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Review Article

Does Red Meat Metabolism Induce Hypertension?

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Abstract

Hypertension is a persistent illness that affects the lives of one billion people worldwide. Hypertension, a nearly symptomless disease, damages blood vessels and organs and often causes a myriad of ailments including serious cardiovascular complications. In many clinical studies, red meat has been found to increase blood pressure and is linked with hypertension. Trimethylamine-N-Oxide (TMAO), a compound produced mainly from the metabolism of red meat by intestinal microbiota, has been recently linked to cardiovascular disease. Careful review of current literature and recent findings suggests that TMAO could be the hypertensive component of red meat. This review provides a novel insight into the mechanism by which TMAO may induce hypertension.

Keywords: Red meat; Hypertension; Carnitine; TMAO

Introduction

Hypertension is a chronic medical condition that affects over 50 million people in the United States [1] and around 1 billion people worldwide [2]. It is defined by the American Heart Association as "having a systolic blood pressure over 140 mmHg or a diastolic blood pressure over 90 mmHg" [3]. In such a high-pressure environment, blood vessels become susceptible to weakness, scarring, blood clots, and plaque buildup. These conditions also increase the workload of the circulatory system, forcing the heart to pump harder to push blood throughout the body. This sometimes results in valve damage or heart failure [3]. While there are many components that contribute to hypertension, researchers have been exploring diet as a potential solution to reduce and control blood pressure in patients.

Our daily diet has continuously shown its significance in health and wellness. Dietary studies have found that traditional Italian pastas rich with tomato sauces are packed with lycopene, a bright red carotene linked to cancer resistance in Italian populations [4]. Another compound, resveratrol, found in red wines, has been linked to reduced incidences of cardiovascular disease [5]; this explains how the French tradition of dining with red wine has helped their hearts. Hypertensive patients struggle to maintain their health every day and with so many conflicting diets claiming to improve wellness, it has become difficult for patients to take their health into their own hands. The metabolization of Carnitine in red meat to trimethylamine-N-oxide (TMAO) has recently received publicity for its role in heart diseases and its potential role in hypertension. Reduction of red meat consumption may be a promising method for hypertensive patients to be able to manage their blood pressure and improve their health.

Several dietary studies have shown that increased red meat (beef, veal, pork) consumption corresponds to increased blood pressure [6-8]. This differs from white meat (poultry, rabbit, and fish) which has shown no negative effects on blood pressure [6]. Other studies have shown that overall meat consumption has no significant effect on blood pressure [9]. The aim of this paper is to discuss current clinical findings on the relationship between red meat and hypertension. This paper also aims to improve upon our mechanistic understanding of red meat metabolization and its effects on blood pressure. Advancing our knowledge on the potential mechanistic pathways of red meat metabolism and their influence on blood pressure could give insight into the pathology of hypertension and allow for development of therapeutic dietary guidelines that will give hypertensive patients an opportunity to regain control of their health.

Evidence from clinical studies

The Dietary Approaches to Stop Hypertension (DASH) study, published in 2000, aimed to identify lifestyle modifications (other than reducing sodium intake, alcohol consumption, and weight) which would reduce blood pressure, manage hypertension, and give people control over their health. In the original DASH diet trial, a combination diet rich in fruits, vegetables, low fat dairy products, whole grains, fish, poultry, and nuts with reduced intake of fats, sweets, and red meats (now known as the DASH diet) was compared to a diet which included increased fruit and vegetable intake (approximately 10 servings per day) and both red and white meats [10]. The study kept sodium intake and body weight constant. It was found that the combination diet reduced systolic BP in hypertensive participants by 11.4 mmHg, whereas the fruit and vegetable rich diet reduced systolic blood pressure by 7.2 mmHg [11]. The decrease in blood pressure in the combination diet is significantly greater than that of the vegetable and fruit diet. This suggests that red meat and sweets, only consumed in the fruit and vegetable diet, could be significant in upregulation of blood pressure. This prompted a series of studies that would assess individual food and components within the DASH diet and their contribution to hypertension.

Red meat was among one of the food groups more carefully studied after the release of the DASH diet study. One research group from Deakin University, Australia, questioned the validity of excluding red meat from the DASH diet. They recruited a group of participants and placed them on a low sodium DASH diet, but incorporated 6 servings of red meat per week in their food regimen [12]. This study had their participants on the experimental diet for 14 weeks. After the 14 weeks ended, participants that had been given a low sodium DASH diet with red meat showed a decrease in systolic blood pressure by 5.6 mmHg [12]. This suggested that red meat was not positively correlated with blood pressure. However, when compared with similar DASH

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studies, this result may be inaccurate. In another DASH diet study conducted by the DASH sodium research group, participants were placed on a low sodium DASH diet for 4 weeks; this resulted in a 7.1 mmHg decrease in systolic blood pressure and an 11.5 mmHg decrease in participants with high Blood Pressure (BP exceeding 120 mmHg) [1]. Considering the longer time frame in the Deakin University study, it would make sense to see a larger or at least equal reduction in blood pressure compared to the DASH sodium research group study if red meat did not play a role in blood pressure elevation. These results seem to imply that red meat is actually offsetting the positive effects of the DASH diet, preventing it from more effectively lowering blood pressure. Whereas a low sodium DASH diet without red meat dropped blood pressure 11.5 mmHg [1], this DASH diet with red meat only dropped blood pressure 5.6 mmHg [12], making it not even half as effective.

There are numerous studies that agree with the idea that red meat consumption increases blood pressure. In one study [7] examining the effects of iron on blood pressure, red meat had significant and direct association with increasing blood pressure. In fact, this study showed that an increase in red meat intake by 103 g/day was associated with an increase of 1.25 mmHg and 0.73 mmHg in systolic and diastolic blood pressure, respectively [7]. A Turkish study that examined urban and rural cardiovascular risk factors also reported that red meat is positively associated with risk of hypertension [13]. Another study on middle-aged women found that unprocessed and processed red meats are associated with increased risk of hypertension whereas poultry is not [6]. Dietary studies like these have made it clear that some components in red meat significantly contribute to the pathology of hypertension.

Components in red meat contribute to hypertension

Many studies have shown that increased red meat consumption increases the risk and incidence of hypertension, but it is still unclear how this change occurs. It has been thought that increased protein consumption could result in higher blood pressure, but according to a scientific statement from the American Heart Association, which examined a great deal of studies regarding diet and hypertension, protein is actually directly associated with reducing blood pressure [14-16]. The INTERMAP Cooperative Research Group further supports this finding, concluding that vegetable protein has an inverse relationship with blood pressure and meat protein shows no significant effect on blood pressure [17]. In the INTERMAP Cooperative Research Group study, however, there was no differentiation made between protein derived from red meat and white meat, therefore there is no reliable way to tell if one played a more significant role on blood pressure than the other. If red meat metabolism does play an important role in increasing blood pressure, it is possible that it is neutralizing the beneficial effects of meat protein. In the DASH trial study, there was a significantly larger decrease in systolic blood pressure with the combination diet (-11.4 mmHg), which included white meat and fish, than in the fruit and vegetable diet (-7.2 mm Hg) which excluded all meats [11]. This scenario supports the idea that white meat has potentially beneficial effects on blood pressure which could be negated by hypertensive mechanisms in red meat metabolism.

Until recently, it was thought that saturated fats found in red meat caused vascular disease. However, a scientific statement released from the American Heart Association (mentioned above) found that several studies have shown that saturated fat intake is not associated with incidents of hypertension [14,18-20]. Another common claim was that the high levels of cholesterol found in red meats caused vascular disease; however, the same American Heart Association statement found few studies that have assessed the effects of dietary cholesterol on hypertension. Of the studies that do exist, there is no significant evidence to prove association between the amount of dietary cholesterol consumed and blood pressure [14,21].

Which components really cause hypertension? Recently, the Hazen's lab published their breakthrough findings in the New England Journal of Medicine [22] and Nature Medicine [23] about the metabolism of Carnitine, found in red meat, to Trimethylamine-N-Oxide (TMAO) by intestinal microbiota. They established a connection between TMAO and heart disease, revealing a potentially novel mechanism for how red meat affects blood pressure [23].

An interesting seven-year study on Chicago men that measured blood pressure and nutrient intake annually warrants the idea that Carnitine may be a key to understanding the role of red meat in hypertension [24]. Of the study participants, middle-aged men who ate between 8-20 servings of beef, veal and lamb per month had an average increase of 0.70 mmHg in systolic blood pressure annually, while pork increased blood pressure by 0.38 mmHg. Men who ate over 20 servings of beef, veal, and lamb per month had an annual blood pressure increase of 0.78 mmHg (compared to pork at 0.24 mmHg). When controlled for age, weight, height, education, cigarettes per day, alcohol consumption, total energy consumption, and other food intakes such as fish, fruits, vegetables, pork, and poultry, these numbers increased, showing consumption between 8-20 servings of beef, veal, and lamb is responsible for an increase of 0.77 mmHg annually and consumption over 20 servings is responsible for an 0.85 mmHg increase [24]. Among all the food groups studied, the group found to increase blood pressure the most was the beef/veal/lamb group; the second highest was pork. These food groups also have the first and second highest Carnitine content, respectively.

According to the NIH report [25], the redder the meat, the more Carnitine it generally contains. Beef is actually the highest Carnitine-containing food, having a range of 56 - 162 mg of Carnitine per 4 oz serving [25] with an average of 81 mg per 3 oz steak [26]. This is followed by pork at 24 mg per 3 oz serving [26]. A 4 oz serving of chicken, which is unassociated with blood pressure [14], contains about 3-5 mg of Carnitine. Beef, which has the highest Carnitine content, increases systolic blood pressure the most, followed by pork. Pork, as shown above, has about 30% of the Carnitine that beef has. Similarly, pork increases blood pressure at approximately 30% of the rate beef does according to the Miura study [24]. This further establishes the importance of Carnitine in blood pressure regulation.

As shown in Figure 1, Carnitine is metabolized in humans by gut microbiota. Once metabolized by the gut microbiota, Carnitine is modified into Trimethylamine (TMA), which is then converted to Trimethylamine-N-Oxide (TMAO) via the flavin-containing mono oxygenases. TMAO consequently reduces bile acid synthesis (which solubilized fats), blocks reverse cholesterol transport, and increases forward cholesterol transport, thus increasing cholesterol levels in the

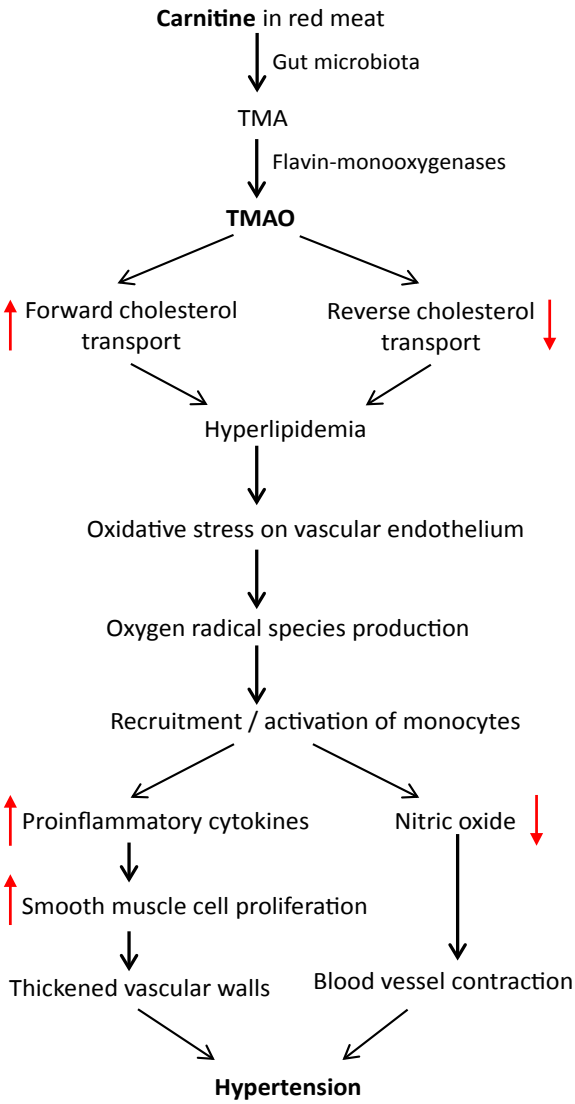

Figure 1: Carnitine from red meat induces hypertension. Hypertension, when paired with hyperlipidemia especially, promotes atherosclerosis and maybe other cardiovascular diseases.

arteries. In fact, in mice fed a Carnitine heavy diet, there was a 35% decrease in reverse cholesterol transport [23]. This lack of reverse cholesterol transport paired with increased forward cholesterol transport results in hyperlipidemia, or the excess of lipids such as cholesterol in the blood. Hyperlipidemia has been shown [27] to induce oxidative stress on vascular endothelium, leading to the production of oxygen radical species at the arterial wall. These events contribute to monocytes and lymphocyte recruitment [27,28]. Monocytes and macrophages upregulate the expression of chemokines and adhesion molecules, reduce nitric oxide bioavailability, and stimulate vascular smooth muscle cell hypertrophy. This leads to vascular dysfunction and remodeling [29-32]. Smooth muscle cell proliferation results in a thickened vascular wall and narrowed lumen, which is known to trigger hypertension [33-37]. The reduction of nitric oxide keeps blood vessels in the contracted state for longer periods of time [38]. It suggests that the presence of TMAO can prompt hyperlipidemia and increase the likelihood of hypertension.

In the breakthrough studies [22,23] done by the research team at the Cleveland Clinic, atherosclerosis was linked with TMAO from red meat metabolism. It is possible that TMAO also induces hypertension which can lead to atherosclerosis. One study investigating the association between hypertension and atherosclerosis found that high blood pressure is not only associated with the presence of atherosclerosis but also with its severity [39]. The same study found that among study participants with atherosclerosis, the likelihood of developing complex atherosclerosis increased 31% for every 10 mmHg increase in pulse pressure [39]. The downstream effects of hypertension may account for the accelerated atherosclerosis seen in the mice of the Cleveland Clinic study. According to the American Heart Association website, high blood pressure can cause microscopic tears in the arteries. These tears are repaired with scar tissue, which is prone to lodging fats [3]. Excessive cholesterol in the blood stream paired with high blood pressure speeds up plaque accumulation and stiffening of the arteries, which could explain the atherosclerosis observed in the laboratory mice [23].

Gut microbiota are essential for the metabolism of Carnitine and production of TMAO from Carnitine. Suppression of the bacteria using antibiotics has been attempted as a medicinal approach to reducing TMAO levels in the body; however, the results have not been promising. Though initially helpful, the gut microbes are quick to adapt and eventually return to full numbers in the intestine [22]. Another downfall to antibiotic treatment is the fact that these gut microbes are important to absorbing nutrients and in the production of secondary bile acids; therefore, a reduction in consumption of food high in Carnitine may be the best way to reduce the effects of TMAO in the body.

Dietary suggestions

Carnitine is an amino acid derivative which the body produces enough naturally to meet the needs of healthy people [26]. Because of its link with increased blood pressure, reducing Carnitine consumption could potentially alleviate high blood pressure by lowering the levels of TMAO in hypertensive patients.

Vegans and vegetarians have been shown to have a reduced capacity to produce TMAO from dietary carnitine [23]. In one study, when omnivores and vegetarians/vegans were both given an 8 oz steak to eat, the TMAO levels in the omnivores increased dramatically in plasma and urine samples whereas the vegan and vegetarian levels increased little to none [23]. Vegans and vegetarians also have lower incidences of hypertension [14,40-43]. This implies that gut microbiota can adapt to their hosts' dietary preferences by acquiring genes that process micronutrients via horizontal gene transfer [23]. With this in mind, a diet that consists primarily of plant-based foods and occasionally supplemented with meat could be the most beneficial way to decrease TMAO and risk of heart disease and hypertension.

The connection between red meat and hypertension is prominent across cardiovascular dietary studies. While it is still unsure exactly how red meat aggravates or induces hypertension, there is a definite possibility that TMAO produced from red meat metabolism by intestinal microbiota plays a significant role in the pathogenesis of hypertension.

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References

1. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001; 344: 3-10.
2. World Health Organization: A global brief on hypertension. 2013.
3. American Heart Association: High Blood Pressure or Hypertension.
4. American Cancer Society: Lycopene.
5. Das DK, Mukherjee S, Ray D. Resveratrol and red wine, healthy heart and longevity. Heart Fail Rev. 2010; 15: 467-477.
6. Wang L, Manson JE, Buring JE, Sesso HD. Meat intake and the risk of hypertension in middle-aged and older women. J Hypertens. 2008; 26: 215-222.
7. Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, et al. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. BMJ. 2008; 337: 258.
8. Metintas S, Arikan I, Kalyoncu C. Awareness of hypertension and other cardiovascular risk factors in rural and urban areas in Turkey. Trans R Soc Trop Med Hyg. 2009; 103: 812-818.
9. Nkondjock A, Bizome E. Dietary patterns associated with hypertension prevalence in the Cameroon defence forces. Eur J Clin Nutr. 2010; 64: 1014-1021.
10. Sacks FM, Obarzanek E, Windhauser MM, Svetkey LP, Vollmer WM, McCullough M, et al. Rationale and design of the Dietary Approaches to Stop Hypertension trial (DASH). A multicenter controlled-feeding study of dietary patterns to lower blood pressure. Ann Epidemiol. 1995; 5: 108-118.
11. Conlin PR, Chow D, Miller ER, Svetkey LP, Lin PH, Harsha DW, et al. The effect of dietary patterns on blood pressure control in hypertensive patients: results from the Dietary Approaches to Stop Hypertension (DASH) trial. Am J Hypertens. 2000; 13: 949-955.
12. Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium Dietary Approaches to Stop Hypertension-type diet including lean red meat lowers blood pressure in postmenopausal women. Nutr Res. 2009; 29: 8-18.
13. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. American Heart Association. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension. 2006; 47: 296-308.
14. He J, Whelton PK. Effect of dietary fiber and protein intake on blood pressure: a review of epidemiologic evidence. Clin Exp Hypertens. 1999; 21: 785-796.
15. Obarzanek E, Velletri PA, Cutler JA. Dietary protein and blood pressure. JAMA. 1996; 275: 1598-1603.
16. Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, et al. Association between protein intake and blood pressure: the INTERMAP Study. Arch Intern Med. 2006; 166: 79-87.
17. Morris MC. Dietary fats and blood pressure. J Cardiovasc Risk. 1994; 1: 21-30.
18. Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, et al. A prospective study of nutritional factors and hypertension among US men. Circulation. 1992; 86: 1475-1484.
19. Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J, et al. Prospective study of nutritional factors, blood pressure, and hypertension among US women. Hypertension. 1996; 27: 1065-1072.
20. Stamler J, Caggiula A, Grandits GA, Kjelsberg M, Cutler JA. Relationship to blood pressure of combinations of dietary macronutrients. Findings of the Multiple Risk Factor Intervention Trial (MRFIT). Circulation. 1996; 94: 2417-2423.
21. Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. Hypertension. 2002; 39: 1000-1006.
22. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med. 2013; 368: 1575-1584.
23. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013; 19: 576-585.
24. Miura K, Greenland P, Stamler J, Liu K, Daviglus ML, Nakagawa H. Relation of vegetable, fruit, and meat intake to 7-year blood pressure change in middle-aged men: the Chicago Western Electric Study. Am J Epidemiol. 2004; 159: 572-580.
25. National institutes of Health. Carnitine. Fact Sheet for Health Professionals.
26. Rebouche CJ. Carnitine. In: Shils ME, Olson JA, Shike M, Ross AC, eds. Modern Nutrition in Health and Disease. 9th ed. Philadelphia: Lippincott, Williams & Wilkins. 1999; 505-512.
27. Alexander RW. Theodore Cooper Memorial Lecture. Hypertension and the pathogenesis of atherosclerosis. Oxidative stress and the mediation of arterial inflammatory response: a new perspective. Hypertension. 1995; 25: 155-161.
28. Alexander RW. The coronary ischemic syndromes: relationship to the biology of atherosclerosis. In: Schlant RC, Alexander RW, eds. Hurst's The Heart. 8th ed. New York, NY: McGraw-Hill Publishing Co. 1994; 1021-1031.
29. Virdis A, Dell'Agnello U, Taddei S. Impact of inflammation on vascular disease in hypertension. Maturitas. 2014; 78: 179-183.
30. Taniyama Y, Griendling KK. Reactive oxygen species in the vasculature: molecular and cellular mechanisms. Hypertension. 2003; 42: 1075-1081.
31. Touyz RM. Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? Hypertension. 2004; 44: 248-252.
32. Virdis A, Neves MF, Amiri F, Touyz RM, Schiffrin EL. Role of NAD(P)H oxidase on vascular alterations in angiotensin II-infused mice. J Hypertens. 2004; 22: 535-542.
33. Schwartz SM, Ross R. Cellular proliferation in atherosclerosis and hypertension. Prog Cardiovasc Dis. 1984; 26: 355-372.
34. Folkow B. Physiological aspects of primary hypertension. Physiol Rev. 1982; 62: 347-504.
35. Tracy RE. Quantitative measures of the severity of hypertensive nephrosclerosis. Am J Epidemiol. 1970; 91: 25-31.
36. Wiener J, Loud AV, Giacomelli F, Anversa P. Morphometric analysis of hypertension-induced hypertrophy of rat thoracic aorta. Am J Pathol. 1977; 88: 619-634.
37. Halpern W, Mulvany MJ, Warshaw DM. Mechanical properties of smooth muscle cells in the walls of arterial resistance vessels. J Physiol. 1978; 275: 85-101.
38. De Caterina R, Libby P, Peng HB, Thannickal VJ, Rajavashisth TB, Gimbrone MA, et al. Nitric oxide decreases cytokine-induced endothelial activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. J Clin Invest. 1995; 96: 60-68.
39. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Petterson TM, O'Fallon WM, et al. Independent association of high blood pressure and aortic atherosclerosis: A population-based study. Circulation. 2000; 102: 2087-2093.
40. Sacks FM, Rosner B, Kass EH. Blood pressure in vegetarians. Am J Epidemiol. 1974; 100: 390-398.

41. De Caterina R, Libby P, Peng HB, Thannickal VJ, Rajavashisth TB, Gimbrone MA, et al. Nitric oxide decreases cytokine-induced endothelial activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. J Clin Invest. 1995; 96: 60-68.

42. Rouse IL, Beilin LJ, Armstrong BK, Vandongen R. Blood-pressure-lowering effect of a vegetarian diet: controlled trial in normotensive subjects. Lancet. 1983; 1: 5-10.

43. Margetts BM, Beilin LJ, Vandongen R, Armstrong BK. Vegetarian diet in mild hypertension: a randomised controlled trial. Br Med J (Clin Res Ed). 1986; 293: 1468-1471.

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