

MEDITERRANEAN DIET, HYPERTENSION AND CARDIOVASCULAR PREVENTION

Mónica Domenech MD, Ramón Estruch MD, PhD, Cristina Sierra MD PhD, Miguel Camafort MD, and Antonio Coca MD, PhD, FRCP, FESC.

Hypertension and Vascular Risk Unit, Department of Internal Medicine. Hospital Clinic (IDIBAPS - Institut d'Investigacions Biomèdiques August Pi i Sunyer), University of Barcelona, Spain.

Hypertension (HT) remains the main risk factor for developing coronary artery disease, congestive heart failure, stroke and kidney disease⁽¹⁾. Its prevalence continues to increase exponentially due to better detection and an increase in other associated factors such as obesity, physical inactivity and diabetes mellitus. Recently published data from the National Health and Nutritional Examination Survey (NHANES) between 2007 and 2010 show that HT affects 33% (77.9 million) of people aged ≥ 20 years in the United States⁽²⁾ and this prevalence is estimated to increase to 37.3% by 2030⁽³⁾. This trend is spreading, even in countries that traditionally have a lower cardiovascular risk, such as Spain, where, in a cohort of 11,957 persons aged ≥ 18 years, 33% (3983 persons) had a BP $\geq 140/90$ mmHg, but $> 40\%$ were unaware of the condition.⁽⁴⁾ These data warn us of the magnitude of the problem and the need to increase efforts to improve the diagnosis, treatment and, especially, the prevention of hypertensive disease.

In 1970, Keys et al were already highlighting the influence of lifestyles on the development and/or prevention of cardiovascular disease (CVD), with particular emphasis on the important role of diet. On this basis, the Seven Countries Study⁽⁵⁾, an ecological study of 12,770 participants aged 40-59 years from Finland, Greece, Italy, Japan, Netherlands, Norway, the United States and Yugoslavia, who were followed for five years, was carried out. The authors found significant differences between different cohorts, with a higher incidence of CVD in Finland, the USA and Holland compared with the Southern European countries and Japan. These differences were not accounted for by other traditional risk factors such as smoking, obesity or physical activity. However, when other factors such as diet were analysed, the authors found a significant association between the consumption of mono- and polyunsaturated fats and a lower incidence of CVD, suggesting that the dietary patterns of the Southern European countries, with a low intake of saturated fat and a high intake of fruits and vegetables, was a decisive factor in lower cardiovascular mortality⁽⁶⁾. The results of this study are the pillar that supports today's growing evidence of the benefits associated with the so-called "Mediterranean Diet" (MD).

The north-south gradient with respect to CVD has been confirmed in several epidemiological studies, as evidenced by data from the MONICA Project (multinational monitoring of trends and determinants in cardiovascular disease)⁽⁷⁾, in which Catalonia, the South of France and Italy showed a lower incidence of and mortality due to coronary heart disease (in both men and women) than Northern European countries and the United States. In light of this evidence, numerous studies have been made showing the benefits of adherence to a "healthy diet" in reducing CVD. Data from the CARDIA study (Coronary Artery Risk Development in Young Adults), published by Liu et al⁽⁸⁾ and conducted in 3154 participants aged 18-30 years, underline the importance

of maintaining a healthy lifestyle over a 20-year follow-up. In this study, adherence to a "healthy diet" increased the maintenance of a low cardiovascular risk profile (28.3% for a healthy diet vs. 22.4% for an unhealthy diet; $P < 0.01$) upon reaching adulthood, thus reducing, the likelihood of future CVD. Therefore, all cardiovascular prevention guidelines placed diets and lifestyles as the cornerstone for reducing and preventing the development of HT and CVD⁽⁹⁾.

The lifestyle changes that have shown benefit in reducing BP values include weight reduction, reduced sodium intake, increased potassium intake, promotion of a reduction in excessive alcohol intake, and the so-called DASH diet (Dietary Approaches to Stop Hypertension)^(10, 11). Initially, this diet potentiated increased consumption of fruits, vegetables and fat dairy products with a relatively low intake of total and saturated fat⁽¹²⁾, although restrictions in sodium intake were later added in order to achieve greater reductions in BP values⁽¹³⁾. The Optimal Macronutrient Intake Trial to Prevent Heart Disease study (OmniHeart), compared three diets based on the DASH diet: one enriched with carbohydrates, the second enriched with vegetable proteins, and the third enriched with monounsaturated fats (MUFA). In patients with hypertension, the vegetable protein diet further significantly reduced systolic BP by 3.5 mmHg and the MUFA diet by 2.9 mmHg compared to the carbohydrate diet⁽¹⁴⁾.

In recent decades, the vasculoprotective potential of diet and its various nutrients has been increasingly recognized, although in recent years more solid evidence on the benefits of the MD, a food pattern based on high consumption of fruits, vegetables and monounsaturated fats, with olive oil being the main source of fat, has emerged, although there is little data on its effect on BP reduction. Since the 1990s, evidence on the benefits of the MD in the prevention of CVD and the reduction of BP and cholesterol levels and/or diabetes, has become stronger, although the level of evidence remains very heterogeneous. As stated, the MD is characterized by a diet rich in fruits, vegetables and cereals, with a high intake of mono- and polyunsaturated fats, and with olive oil being the main source of fat. Likewise, the MD encourages moderate fish and poultry consumption and a low consumption of dairy products, red meat, prepared meats and sweets and pastries. The MD also promotes moderate consumption of wine, preferably red, during meals⁽¹⁵⁾.

Since the pioneering study by Keys et al⁽⁷⁾ until the present day, data have been collected from more than 12 cross-sectional studies included in the ATTICA registry, which included nearly 3,000 participants aged 18-89 years from the Greek region of Attica between 2001 and 2002. The different studies show that adherence to the MD is associated with a reduction in diabetes, obesity, CVD, and an improvement in the lipid

profile and BP values. To this can be added the data from two large cohort studies: the "Greek European Prospective Investigation into Cancer and Nutrition cohort (EPIC)" and the "Estudio de Seguimiento de la Universidad de Navarra (SUN)". The EPIC study now encompasses nearly half a million persons from 10 European countries and is the largest population-based cohort study focused on the beneficial effects of the MD on cardiovascular health. Substudies in Greece, Italy and Spain have found an inverse relationship between adherence to the MD and BP values, the BMI, diabetes mellitus⁽¹⁶⁾ and the tendency to obesity. More recent data from the Greek-EPIC cohort of 23,601 participants free of CVD, showed that increasing adherence to the MD (determined by an increase of 2 points in the MD) was inversely associated with the incidence of cerebrovascular disease (HR 0.85; 95% CI, 0.74 - 0.96). This association was even stronger for women and for ischemic stroke vs. haemorrhagic stroke⁽¹⁷⁾.

The SUN study of more than 15,000 Spanish university students without cardiovascular risk factors showed that adherence to the MD conditioned a lower incidence of metabolic syndrome, diabetes and a reduction in BP values⁽¹⁸⁾. Similar results were observed in the randomized, parallel Medi-RIVAGE study⁽¹⁹⁾ which compared the effects of the MD in 180 patients with metabolic syndrome compared to a control diet (carbohydrates 50-60%, proteins 15-20% protein, total fat, <30%). After two years follow up, patients assigned to the MD had a significant reduction in the prevalence of metabolic syndrome and associated cardiovascular risk factors. Finally, data from the first randomized study in secondary prevention, the Lyon DietHeart Study⁽²⁰⁾, confirmed the benefits of the MD in reducing cardiovascular risk.

The strongest evidence on the benefits of the MD comes from the multicentre, randomized PREDIMED study of 4,774 patients at high cardiovascular risk in primary prevention. Patients were assigned to one of three arms of a dietary intervention: MD supplemented with virgin olive oil (VOO), MD supplemented with nuts, or a control low fat diet. The study was halted prematurely at 4.8 years of follow up in accordance with data obtained in an interim analysis. The PREDIMED⁽²¹⁾ study is the first randomized trial in primary prevention, and showed

that a MD supplemented with in VOO or nuts significantly reduces the incidence of major cardiovascular events, with a HR of 0.70 (95% CI, 0.54 - 0.92) and 0.72 (95% CI, 0.54-0.96), respectively.

Prior studies of the effects of the MD on BP have relied on clinic (office) BP measurements, an approach that is limited by poor reproducibility, the white-coat effect, and observer and patient variability. It is important to remember that 24-hour ambulatory BP (ABP) monitoring is considered the gold standard for the assessment of the effects of interventions on BP, as repeated measurements more accurately reflect usual BP than isolated office measurements. The latest evidence of the beneficial effect of the MD on BP comes from a recent substudy of the PREDIMED study by Domenech et al⁽²²⁾, which included 235 subjects (56.5% female; mean age, 66.5 years) at high cardiovascular risk (85.4% with hypertension). The results showed that the MD supplemented with either extra-virgin olive oil or nuts resulted in significant reductions in 24-hour ABP compared with a control diet in individuals at high risk of CVD. The net differences between the MD supplemented with extra-virgin olive oil and nuts and the control diet were -4.0 for mean systolic BP, -4.3 mm Hg for mean diastolic ABP, and -1.9 mm Hg for both MD after adjustment for between-diet imbalances in baseline BP and for trial changes in antihypertensive medication. The impact of such BP changes, even if their magnitude seems small, could be remarkable at the population level.

In conclusion, today there is stronger evidence that increasing adherence to the MD is associated with lower BP. Taking into account the lack of BP control rates in spite of pharmacological treatment, these results could have public health implications because the MD, a vegetable-based and high-unsaturated fat dietary pattern, seems to be a useful adjunct to established dietary and pharmacological approaches for improving hypertension control while incurring no expense for the health system.

REFERENCES

1. Ford ES. Trends in mortality from all causes and cardiovascular disease among hypertensive and nonhypertensive adults in the United States. *Circulation* 2011; 123: 1737-1744.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics - 2013 update - a report from the American Heart Association. *Circulation* 2013; 127: 143-152.
3. Heidenreich PA, Trogonon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011; 123: 933-944.
4. José R. Banegas, Auxiliadora Gracián, Juan J. de la Cruz-Troca, Luz M. León-Muñoz, Pilar Guallar-Castillón, Antonio Coca, Luis M. Ruilope, Fernando Rodríguez-Artalejo. Achievement of Cardiometabolic Goals in Aware Hypertensive Patients in Spain. A Nationwide Population-Based Study. *Hypertension* 2012; 60: 898-905.
5. Keys A, et al. Coronary heart disease in seven countries. *Circulation* 1970; 41(Suppl 1): 1-211.
6. Menotti A, Keys A, Kromhout D, Nissinen A, Blackburn H, Fidanza F, et al. Twenty-five-year mortality from coronary heart disease and its prediction in five cohorts of middle-aged men in Finland, The Netherlands, and Italy. *Prev Med* 1990; 19: 270-278.
7. Myocardial Infarction and Coronary Deaths in the World Health Organization MONICA Project. Registration Procedures, Event Rates, and Case-Fatality Rates in 38 Populations From 21 Countries in Four Continents. *Circulation* 1994; 90: 583-612.
8. Liu K, Daviglus ML, Loria CM, Colangelo LA, Spring B, Moller AC, and Donald M. Healthy Lifestyle Through Young Adulthood and the Presence of Low Cardiovascular Disease Risk Profile in Middle Age: The Coronary Artery Risk Development in (Young) Adults (CARDIA) Study. *Circulation* 2012; 125: 996-1004.
9. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281-1357.
10. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension* 2006; 47: 296-308.
11. Sacks FM, Campos H. Dietary therapy in hypertension. *N Engl J Med* 2010; 362: 2102-2012.
12. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure: DASH Collaborative Research Group. *N Engl J Med* 1997; 336: 1117-1124.
13. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001; 344: 3-10.
14. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids. Results of the OmniHeart randomized trial. *JAMA* 2005; 294: 2455-2464.
15. Willett WC, Sacks F, Trichopoulos A, et al. Mediterranean diet pyramid: a cultural model for healthy eating. *Am J Clin Nutr* 1995; 61(Suppl): 1402S-1406S.
16. Rossi M, Turati F, Lagiou P, Trichopoulos D, Augustin LS, La Vecchia C, Trichopoulou A. Mediterranean diet and glycaemic load in relation to incidence of type 2 diabetes: Results from the Greek cohort of the population-based European Prospective Investigation into Cancer and Nutrition (EPIC). *Diabetologia* 2013; 56: 2405-2413.
17. Misirli G, Benetou V, Lagiou P, Bamia C, Trichopoulos D, and Trichopoulou A. Relation of the Traditional Mediterranean Diet to Cerebrovascular Disease in a Mediterranean Population. *Am J Epidemiol* 2012; 176(12): 1185-1192.
18. Núñez-Córdoba JM, Valencia-Serrano F, Toledo E, Alonso A, Martínez-González MA. The Mediterranean diet and incidence of hypertension: the Seguimiento Universidad de Navarra (SUN) Study. *Am J Epidemiol* 2009; 169: 339-346.
19. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiendo M, D'Andrea F, Giugliano D. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 2004; 292(12): 1440-1446.
20. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delays J, Mamelle M. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999; 99(6): 779-785.
21. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, and Martínez-González MA, for the PREDIMED Study Investigators. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med* 2013; 368(14): 1279-1290.
22. Domenech M, Roman P, Lapetra J, García de la Corte FJ, Sala-Vila A, de la Torre R, Corella D, Salas-Salvado J, Ruiz-Gutiérrez V, Lamuela-Raventós RM, Toledo E, Estruch R, Coca A and Ros E. Mediterranean Diet Reduces 24-Hour Ambulatory Blood Pressure, Blood Glucose, and Lipids: One-Year Randomized, Clinical Trial. *Hypertension* 2014; 64: 69-76.