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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Manuscript Revision 9178 Final -kn).

Title: African Americans, Hypertension and the Renin Angiotensin System

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers (see attached word documents)

DRAFT & REFERENCES for REVIEWER #2:

(1) Is there any mechanism of bradykinin in African Americans?

ACE insertion/deletion and bradykinin B(2) receptor polymorphisms contributed to the risk of ACEI-related cough in East Asians that was not observed in Caucasians (Nishio et al., 2011). While there are no independent reports, it is possible similar mechanisms could account for the increased incidence of ACEI-related adverse effects in African Americans as their side effect profile is more similar to East Asians.

Ref

Nishio, K., Kashiki, S., Tachibana, H., & Kobayashi, Y. (2011). Angiotensin-converting enzyme and bradykinin gene polymorphisms and cough: A meta-analysis. *World journal of cardiology, 3*(10), 329.

(2) Is there any possibility that African Americans take higher doses of salt than white Americans?

Brown and colleagues found higher 24-hour urinary sodium excretion as a marker of dietary sodium intake among African Americans *(Brown et al., 2013)*. Similar findings have been seen in most of the studies used for validating equations to estimate urinary sodium excretion (Cogswell et al., 2013). A recent study found excess estimated sodium intake in over 97% of adolescents and more than twice the daily sodium intake recommended by the American Heart Association. High sodium intake was positively associated with adiposity and inflammation, and sodium intake was even higher in Whites in comparison to African Americans (Zhu et al., 2014).

Ref

Brown, I. J., Dyer, A. R., Chan, Q., Cogswell, M. E., Ueshima, H., Stamler, J., & Elliott, P. (2013). Estimating 24-hour urinary sodium excretion from casual urinary sodium concentrations in Western populations: the INTERSALT study. *Am J Epidemiol, 177*(11), 1180-1192. doi: 10.1093/aje/kwt066

Cogswell, M. E., Wang, C. Y., Chen, T. C., Pfeiffer, C. M., Elliott, P., Gillespie, C. D., . . . Loria, C. M. (2013). Validity of predictive equations for 24-h urinary sodium excretion in adults aged 18-39 y. *Am J Clin Nutr, 98*(6), 1502-1513. doi: 10.3945/ajcn.113.059436

Zhu, H., Pollock, N. K., Kotak, I., Gutin, B., Wang, X., Bhagatwala, J., . . . Dong, Y. (2014). Dietary sodium, adiposity, and inflammation in healthy adolescents. *Pediatrics, 133*(3), e635-642. doi: 10.1542/peds.2013-1794

(3) Is there any same mechanism between Dahl rat model and African Americans especially in ACE polymorphism?

We were unable to find any reports of ACE polymorphism and BP in Dahl rat model. There was one report of a locus for the inducible, but not a constitutive, nitric oxide synthase cosegregates with blood pressure in the Dahl salt-sensitive rat (Deng & Rapp, 1995) and microsatellite of angiotensin I converting enzyme (ACE) was reported to be associated with the development of salt-sensitive hypertension in the stroke-prone spontaneously hypertensive rat (Nara et al. 1991).

Ref

Deng, A. Y., & Rapp, J. P. (1995). Locus for the inducible, but not a constitutive, nitric oxide synthase cosegregates with blood pressure in the Dahl salt-sensitive rat. *Journal of clinical investigation, 95*(5), 2170.

Nara, Y., Nabika, T., Ikeda, K., Sawamura, M., Endo, J., & Yamori, Y. (1991). Blood pressure cosegregates with a microsatellite of angiotensin I converting enzyme (ACE) in F2 generation from a cross between original normotensive Wistar-Kyoto rat (WKY) and stroke-prone spontaneously hypertensive rat (SHRSP). *Biochem Biophys Res Commun, 181*(3), 941-946.

(4) In a clinical situation, what is the most important organ failure that contributes to the higher mortality of African Americans? I have heard of the importance of cardiovascular factors especially myocardial infarction.

The high mortality rate in African Americans is attributable to cardiovascular disease with African Americans suffering from a three-fold higher death rate from hypertension (Go, 2013).

Ref

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Borden, W. B., . . . Turner, M. B. (2013). Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation, 127*(1), e6-e245. doi: 10.1161/CIR.0b013e31828124ad

RESPONSE TO REVIEWER #3

1. Reference should be made to the most scathing rebuttal against the slave hypothesis of hypertension in blacks. This came from Philip Curtin, an historian of the slave trade on whose work Grim had drawn heavily. Curtin denied any historical validity to the proposition that Africa had traditionally been salt-scarce, and asserted that his own work had been misunderstood or misquoted on this point. He also disputed the mortality estimates cited by Grim noting that these figures were not only incorrect or outdated, but cited so poorly that their original source could not be identified. Indeed, he disparaged Diamond's impressive statistics as "numbers of unknown provenance." Further, Curtin argued that Grim's proposition that a majority of deaths were due to diarrheal disease was equally baseless. He concluded that the Slavery Hypothesis not only lacked supporting evidence, but that what little evidence did exist directly contradicted the theory. (http://ajph.aphapublications.org/doi/pdf/10.2105/AJPH.82.12.1681)

Many of the historical claims which form the basis of the slavery hypothesis for hypertension have been challenged by other authors (Curtin). In question are the key tenets of the theory which implicate salt deficiency in the areas of Africa from which slaves originated, the trauma of the slave trade, and conditions in the Americas as triggers for unnatural genetic selection for renal sodium-retainers (Grim & Wilson; Diamond). According to this theory, these factors collectively evolved into the eventual present-day disproportionately higher blood pressure in African Americans compared with their counterpart whites or African blacks in modern sodium-rich societies (Curtin; Grim & Wilson; Diamond). In the absence of access to records of past salt availability in Africa, slave trade disease states, and dietary salt content in the Americas between the 16th and 19th century, it will be impossible to ever fully confirm or fully refute this hypothesis (Fuchs).

Curtin, P. D. (1992). The slavery hypothesis for hypertension among African Americans: the historical evidence. *Am J Public Health, 82*(12), 1681-1686.
Diamond, J. (1991). The saltshaker's curse. *Natural History, 10*, 20-26.
Wilson, T. W., & Grim, C. E. (1991). Biohistory of slavery and blood pressure differences in blacks today. A hypothesis. *Hypertension, 17*(1 Suppl), I122-128.
Fuchs, F. D. (2011). Why do black Americans have higher prevalence of hypertension?: an enigma still unsolved. *Hypertension, 57*(3), 379-380. doi: 10.1161/hypertensionaha.110.163196

2. Although there are conflicting data, a number of studies have indicated that the sympathetic nervous system may play a role in mediating salt sensitivity. This is based on the findings that many salt-sensitive subjects have higher levels of norepinephrine and decreased levels of dopamine. Norepinephrine is associated with sodium retention and dopamine promotes increased sodium excretion. Both

plasma norepinephrine concentrations and urinary sodium excretion are higher among salt-sensitive than salt-resistant subjects. African American subjects seem to be especially sensitive to the role of dopamine in salt sensitivity. Dopamine is a vasodilator with a natriuretic effect on the kidney. However, when salt-sensitive African Americans are faced with an increased sodium load, they do not have a corresponding increase of dopamine, resulting in increased sodium retention. A similar deficiency of another renal natriuretic/diuretic peptide hormone, kallikrein, has been documented in salt-sensitive individuals. Moreover, although African Americans have a lower level of urinary kallikrein than Caucasians, salt-sensitive whites also have reduced urinary kallikrein excretion.

Some specific features of salt-sensitive hypertension have been characterized. Evidence suggests that the sympathetic nervous system may play a role in the modulation of salt sensitivity. In the presence of salt loading, the typical response of the sympathetic nervous system is to decrease norepinephrine, a known sodium retainer, and to increase dopamine which promotes sodium excretion (Luft &Weinberger; Ely). However in salt sensitive hypertensive individuals, particularly African Americans, there appears to be a dysfunctional response of the sympathetic nervous system in the presence of excess salt. In these patients, salt loading is associated with decreased urinary dopamine levels and the absence of any significant decreases in norepinephrine (Luft &Weinberger; Gill & Grossman). Another factor which is implicated as accounting for differences in salt sensitivity is kallikrein which has been demonstrated to be excreted in lower levels in salt sensitive hypertensive persons, particularly African Americans (Katori & Majima 2004; Katori & Majima 2008). Whether the fact that African Americans consume less potassium, a known kallikrein releaser, is contributory, remains unclear (Katori & Majima 2008; Richardson 2013). Evaluation of the relationship between potassium intake, urinary kallikrein levels and salt sensitivity is warranted using large scale clinical trials.

References

Weinberger M. Salt sensitivity of blood pressure in humans. Hypertension. 1996;27(part 2):481-490.

Luft F, Weinberger M. Heterogeneous responses to changes in dietary salt intake: The salt sensitivity paradigm. Am J Clin Nutr. 1997;65(suppl):612S-617S.

Weinberger M. Hypertension in African Americans: The role of sodium chloride and extracelluar fluid volume. Semin Nephrol. 1996;16(2):110-116.

Ely D. Overview of dietary sodium effects on and interactions with cardiovascular and neuroendocrine functions. Am J Clin Nutr. 1997:65(suppl):594S-605S.

Gill J, Gorssman E, Goldstein D. High urinary dopa and low urinary dopamine-to-dopa ratio in salt-sensitive hypertension. Hypertension. 1991:18:614-621.

Katori, M., & Majima, M. (2004). Roles of the renal kallikrein-kinin system in salt-sensitive hypertension. *Hypertension, 44*(6), e12. doi: 10.1161/01.hyp.0000146401.40304.51

Katori, M., & Majima, M. (2008). Are all individuals equally sensitive in the blood pressure to high salt intake? (Review article). *Acta Physiol Hung, 95*(3), 247-265. doi: 10.1556/APhysiol.95.2008.3.2

3. The authors should also comment on excess adiposity emerging as a natural candidate to explain the higher prevalence of hypertension in blacks, who have a 51% greater prevalence of obesity than whites.

Among the non-biologic factors which could possibly explain the inequity in the occurrence of hypertension among the races, obesity remains a tempting option given its similar trend of increased prevalence in African Americans. Excess adiposity, a reflection of lifestyle habits, has a reported 51% greater prevalence in this population (CDC). In addition, there has been reported an association between obesity, insulin resistance and other adipokine-mediated pathways with the occurrence of salt-sensitivity (Luft &Weinberger). However, National Health and Nutrition Examination Survey (NHANES) data from the 1988-1994 time period show no significant difference in obesity between white men and black men (20.3% and 21.1% respectively) while there was a 46% greater prevalence of hypertension in black men over white men during that same period (Ford & Zhao). Also, Okosun et al have shown that the risk of African American race for high blood pressure remains after adjusting for abdominal adiposity in NHANES III data (Okosun). Therefore the evidence does not support obesity as the sole contributor to the disparity in prevalence of hypertension among blacks although it is not excluded as a contributory factor.

References

Ford, E. S., Zhao, G., Li, C., Pearson, W. S., & Mokdad, A. H. (2008). Trends in obesity and abdominal obesity among hypertensive and nonhypertensive adults in the United States. *Am J Hypertens, 21*(10), 1124-1128. doi: 10.1038/ajh.2008.246

Fuchs, F. D. (2011). Why do black Americans have higher prevalence of hypertension?: an enigma still unsolved. *Hypertension, 57*(3), 379-380. doi: 10.1161/hypertensionaha.110.163196

Luft, F. C., & Weinberger, M. H. (1997). Heterogeneous responses to changes in dietary salt intake: the salt-sensitivity paradigm. *Am J Clin Nutr, 65*(2), 612S-617S.

Okosun, I. S., Choi, S., Dent, M. M., Jobin, T., & Dever, G. E. (2001). Abdominal obesity defined as a larger than expected waist girth is associated with racial/ethnic differences in risk of hypertension. *J Hum Hypertens, 15*(5), 307-312. doi: 10.1038/sj.jhh.1001179

4**. Differences between blacks and whites regarding adherence to treatment should also be addressed**.

One of the obstacles to attaining target blood pressure goals in African Americans is the issue of medication adherence. Low medication adherence rates and higher rates of uncontrolled blood pressures are more common in African Americans (Fuchs; Krousel -Wood 2009; Odedosu & Schoenthaler 2012). Keys to the effectiveness of ACEI therapy is adherence to both pharmacologic and non-pharmacologic therapy particularly in African Americans whose lower adherence rates have been attributable to both patient-related and physician-related factors including medication cost, insurance issues and access to healthcare. Aggressive measures are required to target interventions such as patient education focused on patient misconceptions regarding hypertension, home visits by trained community health workers, culturally appropriate storytelling, home blood pressure monitoring and behavioral counseling – all of which have been associated with improved medication adherence and decreased blood pressure measurements in blacks (Odedosu & Schoenthaler 2012).

Turner BJ, Hollenbeak C, Weiner MG, Ten Have T, Roberts C.Barriers to adherence and hypertension control in a racially diverse representative sample of elderly primary

care patients. Pharmacoepidemiol Drug Saf. 2009 Aug;18(8):672-81. doi: 10.1002/pds.1766. 5.
Fuchs, F. D. (2011). Why do black Americans have higher prevalence of hypertension?: an enigma still unsolved. *Hypertension, 57*(3), 379-380. doi: 10.1161/hypertensionaha.110.163196

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Cardiology.*

Sincerely,

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