

Author's response to reviews

Title: The underlying mechanisms for development of hypertension in the metabolic syndrome

Authors:

Hidekatsu Yanai (yanaih@jikei.ac.jp)
Hiroshi Yoshida (yoshida@jikei.ac.jp)
Yoshiharu Tomono (tomono@jikei.ac.jp)
Kumie Ito (ito@jikei.ac.jp)
Nobuyuki Furutani (furutani@jikei.ac.jp)
Norio Tada (tada@jikei.ac.jp)

Version: 2 **Date:** 7 March 2008

Author's response to reviews: see over

The Editor

Nutrition Journal

Dear Sirs,62

We will submit our revised manuscript entitled “The underlying mechanisms for development of hypertension in the metabolic syndrome (1,922 words, 62 references, and 1 figure)” to *Nutrition Journal*.

According to the comment by reviewers, we corrected everything that reviewers suggested. We will show you the list of modification. We will appreciate your consideration of our manuscript for publication in the section of “Review” in your journal.

Sincerely yours,

Hidekatsu Yanai, MD, PhD

Assistant Professor

Department of Internal Medicine,

The Jikei University School of Medicine,

The Member of American College of Physicians

List of Modification

Reviewer 1

Major compulsory revisions

1. According to comment 1 “As we knew, the main underlying pathophysiologic feature of metabolic syndrome was central obesity and insulin resistance. Elevated blood pressure was one of the abnormal metabolic factors in the definition of metabolic syndrome. Central obesity will induce the elevation of blood pressure. The author had described the effect of insulin resistance on the development of hypertension in the metabolic syndrome. I think if the author could demonstrate the possible mechanism of central obesity on the development of hypertension in metabolic syndrome. It will be much better.

We made a new paragraph about the effect of central obesity on development of hypertension in the metabolic syndrome as the followings. “***Visceral obesity***
Excess food intake and physical inactivity underlie the growing worldwide epidemic of obesity. Hyperglycemia, hyperlipidemia, and hypertension are common in obese individual [8,9]. Visceral obesity has been suggested to play a fundamental role in the

simultaneous development of these disorders [10]. Recent studies have demonstrated that adipose tissue is a major endocrine organ that secretes a variety of bioactive substances, termed adipocytokines. Adipocytokines secretion are altered as obesity develops, which may induce the metabolic disorders. As shown in Figure 1, accumulated visceral adipose tissue produce and secrete a number of adipocytokines, such as leptin, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), angiotensinogen, and non-esterified fatty acids (NEFA), which induce development of hypertension [11]. Visceral obesity is the main cause of the metabolic syndrome, and is associated with development of hypertension in the metabolic syndrome via a variety of pathways (Figure 1). ”

2. According to comment 2 “In page 4, the author found that insulin resistance induces anti-natriuretic effect which stimulates renal sodium re-absorption. Finally, it caused elevated blood pressure and hypertension. Could you describe more evidence to prove the causal relation, especial in the metabolic syndrome?”

We mentioned an evidence to prove the causal relation in the metabolic syndrome as the followings. “Strazzullo P, et al. investigated the relationship between the metabolic syndrome and renal tubular sodium handling [16]. In their study, proximal fractional

sodium re-absorption (FPRNa) was significantly greater in individuals with the metabolic syndrome, as compared with those without the metabolic syndrome [16]. Further, in untreated obese individuals, age-adjusted FPRNa was significantly greater in individuals with insulin resistance as compared with those without insulin resistance [16].”

3. According to comment 3 “In page 5, it would be better to collect more evidences regarding the development of hypertension in metabolic syndrome via sympathetic overactivity. In this paragraph, the author suggested that central obesity and insulin resistance were closed related to sympathetic overactivity. I think if we should focus on the development of hypertension in the metabolic syndrome”

We collected more evidences regarding the development of hypertension in metabolic syndrome via sympathetic overactivity as the followings. “Elevated resting heart rates [20,21], and baroreflex dysfunction have been reported to play an important role in development of hypertension in the metabolic syndrome [22]. Individuals with obstructive sleep apnea (OSA) have a high prevalence of the metabolic syndrome [23,24], and OSA has been reported to be associated with sympathetic overactivity. Obese individuals exhibit an activated renin-angiotensin system [25], which induces

hypertension. The renin-angiotensin system and sympathetic nervous system are linked by a positive feedback relationship [26].”

4. According to comment 4 “In page 6, I think author should find some cohort studies to demonstrate the effect of endothelial dysfunction on the development of hypertension.”

We found the cohort study to demonstrate the effect of endothelial dysfunction on the development of hypertension as the followings. “In a prospective cohort study, each one-unit decrease of flow-mediated dilatation was associated with a significant 16% (95% confidence interval: 12-33%) increase in the multiple-adjusted relative risk of incident hypertension, suggesting that an impaired endothelial vasomotor function precedes and predicts the future development of hypertension [37].”

5. According to comment 5 “In page 8 (regarding to inflammatory mediators), it would be better to describe some common inflammatory factors such as hs CRP to prove the development of hypertension in the metabolic syndrome.”

We mentioned the association between hs CRP and the development of hypertension in the metabolic syndrome as the followings. “Recent cohort studies have demonstrated that high-sensitivity C-reactive protein (hsCRP) independently presents additive

prognostic values at all levels of metabolic syndrome [45]. Ridker PM, et al. suggest a consideration of adding hsCRP as a clinical criterion for metabolic syndrome [45]. Abnormalities in inflammatory mediators have been also reported to be implicated with development of hypertension. A positive relationship between increased serum levels of CRP and the risk for development of incident hypertension in participants of the Women's Health Study [46]. Grundy SM suggests a significant association among inflammation, hypertension, and the metabolic syndrome [47]."

6. According to comment 6 "In page 9 (OSA), I think these descriptions were not enough to convince me to believe that OSA is the underlying mechanism of development of hypertension in the metabolic syndrome. Most of these studies were cross-sectional design. Does author suggest any mechanism between OSA and hypertension? I think it would be better to describe the pathophysiologic mechanism, not the epidemiologic data."

We mentioned the pathophysiologic mechanism of OSA for development of hypertension in the metabolic syndrome as the followings. "OSA is characterized by an increased number of sympathetic bursts, a raised plasma norepinephrine concentration, and a reduction in baroreflex sensitivity [23,24,61], which leaves no doubt as to the

existence of sympathetic activation induced by baroreflex dysfunction, much like what has been observed in the metabolic syndrome. In OSA, the nocturnal episodes of hypoxia and hypercapnia induce the stimulation of arterial chemoreceptors, which could induce sympathostimulating effects [61]. Hyperleptinemia, insulin resistance, elevated angiotensin II and aldosterone levels, oxidative stress, inflammation, and endothelial dysfunction have been also suggested to be possible mechanisms whereby OSA may contribute to development of hypertension [62].”

Minor essential revisions

1. According to comment 1.

We added the AHA/NHLBI definition.

2. According to comment 2.

We moved the sentence “oxidative stress is associated with sodium retention and salt sensitivity” to the paragraph about oxidative stress and endothelial dysfunction.

3. According to comment 3.

We corrected.

Reviewer 2

Minor essential revision

According to the comment.

We cited all articles that reviewer suggested as the followings. “Goodfriend TL, et al. measured plasma aldosterone levels in adults with various values of body mass index [40]. Plasma aldosterone level was higher in obese subjects, but could not be explained by renin and potassium [40]. The best predictor for plasma aldosterone level was abdominal obesity [40]. Elevated renin and aldosterone levels have been observed in subjects with multiple risk factors as compared with those without multiple risk factors [41]. Plasma aldosterone has been reported to be significantly associated with the metabolic syndrome and also with obesity-related hypertension [42,43].”