubin levels were significantly lower in patients with DR compared to those without DR. This suggests that bilirubin may play a protective role against DR by reducing oxidative stress².

Another study found that bilirubin levels were negatively correlated with the severity of DR. Patients with more advanced stages of DR had lower levels of bilirubin, indicating a potential role for bilirubin in the progression of DR³.

Furthermore, a recent study demonstrated that bilirubin may have a protective effect on retinal endothelial cells (RECs) under high glucose conditions. The study found that bilirubin treatment increased the expression of antioxidant enzymes in RECs, reducing oxidative stress and cell death. This suggests that bilirubin may have therapeutic potential in the treatment of DR^{4,5}.

Mild elevations in serum bilirubin levels within the biological reference interval can have a protective effect on the development and progression of diabetic retinopathy. However, when serum total bilirubin levels exceed 16.5 $\mu\text{mol/L}$, which is still within the upper limit of the biological reference interval, there was an increased incidence of developing diabetic retinopathy⁶.

One possible explanation for this increased risk is that higher bilirubin levels may be a marker for underlying metabolic and inflammatory processes that are associated with the development of diabetic retinopathy. For example, hyperbilirubinemia has been associated with increased levels of oxidative stress and inflammation, which can contribute to the development and progression of diabetic retinopathy.

Another possible explanation is that the relationship between bilirubin levels and diabetic retinopathy is not a direct cause-and-effect relationship, but rather an indirect relationship mediated by other factors. For example, bilirubin levels may be associated with other risk factors for diabetic retinopathy, such as high blood pressure or elevated blood sugar levels, which could contribute to the increased risk of developing the disease.

It is important to note that while there is some evidence to suggest that elevated bilirubin levels may increase the risk of developing diabetic retinopathy, this relationship is still not well understood and requires further research. Additionally, the precise mechanisms by which bilirubin may influence the development and progression of diabetic retinopathy are still unclear, and more studies are needed to fully elucidate these mechanisms. However, this may be true only in context to mildly elevated bilirubin and follow-up changes in levels of serum total bilirubin $\geq 2 \mu\text{mol/L}$ had 40% increased risk of incidence of diabetic retinopathy. This suggests that once the baseline total bilirubin level increases to a certain higher level, the risk of diabetic retinopathy would no longer decrease. Furthermore, increased serum total bilirubin beyond the upper limit of biological reference interval is indicative of hepatocellular damage⁶.

Conclusion

In conclusion, bilirubin is a potent antioxidant that plays an important role in protecting cells from oxidative stress. Several studies have suggested that bilirubin may be a useful biomarker for oxidative stress in DR. Lower levels of bilirubin have been associated with the presence and severity of DR, indicating a potential role for bilirubin in the pathogenesis and progression of DR. Future studies may investigate the therapeutic potential of bilirubin in the treatment of DR.

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