



Office of the Dean

May 10, 2016

Fang-Fang Ji, Science Editor
World Journal of Hypertension
Baishideng Publishing Group, Inc.

Dear Dr. Ji:

Thank you for your kind letter concerning our paper, "The role of adipocytes in hypertension" which we submitted for consideration. Ms. Martin and I have carefully reviewed your comments and the comments of the four reviewers in developing a revised letter. Our responses to the comments and a list of all changes in the manuscript follow this note.

We hope our paper is now acceptable for publication in the World Journal of Hypertension.

Sincerely,

Joseph I. Shapiro, M.D., F.A.H.A., F.A.C.P., F.A.S.N.
Dean, Joan C. Edwards School of Medicine
Professor of Medicine Marshall University

Reviewer 1:

This neatly written and soundly discussed review manuscript by Rebecca Martin and Joseph Shapiro summarizes the published data on the role of adipocytes in hypertension and highlight the current knowledge gaps. In order to guide the reader through the rather complex mechanisms by which adipokines, renal function, ROS, eNOS, iNOS and pNaKtide dysbalance induces/attenuates hypertension, a figure would be helpful.

We thank reviewer 1 for the kind comments. We have developed an additional figure (figure 4) to address the concerns raised.

Reviewer 2:

The authors have performed a pedantic assessment of published data on the role of adipocytes in hypertension and detected research gaps, which are relevant for clinicians. Appropriate evaluation of relevant information has been applied, whereas the conclusions are persuasively supported by data interpretation.

We thank reviewer 2 for the supportive comments.

Reviewer 3:

Very good paper Accept to publication Autor may add some data of the possible repercution of obesity treatment on hypertension and RAAS.

We thank reviewer 3 for the kind sentiments. We have included a new paragraph to address the concern raised.

Reviewer 4:

This review is well written regarding hypertension associated with obesity, in particular with adipocytes, including the role of adipokines, renal function, ROS, eNOS, iNOS and pNaKtide. However, readers cannot easily understand hypertension through the mechanism by which excessive NO formation induces hypertension and pNaKtide attenuates hypertension. On the facts obtained by animal models or in vitro studies, the authors had better show a tentative explanation of the role of iNOS, pNaKtide, and so forth as a scheme or a figure

We thank reviewer 4 for the positive comments, and agree with the concern raised. We include a new paragraph detailing response to anti-obesity therapy and a new figure (figure 4) to address this excellent point.

Changes in the manuscript:

Title: No change

Abstract: No change

Body of Text: We have added a paragraph entitled “Current treatments of obesity and their effects on hypertension.” This paragraph appears on page 8 and now reads

“Current treatments of obesity and their effects on hypertension

Currently, there are several treatment methods to deal with obesity, and as it is so closely related with hypertension, treatments for the two can often overlap⁸⁶⁻⁸⁸. The treatments can be broken up into several categories; lifestyle changes (including nutritional changes and exercise addition), drug therapy, and surgical methods⁸⁹. It has been shown that a reduction in a patient’s weight by 5-10% is enough to reduce their risk of cardiovascular complications, including hypertension⁸⁹⁻⁹¹. When looking at the drug treatment route, it is important to consider however that some drugs are not recommended for patients who have pre-existing conditions, such as hypertension or diabetes. Sibutramine, for example, has been associated with small increases in blood pressure and heart rate, and is not recommended for patients suffering from hypertension^{89, 92}. Some drugs that are used to treat hypertension can be used as a weight loss agent, such as the drug orlistat^{89, 93}. These drugs can work on multiple levels; some are known as feeder modulators, and change the way the patient receives signals that the body needs food^{89, 94}. Some effect the formation of agents such as angiotensin II and nitric oxide synthase^{89, 95, 96}. Still others work at the molecular level and effect the afferent signaling that can lead to obesity^{89, 95}. Serotonin drugs have been found to be an effective treatment of obesity, but the downside is they can cause an increased risk of primary hypertension because of their effects on vascular smooth muscle⁹⁷. If we look at surgical approaches, the benefits of surgery on hypertension itself and the abnormal hormonal milieu appear to be huge, at least over the first year or so⁹⁸.”

References: Several new references have been added.

Figures: Figure 4 has been added with a new legend that reads”

Figure 4: Small adipocytes release anti-inflammatory agents such as adiponectin, interleukin 10 (IL10), and interleukin 1 receptor (IL1R) antagonist. Hypertrophy of small adipocytes into large adipocytes changes the biochemical release products, into inflammatory markers (interleukin six (IL6), tumor necrosis factor alpha (TNF α), and monocyte chemotactic protein 1(MCP1)) and other chemicals such as leptin and angiotensin II that contribute to the disease. Increased activation of the sympathetic nervous system also contributes.”