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EDITORIAL

No-Pharmacological Intervention: Pomegranate Juice for the Management of Hypertension and the Improvement of Cardiovascular Health

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The concept of ideal cardiovascular (CV) health, with emphasis on the prevention of CV disease (CVD), was included by the American Heart Association (AHA) among its strategic goals for 2020 [1]. This concept was intended to focus mainly on the promotion of a healthy lifestyle and the adoption of a multifactorial intervention with non-pharmacological or pharmacological means, aiming at the prevention or the effective control of CVD risk factors [1]. Ideal CV health is defined as optimal levels of 3 CVD risk factors [blood pressure (BP), fasting plasma glucose and total cholesterol) and 4 behaviours [body mass index (BMI), smoking, physical activity and healthy diet] [1]. These 7 ideal CV metrics, called life's simple 7, are probably the best available markers of life-time CVD risk [2]. Recent studies have shown that the levels of ideal CV health in the United States to be very low at a community level [3-5] and to be associated with cardiac events [3], stroke [2] and total mortality [6]. A large study was conducted in 5,785 young adults (20-39 years old) from 5 international populations: the Minneapolis Childhood Cohort Study, the Princeton Follow-up Study, the Bogalusa Heart Study, the Cardiovascular Risk in Young Finns Study, and the Childhood Determinants of Adult Health (CDAH) Study; all members of the International Childhood Cardiovascular Cohort (i3C) Consortium [7]. Results of the study showed that ideal CV health, as defined by the AHA, was rare among young participants of the study. An amazingly low (only 1%) percentage of the participants had all 7 health metrics in the 5,785 young adults participating from all international cohorts [7]. Many of the participants had ideal glucose (73%), cholesterol (64%), and were non-smokers (64%); diet (7%) was the least common metric for participants from any of the cohorts [7]. The lowest prevalence of a clinical CVD risk factor from the life's 7 simple was BP; this was normal in only 52% of the participants [7]. The National Health and Nutrition Examination Surveys (NHANES) 2003-2008 evaluated the prevalence of the 7 CV health metrics in 14,515 adults [8]. Participants were stratified in young (20-39 years), middle-aged (40-64 years) and elderly (≥65 years). Less than 1% of subjects exhibited ideal CV health for all 7 metrics. Among CV health behaviors, non-smoking was the most prevalent (60.2-90.4%), ideal Healthy Diet Score was least prevalent (0.2-2.6%) across groups, while ideal BMI (36.5-45.3%) and ideal physical activity levels (50.2-58.8%) were higher in young adults compared with middle-aged or elderly [8]. Ideal total cholesterol (23.7-36.2%), blood pressure (11.9%-16.3%), and fasting blood glucose (31.2-42.9%) were less frequent in older adults compared with young and middle-aged adults. The prevalence of poor CV health status was lowest in young age compared with higher middle and older ages [8]. Again, ideal BP was the least prevalent among clinical CVD risk factors [8].

A relevant Chinese study included 91,698 participants (72,826 men, age 18-98 years-old), free of myocardial infarction and stroke at baseline (2006-2007) [2]. The hazard ratios (HR) and 95% confidence interval (CI) for total stroke according to the adherence to life's 7 simple [0 (reference), 1, 2, 3, 4, 5, and 6/7 ideal CV metrics] were: 1, 0.92 (0.69-1.23), 0.69 (0.52-0.92), 0.52 (0.39-0.68), 0.38 (0.28-0.51), 0.27 (0.18-0.40), and 0.24 (0.11-0.54), respectively (p for trend <0.01), after adjusting for age, sex, education, income and hospital [2]. Similar inverse associations were observed for both ischaemic and haemorrhagic stroke (p for trend <0.01) [2]. In this study, high BP played a major role in stroke incidence [2].

The above data suggest that in the effort of achieving ideal CV health, hypertension should be one of the primary targets, because of its high prevalence in the general population and the low levels of effective control [9]. Moreover, if we can control BP and improve some of the other CV metrics of ideal CV health, this will have significant additive beneficial effects.

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Non-pharmacological interventions to control hypertension or to augment the effects of antihypertensive drug treatment (thereby potentially reducing the need for more drugs), have been used for a long time [10,11]. The recent (2013) ESH/ESC Guidelines for the management of hypertension [12] suggest: salt restriction to 5-6 g/d, moderation of alcohol consumption to <20-30 g/d of ethanol in men and <10-20 g/d in women, increased consumption of vegetables, fruits, and low-fat dairy products, reduction of BMI to <25 kg/m^2 and of waist circumference to <102 cm in men and <88 cm in women, regular exercise (at least 30 min of moderate dynamic exercise on 5 to 7 days per week), and advice/support for smoking cessation [12]. Moreover, high quality evidence suggests that increased potassium intake is beneficial in most adults without impaired renal handling of potassium for the prevention or control of elevated BP and prevention of stroke (reduction of incidence by 24%), without adverse effects on lipid concentrations, catecholamine concentrations or renal function [13]. However, compliance to long-term lifestyle changes to treat hypertension is very low, and special programs and interventions to improve this adherence may need to consider the existing barriers [14]. A low desire, interest or awareness are commonly reported barriers to salt restriction, changes in diet, weight loss, smoking cessation and alcohol reduction [14]. In contrast, the most common barrier to engaging in physical activity to regulate BP is time limitations and the challenge of managing a co-existing physical condition/disease; arthritis (60%), back problems (41%), diabetes (27%), CVD or stroke (27%), asthma (23%) and chronic obstructive pulmonary disease (22%) [14]. Thus, non-pharmacological interventions for the treatment of hypertension are not successful enough [15].

A number of studies have demonstrated the protective effects of foods rich in polyphenols (fruit, tea, wine and cocoa or chocolate and especially citrus fruit) against several CVD risk factors such as hypertension, low density lipoprotein (LDL) particle oxidation and endothelial dysfunction [16-18]. The pomegranate tree (Punica granatum), considered to be originated in the Garden of Eden (modern Mesopotamia and specifically Iran), has been extensively used as a folk medicine in many cultures [19]. Today, it is widely cultivated throughout the Mediterranean region of southern Europe, the Middle East and the Caucasus region, northern and tropical Africa, the Indian subcontinent and the drier parts of Southeast Asia [19]. Introduced into Latin America and California by Spanish settlers in 1769, pomegranate is also cultivated in parts of California and Arizona. Edible parts of pomegranate fruits (about 50% of total fruit weight) comprise 80% juice and 20% seeds. Fresh juice contains 85% moisture, 10% total sugars, 1.5% pectin, ascorbic acid and polyphenols [19]. Pomegranate fruit is considered as a heart-healthy fruit [19,20]. Pomegranate is rich in polyphenolic-type antioxidants, including tannins, anthocyanins and several other types of flavonoids [20,21]. The soluble polyphenol content in pomegranate juice (PJ) normally ranges between 0.2 and 1.0% depending on the fruit variety, and mainly comprises tannins, ellagic anthocyanins, catechins, and gallic and ellagic acids [20,21]. Despite the previously reported CV health benefits of pomegranate and its high content in polyphenols and flavonoids [20-22], there have been very few studies on the anti-hypertensive effects of PJ [23]. A very recent study included 21 hypertensive patients (aged 30-67 years) [23]. These were assigned to receive either PJ (150 ml/day in a single occasion between lunch and dinner; n = 11) or the same amount of water (n = 10) for a period of 2 weeks. PJ consumption was associated with significant reductions in systolic BP (p=0.002) and diastolic BP (p=0.038), but not flow mediated dilation (FMD) (p>0.05). Serum levels of vascular cell adhesion molecule 1 (VCAM-1) (p=0.008) were significantly reduced by PJ while those of E-selectin were elevated (p=0.039). However, no significant PJ effect was observed on serum levels of intercellular adhesion molecule 1 (ICAM-1), high-sensitivity C-reactive protein (hs-CRP), lipid profile, and interleukin-6; this null effect might be due to the short duration of the study [23]. Therefore, consumption of PJ for 2 weeks has effective hypotensive action and may also improve endothelial function. These findings suggest PJ as a beneficial cardioprotective supplement for hypertensive subjects, with actions extending beyond BP reduction [23]. In an earlier (2001) study in hypertensive patients, the consumption of PJ (50 ml, 1.5 mmol of total polyphenols per day, for 2 weeks) decreased serum angiotensin converting enzyme (ACE) activity by 36% and systolic BP by 5% [24]. Similar inhibitory effect (31%) of PJ on serum ACE activity was also observed *in vitro* [24]. Since a reduction in serum ACE activity was previously shown to attenuate atherosclerosis, PJ can offer protection against CVD, which could also be related to its inhibitory effect on oxidative stress [24]. Another study demonstrated reduced BP in patients with carotid artery stenosis who had consumed pomegranate juice for 3 years [25]. Ten patients were given PJ for 1 year with 5 patients continuing consumption for up to 3 years. Systolic BP was reduced by 21% after 1 year of PJ consumption and was not further reduced during the 3 years of PJ use [25]. In this study, serum paraoxonase-1 (PON-1) activity was increased by 83%, whereas serum LDL basal oxidative state and LDL susceptibility to copper ion-induced oxidation were both significantly reduced by 90% and 59%, respectively, after 12 months of PJ consumption [25]. Furthermore, serum levels of antibodies against oxidized LDL were decreased by 19%, and in parallel serum total antioxidant status was increased by 130% after 1 year of PJ consumption [25]. In the control group, common carotid intima-media thickness (cIMT) increased by 9% during 1 year, whereas PJ consumption resulted in a significant cIMT reduction, by up to 30%, after 1 year [25]. For all studied parameters, the maximal effects were observed after 1 year of PJ consumption. Further consumption of PJ, for up to 3 years, had no additional beneficial effects on IMT and serum PON-1 activity, whereas serum lipid peroxidation was further reduced by up to 16% after 3 years of PJ consumption [25]. Total and LDL cholesterol were not significantly affected. Regarding the effect of PJ on triglycerides (TGs), recent data suggest an inhibitory activity of PJ on TGs biosynthesis, which could be attributed to a direct effect of PJ on diacylglycerol acyltransferase 1 (DGAT1) activity [26]. In a larger study in subjects with moderate coronary heart disease risk, PJ consumption (240 ml/day, n=146) or a control beverage (n=143) for up to 18 months had no significant effect on overall cIMT progression rate, but may have slowed cIMT progression in subjects with increased oxidative stress and abnormalities in the TG-rich lipoprotein/ high-density lipoprotein (HDL) axis [27]. Regarding HDL,

the association of PON-1 with HDL stabilizes this antioxidant enzyme. In high-risk patients, especially those with diabetes, PON-1 dissociates from HDL and, as a consequence, becomes less active [28]. PJ consumption augments PON-11 stability and increases its activity; this could lead to retardation of atherosclerosis development [28], especially PJ from the "wonderful" variety of the fruit [29]. Overall, PJ has at least 20% greatest antioxidant potency than a variety of other antioxidant beverages, including apple juice, açaí juice, black cherry juice, blueberry juice, cranberry juice, Concord grape juice, orange juice, black tea, green tea and white tea [30]. Similar benefits ofPJ consumption were observed in diabetic patients. Indeed, PJ consumption by diabetic patients resulted in anti-oxidative effects on serum and macrophages without worsening glycemic control [31]. Moreover, arterial stiffness of the common carotid arteries in 73 patients with at least one CVD risk factor that consumed PJ ("wonderful" variety, 240 mL/d for 1 year) showed trends to increased elasticity in the PJ-treated group versus the placebo-treated group (who received a beverage of similar caloric content, flavor and color) [19]. However, a single dose of PJ following a high-fat meal had no effect on reflection index, stiffness index or diastolic BP, but lowered postprandial plasma TGs concentrations and suppressed the postprandial increase in systolic BP following the high-fat meal [32].

Beyond hypertension, oxidative stress is also causally related with several CVD risk factors such as diabetes, dyslipidaemia, metabolic syndrome and smoking; oxidative stress has been proved to play a key role in the pathogenesis of atherosclerosis [33]. Oxidized LDL (Ox-LDL) is present in atherosclerotic lesions and in plasma from patients with CVD, and it correlates with the presence of angiographically documented complicated plaques [33], thus identifying patients who are at increased risk for future myocardial infarction, independently of other risk factors [34]. Since PJ contains very potent antioxidants (tannins, anthocyanins), which are also considered potent anti-atherogenic agents, it might attenuate atherosclerosis development by reducing oxidative stress in these patients [34]. Indeed, human plasma obtained from healthy subjects after 2 weeks of PJ consumption (50 mL PJ concentrate/day, equivalent to 1.5 mmol total polyphenols) demonstrated a significantly ($p<0.01$) decreased susceptibility to free radical-induced lipid peroxidation, in comparison to plasma obtained at baseline prior to PJ consumption initiation, as measured by lipid peroxides formation or by total antioxidant status in serum [31,35]. Very recently, a study evaluated a product a new functional beverage based on a de-alcoholized red wine matrix supplemented by a pomegranate extract. This product is expected to have even more potent antioxidant action [36].

Regarding patients with metabolic syndrome (one of the components of which is hypertension), it has been demonstrated that PJ exerts hypoglycaemic effects by increasing insulin sensitivity, inhibiting α-glucosidase, and modulating glucose transporter type-4 function, but also lowers total cholesterol and exerts anti-inflammatory effects through the regulation of peroxisome proliferator-activated receptor pathways [37].

Finally, during the last 15 years, numerous studies reported promising results on the anticarcinogenic, and anti-inflammatory properties of PJ, focusing on treatment and prevention of cancer (mainly prostate), dental conditions, erectile dysfunction, bacterial infections and antibiotic resistance, and ultraviolet radiation-induced skin damage [38].

In conclusion, current data suggest that long-term (at least for 1 year) use of PJ has a beneficial effect on BP, improves endothelial function, reduces arterial stiffness and delays or reverses the progression of atherosclerosis. These effects could result in an improvement in CV and overall health status. Therefore, PJ might be useful as an adjunctive therapy for the management of hypertension on top of other non-pharmacological interventions or drug therapy. The use of PJ might reduce the number of drugs or their doses for patients requiring antihypertensive drug therapy. PJ might be more useful in patients with hypertension and high oxidative burden such as those with diabetes, obesity, metabolic syndrome or who smoke. However, our knowledge on the CV effects of PJ are based on studies with a small number of patients and limitations in their design. Therefore, future long-term well-designed studies with polyphenols-rich foods (alone or in combination), but also with isolated phenolic compounds would provide valuable data to establish public health recommendations on the use of polyphenols for CVD and overall health protection.

CONFLICT OF INTEREST

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