Reviewer-1

Mbata et al. outline current data on the role of metabolic syndrome and its components on retinopathy in subjects with and without established history of diabetes. I have some concerns, which require attention.

Major comments

1-The authors could discuss the role of eicosanoids (leukotrienes, prostacyclin, and thromboxane), hypoxia-inducible factor-1, and growth factors (vascular endothelial growth factor and platelet- derived growth factor) in diabetic and metabolic syndrome-associated retinopathy. A new section is now added on page-5
A new section on the role of eicosanoids is added on page 18.

2-Current treatment recommendations for diabetic retinopathy could be mentioned. A new section on the current therapeutics is added on page 6.

3-The authors could make a figure that presents the pathways leading to the development of retinopathy in subjects with and without history of diabetes. Three separate diagrams are included to depict different pathways involved in type-1 diabetes, metabolic syndrome and type-2 diabetes.

Reviewer-2

Mbata et al., have surveyed the literature aimed at describing the relationship between diabetic retinopathy (DR) and metabolic syndrome (MeS). As the authors state, the notion that type 1 and type 2 diabetes are associated with DR, a key manifestation of hypertriglyceridemia-induced damage to the retinal microvasculature, is overwhelmingly supported by many studies. Many of these studies have been discussed in detail in the Review. However, based on the title of the review "Diabetic Retinopathy and the Metabolic Syndrome: Beyond hyperglycemia", I was expecting that the authors will be specifically dealing with the paradoxical relationship between DR and MeS, with concrete examples that conform to the conventional view as well as research showing that MeS (without hyperglycemia) may also cause DR. Therefore, the authors need to specifically discuss studies that investigated the relationship between DR and MeS without hyperglycemia (one of the 5 criteria of MeS outlined in the Table 1). This point is well-taken and the revised version has been revamped to reflect these changes.

A curious reader is unlikely to gain much of substance from authors' laundry-list of mechanisms involved in DR if alternative mechanisms that do not involve an active role of hyperglycemia are not explicitly discussed. To achieve this goal, the authors need to present a more discerning view of the literature that deals with DR and its relationship to MeS, with and without hyperglycemia. This would entail re-writing the sections that deal with mechanisms of DR to elaborate processes that occur. This point is well-taken and the revised version has been revamped to reflect these changes.

In light of these changes the BODY of the Review, the ABSTRACT, CORE TIP and CONCLUSION sections will need to be drastically revised. Corrected as suggested.

THOROUGH EDITING: in order to RECTIFY the Proper Usage of English language and Grammar. Corrected as suggested.

Reviewer-3

Authors should also emphasise the role of NAFLD, further expression of the Metabolic Syndrome, while taking into account the micro-macro circulation of Diabetes Mellitus.
A new section on the correlation of NAFLD and retinopathy is added on page 10.

Reviewer-4

The review is relevant once the prevalence of metabolic syndrome has increased in recent years. The mechanisms of development of retinopathy in these patients with and without establish history of diabetes should be discussed. There are few corrections in manuscript:

1) In introduction section is necessary to characterize the metabolic syndrome. According, the metabolic syndrome not is a disease; this is a condition when the individual have three or more risk factors associated. The section on metabolic is syndrome is now included in the introductory section on page-4.

2) In introduction section, first paragraph, eleven line, to delete the parenthesis after glucagon. Done
The second part of the sentence is confusing: "or hormones that can interfere with insulin secretion such as catecholamines", repeating the previous information, so suggest excluding this part. "These endocrine disorders are associated with sustained release of hormones that are antagonistic to insulin action including growth hormone, glucocorticoids, catecholamines or glucagon), or hormones that can interfere with insulin secretion such as catecholamines". The second part was eliminated as suggested.

3) In introduction section, first paragraph, eighteen line, the word Insulin is in capital letter; twenty line, the same with Acromegaly. Corrected as suggested.

4) The purpose of review not is clear at the end of the introduction section: "Therefore, the focus of this review will be on development of diabetic retinopathy lesions in patients with primary DM either type-1 or type-2 rather than secondary diabetes." Not is commented about metabolic syndrome (is the title). So, suggest rewrite similar as is in the abstract section: "This review will summarize the current literature on the prevalence and impact of the metabolic syndrome on retinopathy in subjects with and without established history of diabetes. This review will also discuss some of the mechanisms through which components of the metabolic syndrome can contribute to the development of retinopathy. Corrected as suggested.

5) In the Development of Retinopathy in Subjects without a History of Diabetes section, on second paragraph, ten line, the name of study is "The Hoorn", correct for the Hoorn. Corrected as suggested.

6) The sentence: In addition, Hb A1c level and waste to hip ratio (WHR) were risk factors in the nondiabetic individuals [30]. These finding suggest that retinal pathologies begin to develop prior to a clinical diagnosis of hypertension and/or that other conditions play a role and cumulatively result in retinopathy." These results in reference number 30 are sufficient to affirmation? Corrected as suggested
Correct the Hb A1c for HbA1c. Corrected as suggested.

7) In the Retinopathy in subjects with Metabolic Syndrome but no history of diabetes section, on second paragraph, eleven line, the sentence: "However, other studies looking at individuals older than 40 and obese, calculated using BMI, found no significant correlation between the metabolic syndrome and retinopathy independent of diabetes (reviewed in[85])." Why the reference is written between "reviewed" inside parentheses? The original reference is cited and "reviewed in" was removed.

8) There are two sentence in different moments on manuscript that are repeated: In the Insulin resistance and the Metabolic Syndrome section, and in the Retinopathy in subjects with Metabolic Syndrome but no history of diabetes section. "This could be attributed to the inability of the BMI calculation to accurately estimate body composition[61, 62]." The statement was removed from second section.

9) "Given that hyperglycemia and hypertension are the strongest risk factors for the development of retinopathy lesions, and that the metabolic syndrome is strongly associated with the development of these conditions,...This section has been modified to highlight the role of metabolic syndrome in DR.