Genetic Epidemiology of Hypertension: An Update on the African Diaspora

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Hypertension is a serious global public health problem, affecting approximately 600 million people worldwide. The lifetime risk of developing the condition exceeds 50% in most populations. Despite considerable success in the pharmacological treatment of hypertension in all-human populations, the health-care community still lacks understanding of how and why individuals develop chronically elevated blood pressure. This gap in knowledge, and the high prevalence of hypertension and associated complications in some populations of African descent, have led some to conclude that hypertension is a ''different disease'' in people of African descent. Despite considerable evidence from epidemiologic studies showing that blood pressure distribution in populations of the African diaspora spans the known spectrum for all human populations, theories in support of unique ''defects'' among populations of African descent continue to gain wide acceptance. To date, no known environmental factors or genetic variants relevant to the pathophysiology of human hypertension have been found to be unique to Black populations. However, available genetic epidemiologic data demonstrate differential distributions of risk factors that are consistent with current environmental and geographic origins. This review summarizes the available evidence and demonstrates that as the exposure to known risk factors for hypertension (eg, excess consumption of salt and calories, stress, sedentary lifestyle, and degree of urbanization) increases among genetically susceptible individuals, the prevalence of hypertension and associated complications also increases across populations of the African diaspora. This observation is true for all human populations. (*Ethn Dis*. 2003;13[suppl2]:S2-53–S2-66)

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Introduction

The prevalence of chronic elevation of blood pressure, and the resulting morbidity, are sufficiently high to justify viewing the condition as a serious global public health problem. Approximately 600 million people worldwide are hypertensive, and three million die annually as a direct result of the condition.[1] High blood pressure (hypertension) is the most common cardiovascular condition afflicting human beings, and the lifetime risk of developing the condition exceeds 50% for most populations.[2]

Hypertension represents the upper quintile of blood pressure distribution in a population.[3] This means that there is no distinct dividing line or criterion separating those with high blood pressure (hypertensive) from those without the condition (normotensive); the proportion of hypertensive subjects in a population is, therefore, arbitrary. The most widely used criterion for identifying hypertensive individuals is that chosen by the World Health Organization: systolic pressure above 160 mm Hg, and diastolic pressure above 95 mm Hg.[4] Pressure values greater than these sharply increase the probability of end-organ damage.[5,6] The 1999 WHO-ISH guidelines recognize that ''high normal'' blood pressure (130/85 to 140/90 mm Hg) also poses a threat to vital organs. Consequently, the guidelines divided hypertension into 3 grades of severity, in harmony with the United States Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).[1] The disability and mortality caused by the hypertension-related damage sustained by the kidneys, brain, and heart, are the factors that make hypertension such a serious public health problem.[5,6] Given the association between hypertension and damage to these vital organs, control of high blood pressure clearly ranks as one of the most important concerns of the public, as well as of healthcare professionals.[1]

The US prevalence rate of hypertension is 25%–33% of the adult population.[7,8] A similar prevalence rate has been found in Europe.[9–11] In Africa,[8,12,13] Asia,[14–16] and South America,[17,18] prevalence rates ranging from 5% to 33% have been documented. While much has been achieved in controlling the incidence of fatal outcomes from hypertension-related diseases in the industrialized world, there are indications that the rate of improvement has peaked, and is now declining.[19–21] The trend in poorer countries is toward increased rates of risk factors for hypertension, including urbanization, smoking, obesity, and type 2 diabetes.[22] The added burdens of infectious diseases, poverty, and poor health care, paint a bleak picture for Africa and its diaspora.

Classifications of Hypertension

The mechanisms underlying approximately 95% of hypertension cases remain unknown, and have proven exceedingly difficult to decipher. These cases with unknown etiology are categorized to as idiopathic, essential, or primary, hypertension.[23] When the specific defect responsible for high blood pressure is known, the condition is generally classified as secondary hypertension.[23] Secondary forms of hypertension make up approximately 5% of all cases of hypertension, and include both Mendelian forms (with specific gene defects), and those forms in which identifiable organ abnormalities are responsible for increased blood pressure. Specific renal, endocrine, neurogenic, and congenital defects, in addition to pharmacological

agents, are known to be responsible for a majority of cases of secondary hypertension.[23] Although its pathogenesis remains unclear, toxemia during pregnancy may be included in this group, because it is a complication of gestation.[23]

Hypertension Due to Single Gene Defects

Mendelian forms of hypertension are due to single gene abnormalities, and considerable progress has been made in the identification of the defects underlying these forms of hypertension.[24] It is interesting to note that the single gene defects identified so far appear to converge on the pathway that regulates salt absorption.[24] Mutations causing glucocorticoid-remediable aldosteronism,[25] syndrome of apparent mineralocorticoid excess,[26] and Liddle's syndrome, all result in increased sodium reabsorption by the kidneys.[27] In all 3 conditions, the increased sodium reabsorption is associated with moderate to severe hypertension. Mutations causing pseudohypoaldosteronism type 1,[28] and Gitelman's syndrome, on the other hand, reduce blood pressure by diminishing renal salt reabsorption.[24,29,30]

Genetic Factors in the Etiology of Primary Hypertension

Unlike the Mendelian forms of hypertension, primary hypertension is a complex trait resulting from the interaction between environmental and genetic factors; epidemiologic evidence suggests a multi-factorial origin.[31–34] The noted complexity, a highly context-dependent phenomenon, makes the search for the underlying pathophysiology of essential hypertension a daunting task. Identification of relevant molecular variants in candidate genes with consistent effects in different populations has met with limited success. However, the influence of genetic variance on blood pressure has been reasonably established. Epidemiological studies suggest that a substantial proportion of inter-individual variation in blood pressure is determined by inherited factors. Population studies controlling for confounding physical and environmental variables, as well as studies of monozygotic and dizygotic twins, including those raised in separate environments, affirm the influence of transmissible factors in the distribution of blood pressure.[31,35–43] Heritability estimates range from 20% to more than 70%. One of the few studies conducted in Africa on familial clustering of blood pressure reported heritability estimates of 45% for systolic blood pressure, and 43% for diastolic blood pressure.[44] A recent report on blood pressure heritability in West Africa was 34% for systolic blood pressure (SBP), and 29% for diastolic blood pressure (DBP).[45] These studies, and several others, provide evidence to suggest that the closer the genetic resemblance of individuals, the closer their blood pressure distribution. Despite the many reports associating various genetic loci with primary hypertension, the genetic component of the condition remains to be quantified. It has become fairly obvious that success in the identification of the factors responsible for, and the processes involved in, the pathogenesis of primary hypertension will require the input of a variety of social and biomedical scientists, as well as the evolution of new ideas and analytical tools.

Epidemiological studies suggest that a substantial proportion of inter-individual variation in blood pressure is determined by inherited factors.

Experimental Models

Animal models of hypertension conclusively demonstrate that high blood pressure has important genetic determinants. Before the discovery of restriction endonucleases, which launched the revolution in recombinant DNA technology, animal breeding experiments provided the best means of studying the direct contributions of genetic loci to the hypertension phenotype. Since then, it has been possible to construct specific mutant genes, introduce them into the germ-lines of animals, and then study their phenotypic effects throughout the life of such chimeric or transgenic organisms. The first successful transgenic animal hypertension model was developed by the introduction of the mutant mouse *Ren*-2 renin gene into the rat genome. Expression of the gene was found to cause severe hypertension in the rats.[46] Similarly, introduction of the rat angiotensinogen gene into the germ-line of mice caused hypertension in the resulting transgenic animals. In this case, the hypertension was apparently caused by over-expression of the introduced gene in the liver and brain.[47] However, experimental models of the genetics of hypertension have made only a limited impact on our understanding of the pathogenesis of the human variety of the condition.

Genetic Models

Although it is accepted that primary hypertension has important genetic determinants, the number and kind of genes involved are unknown. Platt suggested that primary hypertension was linked to a dominant gene with variable penetrance.[48] On the other hand, Pickering was of the opinion that the unimodal distribution of blood pressure in the general population implies that the condition is a polygenic disorder.[49] Lately, Williams and his colleagues have proposed primary hypertension as a multigenic disorder, in which 2 or 3 major gene aberrations, set upon a background of multiple minor genetic aberrations, predispose individuals to primary hypertension.[50] The pattern of blood pressure distribution in the general population suggests that several genes may be

involved in the etiology of primary hypertension.[51,52] Primary hypertension is, as far as we now know, both polygenic (ie, the simultaneous presence of mutations in multiple genes may be required), and heterogeneous (ie, mutations in any of several genes may result in an identical phenotype). It is, therefore, possible for individuals carrying predisposing alleles not to have the condition (incomplete penetrance). The possibility also exists that the condition may be present without predisposing alleles (phenocopy). Overall, the pattern of inheritance of hypertension fits into the autosomal dominant mode with variable expression.[52]

The complex characteristics of primary hypertension, combined with our lack of knowledge about its pathophysiology, have made the search for candidate loci a humbling process. Attempts to determine the genetic basis of primary hypertension have, unfortunately, also led to overtly optimistic interpretations of individual findings that have proved difficult to replicate. None of these findings have brought us any closer to understanding the genetic basis of primary hypertension. It is possible that the various individual findings of linkages and associations with genetic loci reported so far, most of which rely on similar methodology, may, in fact, have nothing to do with the pathologic processes underlying primary hypertension. Some of these findings link primary hypertension with non-coding regions of candidate genes, and these regions have not been demonstrated to have any functional effects on the encoded proteins.[53] Although recent reports have acknowledged the complex nature of primary hypertension, they have often failed to consider this complexity in analytic strategies, paying only scant attention to gene-environment, and/or gene-gene interaction at the analysis level.

As shown by Williams and colleagues, individual genes that demonstrated no association do, in fact, show evidence of gene-gene interactions with associated disease.[54] Even when such interactions are considered, the task of factoring in the nature of such interactions remains, since it is possible for gene-gene interactions, and gene-environment interactions, to be additive in some cases, and synergistic in others.[55] Future models of primary hypertension, and, presumably, other complex disorders, need to account for the potential simultaneous influence of multiple genes, and multiple environmental factors, in the pathogenic processes of primary hypertension.[51,56,57]

INTERMEDIATE PHENOTYPES

Physiological systems involved in the regulation of blood pressure have been identified and understood for some time now; however, it is still not apparent how malfunctions in these systems result in primary hypertension. Consequently, before the availability of genome-wide scanning technology, genetic studies relied on intermediate phenotypes as markers of causative loci. Intermediate phenotypes, or biochemical markers represent crucial steps in the blood pressure regulatory pathway, the malfunction of which may increase blood pressure. Intermediate phenotypes vary considerably, and may range from poorly understood conditions such as "salt sensitivity," to "low-renin," and to specific plasma peptides or proteins, such as insulin and angiotensinogen and complex ligand receptors. Until recently, genetic studies of primary hypertension were based on the assumption that certain biochemical markers (or intermediate phenotypes) are determined by specific gene variants, even when various forms of the gene have not been associated with any functional effect or defect.[53,58] This assumption may partly explain why, despite knowledge of physiology of blood pressure regulation, no robust biochemical markers have been identified for molecular genetic research, or for the purposes of diagnosis and therapeutic intervention.

ENVIRONMENTAL FACTORS

Unlike the results from molecular investigations, higher success rates have been achieved in the identification of important environmental factors in the etiology of primary hypertension, at both the individual and population levels. Some of the major risk factors include psychosocial stress, obesity, salt intake, smoking, alcohol consumption, and level of physical activity.[8,59,60] Research has demonstrated that not all individuals in a high-risk setting develop primary hypertension, which means that the effects of one, or all, of these risk factors on a susceptible individual may vary, depending on the nature of the individual's genetic susceptibility.

Although widely acknowledged as a major risk factor, the systematic quantification of the impact of psychosocial stressors has proven difficult.[61] Nevertheless, several observations suggest that psychogenic arousal can influence vascular tone.[61,62] Factors such as individual personality, socioeconomic status, and the cultural environment, may, in fact, influence the extent to which an individual's cardiovascular system responds to social challenges in the short term, and, perhaps, even in the long term.[63–65] Among populations of African descent, data now exist that show the influence of psychosocial factors on primary hypertension risk in Africa, the Caribbean, and the United States.[61,62,66,67] It has also been consistently observed that ethnic groups living with discrimination, particularly racial discrimination, experience higher blood pressure levels, and, consequently, higher prevalence rates of primary hypertension. Blood pressure distribution in the populations of African descent in South Africa and North America are cogent examples.

It is now widely recognized that obe-

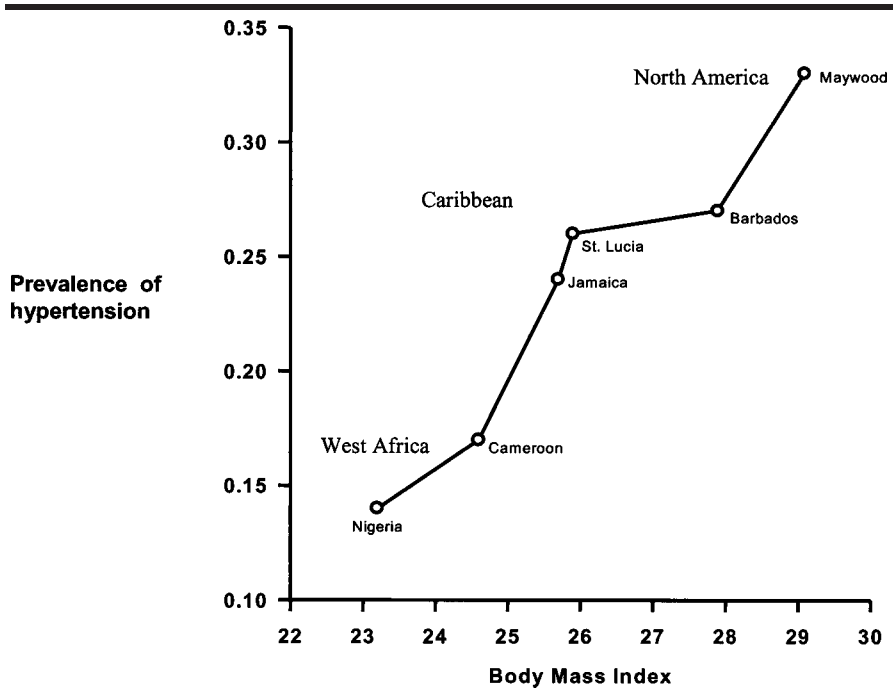

Fig 1. Prevalence of hypertension by mean body mass index (BMI) among populations of the African Diaspora. Adapted from Cooper et al, 1997

sity significantly increases the risk of primary hypertension. The impact of increasing body mass index (BMI) on primary hypertension prevalence has been clearly demonstrated in several populations.[68,69] As shown in Figure 1, Cooper et al demonstrated that the prevalence of hypertension increased monotonically with increasing BMI, across populations of the African diaspora.[8] A similar relationship exists between BMI and type 2 diabetes in the same populations (Figure 2).[70]

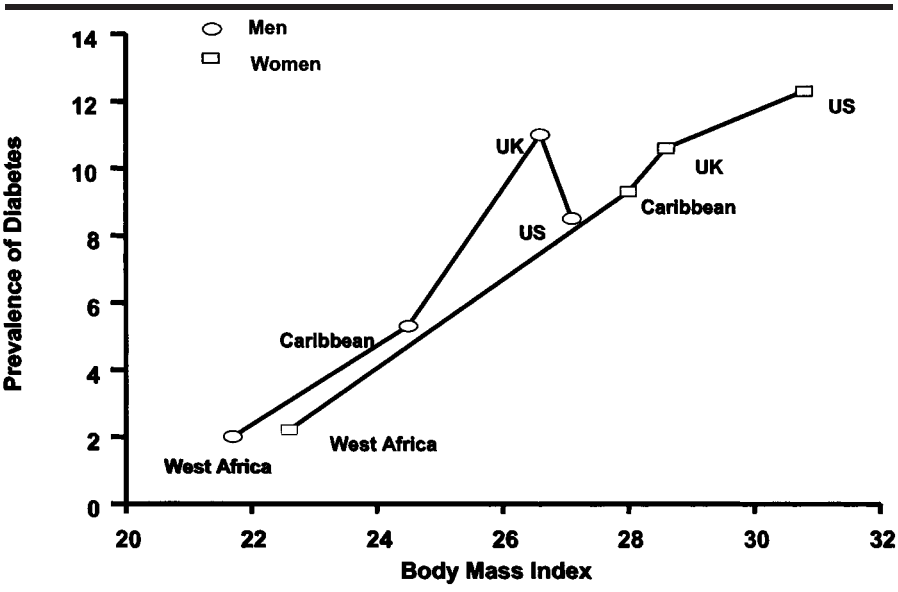

Fig 2. Prevalence of diabetes (type 2) by mean BMI and gender in populations of the African Diaspora. Adapted from Cooper et al, 1997

The powerful effect exerted by salt intake on the pathogenesis of primary hypertension was demonstrated in the 1960s and 1970s. Cruz-Coke observed that among Easter Islanders, blood pressure levels remained low throughout life; however, when members of this population moved to Chile, blood pressure rose to levels similar to those found in the United States.[71] When Polynesians living in a low blood pressure community on the Island of Tokelau migrated to New Zealand, a high blood pressure community, their systolic blood pressures increased over 5 years. No similar increase was recorded in those who remained in Tokelau.[72–74] Poulter and colleagues made similar observations among the Lou who migrated from rural Kenya to urban Nairobi.[75] In addition, blood pressures apparently fall when rural migrants to the city return to their rural environments.[75,76] Analyses of blood pressure in 4 remote populations in the Intersalt study indicated that even a small increase in salt intake was accompanied by a corresponding increase in both systolic and diastolic blood pressure measurements.[77] In an earlier study among 6 Solomon Island populations with similar lifestyles, Page and colleagues found that high blood pressure was virtually absent in all but the one community, which used salt-water for cooking.[78] Recently, Cooper et al demonstrated a clear and consistent relationship between sodium intake and prevalence of primary hypertension in multiple populations of African origin.[8] Based on meta-analysis of data from published reports of blood pressure and sodium intake for 24 different communities (47,000 people) world-wide, Law and colleagues concluded that the association of blood pressure with sodium intake is substantially more pronounced than previously thought.[79]

Though the relationship between salt intake and primary hypertension is

widely recognized, it has been difficult to explain the variations in the effects of salt on individuals. Future discovery of the genetic and pathophysiologic bases of hypertension caused by single gene defects, will, perhaps, enhance our understanding of the role of salt in the etiology of primary hypertension.[24] It is not yet clear, however, whether salt sensitivity predisposes individuals to primary hypertension, or if primary hypertension enhances an individual's sensitivity to the effects of salt on blood pressure.

Although there may be no clear relationship between salt intake, or excretion, and blood pressure, in randomly selected normotensive and hypertensive subjects, a subset of patients, particularly African Americans, with primary hypertension (about 50%) are salt sensitive.[80,81,82] The hypertensive population contains more salt-sensitive individuals than are found in the general population.[83,84] Studies in families have demonstrated that the decreased salt-handling ability commonly found in hypertensives may be inherited.[85] Even the changes in blood pressure following salt restriction show significant familial aggregation, with highly significant sibling-sibling and twin-twin resemblances.[86] However, not all hypertensives are salt sensitive and salt-sensitive hypertensives may not differ from normotensives in their tendency to gain weight and retain sodium in the short term, following salt loading.[87] This fact re-emphasizes the multi-factorial origin of primary hypertension.

The sodium ion is, by no means, the only ion known to influence blood pressure. Again, it is unclear whether other ionic disturbances observed in primary hypertension derive from the perturbation of sodium ion regulation, or independently contribute to chronic increases in blood pressure. However, supplementation with potassium, and, less certainly, calcium, is recognized as an important adjunct in the prevention and control of hypertension.[88] The effects of these ions, and other dietary substances, may be important in the etiology of primary hypertension, as well as in intervention measures, but remain largely ignored, perhaps because of the currency of the salt sensitivity hypothesis.

HYPERTENSION IN PEOPLE OF AFRICAN DESCENT

Despite detailed knowledge of blood pressure control mechanisms, it has not been possible to specify the central physiologic alterations that lead to primary hypertension in any given individual or population. In contrast, variations in hypertension risk among population groups have been detected in a wide range of studies. The excess risk experienced by African Americans is among the most fundamental observations on the distribution of blood pressure in human populations.[89,90] Despite the consistency of the epidemiologic data on ethnic variations in hypertension, relatively little is known about the causes of the ethnic risks. This lack of knowledge has generated much speculation, and has led to many bizarre hypotheses that only serve to reinforce the ideology that there is an essential and inherent difference between the genetic predispositions of people of African ancestry, and people of European descent.[91,92]

Unfortunately, though probably unintended, some of these hypotheses have gained the status of facts in the public's perception, and among health professionals. These untested hypotheses have gained so much currency in the media and medical literature, that they are sometimes received as factual.[93–96] These developments have led to the notion that people of African descent have various unique genetic defects imposed upon them by their peculiar passage into the New World, which make them especially prone to the ravages of high blood pressure. There are even suggestions that primary hypertension in people of African descent may be an entirely different condition from the condition with similar clinical consequences seen in Caucasians.[91–93] However, it is important to emphasize that there is no evidence that people of African ancestry have a unique genetic background predisposing them to a unique type of primary hypertension. Although the proponents of such speculations may not have ill intentions, the manner in which their speculations have been perceived, unfortunately, reinforces certain social prejudices, which can only be detrimental to people of African ancestry, and may obstruct, rather than enhance, scientific progress in this area. Scientific information must be provided, regardless of how it would influence public perception; however, the opinions of investigators do not represent scientific data, and the social consequences of presenting these opinions to the public should be considered. The impact of such speculations on the quality of health care provided to people of African descent, where such care is available, remains to be properly documented. However, there is adequate documentation to prove the existence of disparities in the quality and quantity of health care delivered to members of racial/ethnic minority groups.[97] The real problem facing primary hypertension genetics research is the lack of a coherent hypothesis, based on fact, which can be systematically tested and expanded to include available empiric information. When better hypotheses for primary hypertension are developed, loci and concepts, other than those which are currently available, may form the basis of future research.

Survey results from Africa consistently show that even within groups, the prevalence of primary hypertension increases as the environments in which they live approximates the environment in the Western world, suggesting that the contribution of genetic background to primary hypertension in Africa and Africans elsewhere is not as strong as is

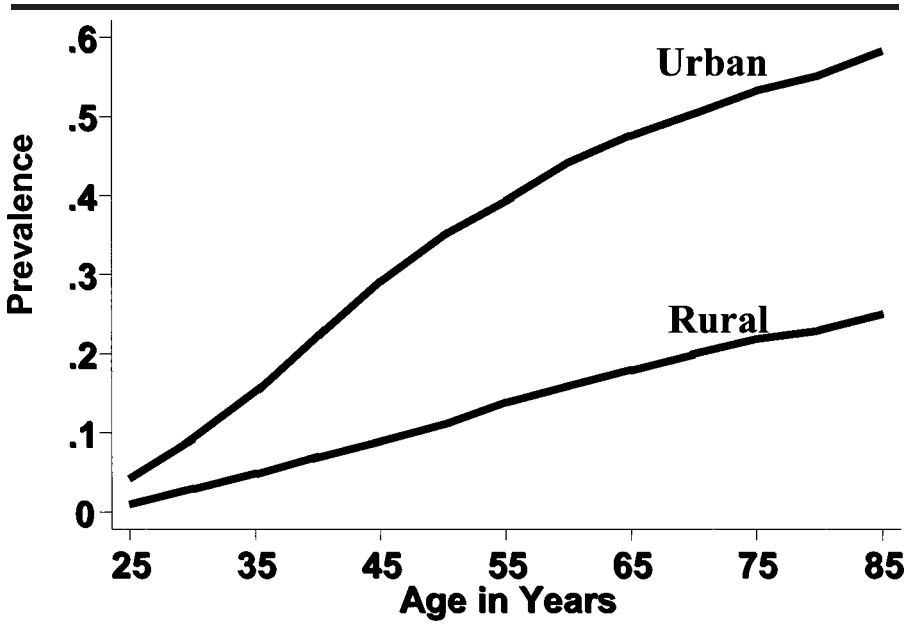

Fig 3. Prevalence of hypertension by age in rural and urban Nigeria. Adapted from Cooper et al, (unpublished data)

often portrayed.[8,98,99,106,107] It is unlikely that a complex condition, such as primary hypertension, will have the simplistic explanations provided by some of the more bizarre hypotheses, which are based on no consistent data, other than the observed excess prevalence of primary hypertension among people of African descent living in the Western world. Maintaining blood pressure is the basis of tissue perfusion, on which biological life depends. Neuronal, endocrinic, psychological, muscular, renal, hematological, and other mechanisms, all play a part in this highly conserved and complex process. The gradual age-related development of primary hypertension suggests that the condition may begin with sequential physiological derangements that occur over time, until a critical stage is attained when the developments become irreversible, inexorably leading to primary hypertension. It is, therefore, more likely that the fundamental basis of primary hypertension in the majority of human beings, regardless of race, will be essentially the same. A certain minimum cluster of genetic aberrations may be necessary to predispose an individual to develop primary hypertension, and this cluster is not likely to vary in any consistent or radical pattern between individuals. It is, however, likely that differential frequency (rather than absence or uniqueness) of these clusters of genes may occur by some "population" grouping, which may not be consistent with current racial or ethnic groupings.

The minimal size of the human genome, and the complex mechanism it eventually controls, makes it highly unlikely that in a polygenic disorder involving hundreds of genes, such as primary hypertension, widely different sets of genes will occur in different people, or that these different sets of genes will follow racial lines. The excess prevalence of primary hypertension among people of African descent living in the Western hemisphere is likely due to the severity of exposure to environmental factors, interacting with a genetic background, which would not necessarily be unique to people of African descent. Genetics, alone, will not explain the excess prevalence of the numerous other medical and social conditions, such as type 2 diabetes, obesity, poverty, higher rates of incarceration and abortions, and lower attainment of higher education, which are found among people of African descent in North America, Europe, and South Africa, nor can genetics alone explain the excess prevalence of primary hypertension.[70,100–104] In essence, the role of genetics in reducing health disparities is highly questionable, and may, indeed, present a distraction from attempts to study and implement effective preventive and control strategies.

EPIDEMIOLOGY

Recent data demonstrate a gradient in risk across the African diaspora, with standardized prevalence rates of 7%–14% in West Africa, and 26% in the Caribbean, compared to 33% in the United States.[8] This pattern parallels the gradient in known risk factors, with obesity, alone, accounting for a third of the excess in the United States, compared to Africa.[8] Within Africa, urbanization, or Westernization, appears to have similarly deleterious effects on the population's risk of developing primary hypertension. This phenomenon is clearly demonstrated in Figure 3. Among the Yoruba people in the Ibadan area, blood pressure increased as adults migrated from rural to urban communities.[105] In South Africa, the level of urbanization determined the extent to which the prevalence rates of primary hypertension increased with age.[98] Similarly, although both urban and rural men demonstrated increased cardiovascular reactivity in response to acute stress, urbanized men showed a greater change (42%) compared to rural men (28%). In addition, among men who were 45 years of age or older, urbanization was associated with a higher risk of developing cardiovascular disease, because their total peripheral resistance reactivity increased the most during the

application of stress.[106] Seedat and colleagues also found the prevalence rate of primary hypertension in urban South African Zulus to be 25%, compared with 16% in a rural Zulu cohort.[107]

Findings from East Africa suggest an almost immediate increase in blood pressure following urbanization.[108] In Tanzania, the prevalence rates of primary hypertension in both rural and urban settings ranged from 20%–33%.[109] An earlier Tanzanian study found the urban prevalence rate of primary hypertension to be 30%, compared to 12% in rural areas.[110] However, in Kenya, also in East Africa, only 6% and 10% of people in rural and urban locations, respectively, were afflicted with primary hypertension.[111,112]

In Cameroon, the urban prevalence rate of primary hypertension was 11%, and about 7% in rural regions, with a preponderance of women being afflicted (18%), compared to men (9%). The same study found 17% and 3% prevalence rates of obesity in urban and rural communities, respectively. Also, levels of physical activity were found to be significantly lower in the urban areas.[12] In the Gambia, where 7.1% had blood pressure measurements of 160/95 mm Hg and higher, and 18.4% had measurements of 140/90 mm Hg or more, the urban prevalence rate of primary hypertension was only slightly higher (by 0.7%), though the urban population had significantly higher systolic and diastolic blood pressure measurements.[113] Some studies have not found any significant difference between urban and rural environments,[114] while others reported higher rural prevalence rates.[115] These wide variations, which are probably due to difference in research methodologies, have been observed in several surveys on the continent.[116,117] However, in primary hypertension, there appears to be a consistent rural-urban gradient averaging about 4%,[12,105,113] and residing in rural Africa south of the Sahara appears to place minimal strain on the cardiovascular system.

GENETICS

The most widely studied genes in the various attempts to isolate the genetic loci responsible for primary hypertension have been those that encode for peptides, proteins, and receptors, which are known to have important physiological roles in blood pressure regulation. The advent of molecular genetics has made it possible to move from speculation to direct measurements of the contribution of the genetic backgrounds of both individuals and groups to observed blood pressure variability. However, it will take time for this technology to provide the required information, because many of the molecular genetic studies undertaken rely on the intermediate phenotype/candidate gene approach, which assumes that the premises of current hypotheses are valid. These studies are also inherently deficient because they investigate gene structure, rather than gene function, in a dynamic system that has a direct effect on all body functions.

Across the African diaspora, genes of pressor systems, including the renin-angiotensin-aldosterone-system (RAAS), and the adrenergic system, have been more frequently studied. However, some studies of people of African descent have investigated possible associations between primary hypertension and genetic loci of counter-pressor mechanisms, such as the atrial natriuretic peptide (ANP), and kallikrein-kinin systems. Reports have also been made from studies of genes that encode for G proteins and subunits of epithelial sodium channels—driven by the hypothesis that people of African descent show greater sensitivity to the deleterious effects of salt, compared to those of European origin.

Earlier studies of polymorphisms of the renin gene, based on observations that people of African descent have "low-renin" hypertension, were largely negative, and that locus appears to have been abandoned altogether.[118–120] The over-used insertion/deletion polymorphism of the angiotensin-1 converting enzyme (ACE) gene is still being investigated as a possible locus for primary hypertension.[121–123] The proliferation of data on this polymorphism is not unrelated to the ease with which it can be detected. Despite the worldwide attention, the physiological relevance of the ACE polymorphism has not been adequately elucidated, though the homologous deletion genotype has been associated with increased levels of ACE, as well as with increased risk of heart disease.[124–127] A collaborative investigation of the angiotensinogen (AGT) gene in siblings from Utah and Paris found both linkage and association between primary hypertension and AGT molecular variants M235T and T174M, which galvanized researchers in this field.[128] However, their results were later inconsistently replicated in other populations. The benefits of the various investigations in this area are hard to assess or justify, as no diagnostic or intervention strategies have materialized.[129,130] That initial enthusiasm has been tempered by the realization that primary hypertension is a rather complex disorder, with complex genetic determinants, for which single gene analyses yield little dividend. Deciphering the genetic basis of primary hypertension may lie just beyond the resolution power of current diagnostic laboratory techniques and statistical considerations. Clearly, new techniques are warranted.

Recently, Nkeh and colleagues reported an association between variants of the atrial natriuretic peptide gene and normal blood pressure.[53] This finding implies that, in South Africans, a certain variation in the structure of the ANP is protective against primary hypertension. However, it is unlikely that a variation in a non-coding part of the ANP gene, which has no physiological relevance and exists at a low frequency, even among hypertensive subjects, would have such a dramatic effect on blood pressure. Earlier studies involving the same ANP locus in people of African

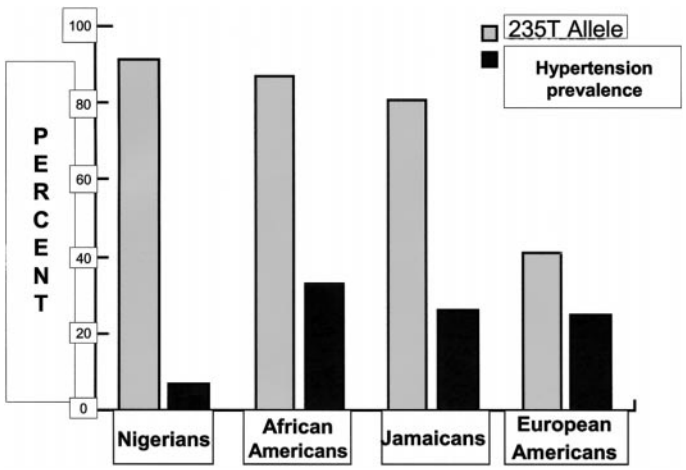

Fig 4. Association between M235T variant of the angiotensinogen gene and hypertension in populations of the African Diaspora. Adapted from Rotimi et al, 1997

ancestry reported both an association, and a lack of association.[131–133] Gene encoding receptors of the Kallikrein-kinin system, a counter-pressor system, have also been studied, and an increased prevalence of the C^{-58} allele was reported in hypertensive African Americans.[134] Associations between polymorphisms of adrenergic loci and primary hypertension have also been found in people of African descent.[135–138]

Dong and colleagues recently reported an association between hypertension and the C825T polymorphism of the G protein beta-3 subunit, in a group of first generation people of African descent in England.[139] This finding was apparently replicated in 3 other studies enrolling subjects of European origin.[140–142] However, as with other candidate gene studies, replications have been inconsistent.[143,144]

Several studies have reported associations between hypertension and molecular variants of the epithelial sodium channel. Investigators in Europe reported associations between primary hypertension and the T594M mutation of beta-subunit of the epithelial sodium channel, in West Africans and African Caribbeans living in England.[145–148] These investigations were based on the assumption that certain features of Liddle's syndrome, such as early onset of high blood pressure, low plasma renin activity, and reduced aldosterone levels, are also features of primary hypertension in people of African descent. The mutations that cause Liddle's syndrome result in increased sodium retention and hypertension, probably by increasing the activity of the sodium channel.[149] Results from a Caribbean cohort demonstrated a lack of linkage evidence between primary hypertension and the 3 subunits constituting the epithelial sodium channel expressed in the distal nephron, in affected siblings pairs.[150]

Contrary to the theory that major genetic changes occurred among African Americans due to the constriction of genetic variability imposed by the harsh and inhuman conditions of the Middle Passage,[151] a study comparing US-born and Africa-born health professionals reported no difference between 3 genetic loci (G-protein, AGT 235, and ACEI/D) that have been previously associated with increased primary hypertension risk in African Americans. Similarly, there were no discernible differences between genetic loci or biological variables, such as plasma renin and ACE activity; although the AGT 235 homozygous T genotype occurred more frequently among Africans.[152] Similar observations were made by Rotimi et al in their earlier analysis comparing allele frequency of AGT 235 in different populations of African descent.[130] As shown in Figure 4, Nigerians, who exhibit the highest frequency of the T allele, also have the lowest prevalence rate of hypertension.[130] The frequency of the T allele has not been significantly altered by the Middle Passage, and does not appear to be relevant to the etiology of primary hypertension in these populations. However, because of the physiologic importance of the renin-angiotensin-aldosterone system, the finding of an association between primary hypertension and angiotensinogen, and as a model system for hypertension research (Table 1), the system continues to receive intense research attention.[130]

Table 1. Comparison of AGT concentration and allele frequency of AGT Gene (M235T and T174M) in control and hypertensive Nigerians*

Variable	Control Subjects	Hypertensive Subjects	*P*†
N	138	116	
Age	54.1 ± 14.1	54.4 ± 11.8	.870
BMI	22.0 ± 4.2	24.1 ± 4.9	.001
Systolic BP	118.0 ± 13.1	162.0 ± 28.7	.001
Diastolic BP	70.6 ± 10.2	96.6 ± 15.1	.001
AGT concentration (ng A-1/mL)	1474.1 ± 417.7	1604.2 ± 374.1	.020
M235T allele, %	90.2	92.2	.419
T174M allele, %	2.8	4.7	.252

* Rotimi et al, 1997.
† *P*, hypertensive subjects vs control subjects.
M = methionine; T = threonine; A-1 = angiotension I.

Among African Americans, an association has been reported between primary hypertension and a microsatellite locus of the 11-beta hydroxysteroid dehydrogenase type 2.[153] Normally, the mineralocorticoid receptor is selectively activated by aldosterone, even though both aldosterone and cortisol have equal affinity for the receptor. The enzyme 11-beta hydroxysteroid dehydrogenase type 2 extensively metabolizes cortisol to cortisone, which has no affinity for the mineralocorticoid receptor. Mutations that result in a loss of function in the enzyme, lead to the syndrome of apparent mineralocorticoid excess (and hypertension), caused by stimulation of the mineralocorticoid receptor by the circulating high levels of cortisol.[55,154]

Current technology allows investigators to move further, from examining single genes in polygenic conditions, to generalized searches across the entire genome for multiples of candidate regions. The hope is that genome-wide scans, which do not make the assumptions inherent in the intermediate phenotype/candidate gene approach, will provide new candidate loci for investigators. Using this approach, Cooper et al recently reported moderate linkage signal of blood pressure to chromosomes 2p, 3p, and 19q, among 792 individuals in 196 Nigerians families.[155] Rice et al reported linkage signals on chromosome 2q, 3p, and 12q, with resting blood pressure, in their HERITAGE family study of 114 African-American, and 99 Caucasian, families.[156] In their multi-center study of the genetic and environmental factors related to hypertension, Wilk et al reported evidence suggestive of linkage on chromosome 4 in both Caucasian, and African-American hypertensive sib pairs, indicating that further investigation in that region may be warranted, in order to locate the gene influencing variability in resting heart rate.[157]

DeWan et al reported strong linkage signal on chromosome 3 with creatinine clearance, a commonly used measure of kidney function, among hypertensive African Americans.[158] This finding, if substantiated, may represent a significant contribution to our understanding of why African Americans seem to suffer a higher rate of kidney diseases as a result of elevated blood pressure.[159,160] However, adequate control for the important influence of differential access to health care, and the existence of multiple co-morbid conditions, must be carefully evaluated before invoking genetic explanations for the observed racial/ethnic differences in susceptibility.

PHARMACOGENOMICS

Current diagnostic, treatment, and preventive strategies, are not likely to halt the growing epidemic of primary hypertension, especially in resource-poor nations. It is hoped that understanding the genetic basis of primary hypertension will provide better understanding of important environmental factors and lead to the design of more effective preventive strategies. It is also anticipated that elucidating the underlying genetic architecture of blood pressure will lead to better diagnosis, and reveal new intervention strategies and novel targets for drugs development, perhaps yielding more specific/individualized therapy. Considering treating primary hypertension with gene therapy, given current knowledge and technology, is, perhaps, overly optimistic.

Many clinical trials are beginning to provide evidence that the treatment of primary hypertension may be optimized by prescribing drugs that follow genetic characterization of individuals. Though still in its infancy, when this effort is developed, it would reduce the tendency to provide health care according to some ill-defined ethnic differences that have no relevance to disease. For example, a Swedish clinical trial found that aldosterone synthase (CYP11B2)-344C/T polymorphism was related in response to irbesartan, but not to atenolol. Patients with the TT variant of this polymorphism showed the greater response.[161] Similarly, a German study also found that the genotype of CYP11B2 predicted response to the angiotensin AT_1 receptor antagonist' candesartan.[162] In addition, monotherapy with amiloride effectively controlled high blood pressure in people of African descent living in the United Kingdom, who exhibited the T594M variant of the epithelial sodium channel (found in 5% of people of African origin).[163] This drug specifically inhibits overactive sodium channels, and effectively controls blood pressure in Liddle's syndrome. However, a study comparing the activity of the epithelial sodium channel using amiloride as an inhibitor, concluded that African Americans may have less epithelial sodium channel activity, compared to their counterparts of European descent.[164]

The results of these molecular genetic studies suggest that, in the future, drug treatment of chronic diseases, such as primary hypertension, will require the input of genetic analysis. In the treatment of certain leukemias in children, genotyping is already mandatory for optimum benefit.[165] Safety and efficacy outcomes of clinical drug trials may also improve when participants' genotypes are utilized, instead of invoking nebulous concepts, such as ethnicity. Working from favorable drug responses in patients known to have a specific cluster of certain genetic polymorphisms may assist in attempts to decipher the pathophysiology of primary hypertension. In the end, the promise of pharmacogenomics is individualized medicine, which may, in the future, allow us to make individually tailored therapeutic treatment decisions.

INTERVENTION

Drugs that work on components of the RAAS, such as inhibitors of the angiotensin-1 converting enzyme, and the receptors of angiotensin II, have made a

significant impact on the management of hypertension and hypertension-related diseases, as have medications that modify renal function, and the activities of the adrenergic system. In fact, investigations into the genetics of hypertension were often driven by knowledge of the effects of these drugs. These, and similar pharmacological agents, will continue to be the mainstay of therapeutic interventions; however, the enormity of the problem posed by primary hypertension requires a multifaceted approach to risk assessment and intervention.

Globally, the WHO-ISH guidelines described excess body fat as the most important factor predisposing individuals to primary hypertension and considered smoking cessation to be the single most powerful lifestyle measure for the prevention of the complications of high blood pressure.[1] Salt intake reduction, smoking cessation or avoidance, weight loss, and increased physical activity, all produce positive, measurable effects on primary hypertension and its complications.[1]

It was recently demonstrated that, with careful implementation, a reduction in salt intake is an effective strategy for lowering blood pressure at the population level. In this study, Adeyemo et al[166] investigated the feasibility of achieving a reduction in dietary sodium intake in free-living individuals, using a dietary intervention among 82 normotensive adults in southwest Nigeria. Participants (49 men and 33 women) received dietary advice on reducing sodium intake, and then maintained the reduced sodium diet for a 2-week period. Blood pressure and 24-hour urinary excretion of sodium were measured at baseline, and after 2 weeks on the reduced sodium diet. Twenty-four hour urinary sodium excretion fell by 76.9 (95% CI 59.7, 94.1) mmol/24 hours among men, and by 79.4 (95% CI 59.4, 99.1) mmol/24 hours among women. On the low sodium diet, systolic blood pressure fell by 4.7 (95% CI 1.9, 7.4) mm Hg among men, and by 7.0 (95% CI 2.6, 11.4) mm Hg among women, while diastolic blood pressure decreased by 1.9 (95% CI −0.3, 4.1) mm Hg among men, and by 1.6 (95% CI −1.8, 5.0) mm Hg among women. These findings led the authors to conclude that it is possible to effect a significant reduction in sodium intake, with simple dietary intervention, in free-living individuals in developing countries.[166]

Given the high cost of hypertension medication relative to income in the developing parts of the world, effective preventive strategies represent the primary hope for reducing the impact of elevated blood pressure on morbidity and mortality. Further studies addressing the implementation of effective preventive strategies are urgently needed in different settings in developing countries.

In the African diaspora, particularly in Africa south of the Sahara, and in the Caribbean, where all the countries are inexorably urbanizing and Westernizing, education to increase awareness of the dangers imposed by certain lifestyle changes is necessary. If the current trend of urbanization combined with lack of awareness continues, the danger for Africa is that its fairly young population will be living in a high-risk environment when it reaches the age at which primary hypertension generally manifests. It is clearly unacceptable that, in certain parts of African, for example, the prevalence of primary hypertension is as high as 33%, while, in others, less than 2% of the population has heard of the condition.[109,167] Awareness and simple preventive measure will be beneficial for the African diaspora, because even when an effective cure is found, it is unlikely that the majority of the people of Africa and its diaspora will benefit in the short term. An effective cure for malaria has been available for more than 50 years, yet the high-risk environment for malaria that exists in Africa south of the Sahara has defied containment attempts.[168,169] Africa is being transformed into a high-risk environment for primary hypertension, and when this is coupled with the high degree of ignorance of risk factors, a cure would have little effect on its ravages, unless the cure is free, widely available, and provides immunity to risk factors.

Evidence exists in several populations that even mild reduction in blood pressure level as a result of reduced salt intake, weight loss, stress reduction, and increased physical activity, significantly reduce the prevalence of hypertension and associated complications.

CONCLUSIONS

As lifespan increases in the African diaspora, long-term efforts must be made to reduce the burden of hypertension. Evidence exists in several populations that even mild reduction in blood pressure level as a result of reduced salt intake, weight loss, stress reduction, and increased physical activity, significantly reduces the prevalence of hypertension and associated complications. Though seemingly simple, implementing these lifestyle changes, especially in urban settings, has proven to be quite difficult in all human societies.

It is anticipated that the growing success in understanding the genetic backgrounds leading to susceptibility or resistance to complex diseases, including hypertension, will facilitate the development of more effective and efficient preventive and control strategies. In ad-

dition, these successes at the molecular level may, in the long run, lead to the development of less expensive drugs with fewer side effects. In the end, genetic epidemiology promises to help us understand how different genetic backgrounds interact with various environmental factors, to increase, or decrease, individual susceptibility to common complex diseases.

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