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Influence of genetics and genomics on the treatment with antihypertensive diuretics

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ABSTRACT

Introduction: arterial hypertension is considered a worldwide health problem. Several pharmacological studies report adverse effects associated to the influence of genetic and genomic component in antihypertensive drugs, based on the use of the principles of pharmacogenetics and pharmacogenomics. Objective: to describe the influence of the genetic and genomic component in the treatment with antihypertensive diuretics. Method: a literature review was conducted from April to May 2021. The available resources in PubMed/MEDLINE and SciELO were used. Of 32 references found using the health sciences descriptors, 29 bibliographic references that met the selection criteria were consulted. Development: genetic variants that impair drug-receptor interactions or subsequent intracellular signaling can change pharmacodynamics and drug efficacy. The effects of diuretics are made through different mechanisms; several candidate genes have been suggested to influence individual responses to these drugs. Improvements in blood pressure in response to hydrochlorothiazide treatment have been observed in GC genotype carriers compared to CC genotype carriers. Conclusions: genetic polymorphisms influence the response to diuretic antihypertensives since they intervene in salt sensitivity and plasma renin concentrations. Better antihypertensive responses are evidenced in individuals carrying the AA+AG genotypes compared to GG carriers.

Keywords: Antihypertensives; Adverse events; Diuretics; Genes; Pharmacogenetics.

Arterial Hypertension (HT) is considered a modifiable risk factor that frequently leads to cardiovascular complications. According to estimates, more than 116,4 million people worldwide suffer from this condition, which is associated to 203 deaths everyday[1].

The treatments currently used in patients with arterial hypertension can be pharmacological and non-pharmacological; the first one includes the use of hypotensive drugs and it consists of a stepwise therapy that starts with low doses of a drug, to which another drug will be added successively according to need; the latter is aimed at reducing those factors that can raise blood pressure[2].

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The current therapeutic arsenal of antihypertensive drugs is very broad and diverse. There are six main groups of agents for the treatment of hypertension: beta blockers, alpha blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and diuretics[3].

Diuretic drugs are classified into three groups: loop or high-ceiling diuretics, potassium-sparing, thiazides and related drugs; these do not act directly on body water, but through sodium (natriuretic diuretics) or osmolarity (osmotic diuretics), helping the human organism to eliminate excess fluid and salt, thereby causing the kidneys to produce urine. These drugs are used worldwide and particularly in Cuba on a large scale[3,4].

While certain demographic factors such as age, sex, and race can help guiding the selection of an antihypertensive agent over another, to a large extent the strategy that patients receive is based on trial and error. Human genome sequencing was identified in 2003[5], a medical breakthrough that ushered in the hope of an individualized HT treatment approach for patients.

Single nucleotide polymorphisms (SNPs) are the most frequent variation in the human genome, consisting of the presence of two or more different nucleotides (alleles) at the same position in

general population. Some alleles can affect the amount or function of the protein encoded by the gene. Therefore, some alleles may be of functional relevance, as they may affect the amount and/or activity of gene products in cells, and may change the pharmacokinetics or pharmacodynamics of the drug depending on the individual genotype[5].

Pharmacogenetics is the study of the effect of genetic polymorphisms on pharmacological response and adverse effects; on the other hand, pharmacogenomics is a broader term used to describe all the genes in the genome that may affect drug response[6]; although pharmacogenomic studies have not yet been widely reported for antihypertensive drugs.

Genomic studies have confirmed that genetic factors are related not only to blood pressure (BP) elevation, but also to interindividual variability in response to antihypertensive treatment. Due to the polygenic nature of hypertension, a single drug cannot be used as a relevant clinical target for all individuals[6]; therefore, the analysis of complex traits, such as drug response phenotypes, must involve the assessment of multidrug interactions.

The low efficacy of some therapies could be related to interindividual genetic variability. In fact, genetic studies of families have suggested that heritability represented 30 % to 50 % of the interindividual variation in BP7, so the aim of the present review article is to describe the influence of the genetic and genomic component on treatment with diuretic antihypertensives.

METHOD

A literature review was carried out in the period from April to May 2021. The evaluation included theses published in repositories, as well as articles from national and international journals. The search was carried out in PubMed/MEDLINE and SciELO databases.

The consultation was performed under the terms (according to the Health Sciences Descriptors) "Antihipertensivos", "Diuréticos", "Farmacogenética", "Genes" and "Efectos adversos" for Spanish; for English "Antihypertensive Agents", "Diuretics", "Pharmacogenetics" and "Adverse Effects" were used.

Two search strategies were used, one for Spanish: [(Antihipertensivos) AND (Diuréticos)] AND [(Farmacogenética) OR (Genes)] AND (Efectos Adversos); and another for English: [(AntihypertensiveAgents) AND (Diuretics)] AND [(Pharmaconetics) OR (Genes)] AND (Adverse Effects); once the search was carried out, 51 journal articles were found.

For their use, the publications found were subjected to the inclusion criteria of the review (relevance to the subject matter of the study, describing the influence of genetics and genomics on treatment with diuretic antihypertensives).

Complying with the characteristic of being novel, having been published between 2017-2021 and being review articles, original articles, case presentations, theses. Those published prior to 2017, that did not address the influence of genetics and genomics on treatment with diuretic antihypertensives, as well as letters to the editor and editorials, were excluded.

DEVELOPMENT

Adverse cardiovascular outcomes and BP reduction by the use of available antihypertensive drugs are largely characterized by interindividual variability, for which the underlying causes are not fully elucidated and few consistent predictors have been identified[8].

Differences in drug response among individuals may be explained by the amount of drug reaching its receptor (pharmacokinetics) or by differences in response triggered by drug-receptor interactions (pharmacodynamics)[8]. Genetic variants that affect absorption, distribution, metabolism, and elimination, can alter pharmacokinetics and thus drug response and toxicity.

In addition, genetic variants that impair drug-receptor interactions or subsequent intracellular signaling can change the pharmacodynamics and drug efficacy[8].

Diuretics, especially thiazide types, are the first-line drugs for most patients with hypertension. The thiazide diuretic hydrochlorothiazide inhibits the sodium chloride cotransporter expressed in the distal convoluted tubule of the nephron[9].

The initial antihypertensive effects of these drugs involve increased sodium excretion (natriuresis) and decreased extracellular volume, resulting in reduced cardiac output. In addition, these drugs exert long-term adverse effects through a decrease in vascular resistance[9].

Each nephron segment has specialized mechanisms in its epithelium for the transport of certain ions; therefore, diuretic action in a given segment will cause a characteristic pattern of water and electrolyte elimination and vice versa, from a pattern of ionic elimination it is possible to deduce, at least approximately, the segment where the diuretic acts[9].

The effects of diuretics are carried out through different mechanisms, and several candidate genes have been suggested to influence individual responses to these drugs[10].

The efficacy of hydrochlorothiazides (HCTZ) used in monotherapy may be reduced by factors associated to interindividual variation, leading to an increased mortality among patients with uncontrolled hypertension[10].

Thiazides may cause hypokalemia, alter glucose tolerance, or increase serum cholesterol and uric acid levels; susceptibility to adverse reactions[10] may also be related to interindividual variation, age, sex, and ethnicity.

Singh *et al*.[11] claim that single nucleotide polymorphisms (SNPs) within 3-hydroxy-3-methylglutaryl-COA synthase (HMGCS) in African Americans and Caucasians are associated with elevated blood glucose levels after treatment with chlorthalidone and HCTZ.

On the other hand, Carey *et al*.[12] report that the ADD1 gene encodes α-adducin, which is a cytoskeleton- related protein that modulates ion transport. Their study further revealed that polymorphisms within the angiotensin converting enzyme (ACE) inhibitor and sterol regulatory element-binding protein 1 (ADD1) genes affected BP responses to HCTZ.

In their study, Eadon *et al*.[13] demonstrate a significant relationship between angiotensin-converting enzyme II (ACE II) genotypes and the DD genotype; thus, changes in BP were evidenced. They also demonstrated that carriers of genotype II showed better antihypertensive responses to HCTZ than those carriers of the DD genotype itself.

A study by Surendran *et al*.[14] in Chinese population revealed that this polymorphism modulated HCTZ responses in each sex. In men, carriers of the DD genotype, the effects of antihypertensive therapy were better than those in women, carriers of the ECA II genotype.

However, other studies did not demonstrate such relationship. In a GenHAT (Genetics of Hypertension Associated Treatments) study, several candidate hypertension-related genes were analyzed in individuals to determine the possible variants of six genes that affect antihypertensive drug response[15].

The results indicated that the DD genotype does not influence BP reduction or cardiovascular outcomes in patients on ACE inhibitors treatment compared to the ID and II alleles. For the ADD1 Gly460Trp polymorphism, a considerable relationship was revealed for the GliGly vs. GlyTrp and GlyGly vs. TrpTrp genotypes[15].

Another study by Morrell *et al*.[16] indicates that carriers of the Trp allele for the Gly460Trp polymorphism in the ADD1 gene have decreased basal plasma renin activity and improved antihypertensive responses to HCTZ treatment compared to Gly/Gly homozygotes. These studies suggested that this polymorphism (rs4961) could modulate renal sodium handling by changing ion transport across the cell membrane.

Manosroi *et al*.[17] claim the presence of the T allele for the C825T polymorphism (rs5443) in the GNB3 gene and that it is associated with the formation of an RNA splice variant lacking nucleotides 498-620 within exon 9, resulting in structural modifications of the β3 subunit of the G protein and modulation of signal transduction.

They jointly indicated that GNB3, which encodes the β3 subunit of the G protein, is another gene possibly involved in responses to HCTZ treatment[17]. This family of proteins is involved in the signals transduction from membrane receptors to a wide range of intracellular effectors.

In a study by Louca *et al*.[18], it was found that the T allele is related to improved antihypertensive responses to HCTZ and that this effect is related to gene dose. Since a larger study provided conflicting results, the relation between the rs5443 polymorphism and hydrochlorothiazide responses requires confirmation.

Williams *et al*.[19] reports that the effects to four classes of antihypertensive diuretic drugs, including HCTZ of the SNPs in male patients of European descent, more than 80 different polymorphisms were identified. However, they found a significant relation only for the aldehyde dehydrogenase member 1 and the chloride intracellular channel 5 (CLIC 5).

Magvanjav *et al*.[20] suggested that two other ADH gene family members (ALDH1A2 and ALDH7) are related to hypertension in African Americans, whereas ALDH2 was associated with BP control in an East Asian population. Their genomic association analysis verified a relationship between the SNP rs261316 in the ALDH1A2 gene and uncontrolled BP after treatment with a thiazide diuretic / β-blocker combination in white patients.

In African American populations, SNPs within the lysozyme (LYZ) fibroblast growth receptor substrate 2 (FRS2) genes located on chromosome 12q15 were shown to exert an effect on the HCTZ response[21].

In the study by Ferdinand *et al*.[21], it was shown that African Americans carrying the ATC haplotype a combination of alleles for SNPs rs317689 (A), rs315135 (T) and rs7297610 (C) respond to HCTZ much better than in people with ACT or ATT haplotypes.

However, the study by Sá *et al*.[22] found that the ATT haplotype in the African American population was also associated with a good HCTZ response. Furthermore, a reduced expression was observed in African Americans who were CC homozygotes for the SNP rs7297610, but not in T carriers, implying a relation between the variant expression of

African Americans and HCTZ response.

The results of the study by Tu *et al*.[23] on BP response to hydrochlorothiazide in white hypertensive individuals reported a strong correlation between hydroxy-delta-5-steroid dehydrogenase, 3β- and the steroid δ-isomerase 1 (HSD3B1), and BP response.

Studies also demonstrated the relationship between the genetic variants in HSD3B1 and the variation of HT or BP because HSD3B1 encodes the enzyme 3β-hydroxysteroid dehydrogenase[23], which is of key importance in the biosynthesis of endogenous aldosterone and ouabain.

In the studies of Christian *et al*.[24], the CC genotype at rs6203 was associated with hypertension or higher BP values. In turn, he demonstrated that a genetic polymorphism (rs4149601G/A) in the neural precursor cell expresses, developmentally regulated 4-like, E3 ubiquitin protein ligase (NEDD4L), which led to the formation of a cryptic splice site in NEDD4L[24].

The results of the study by Ma *et al*.[25] study, involving Caucasian hypertensive patients found that the presence of the G allele upregulated the epithelial sodium channel (ENaC) and further increased sodium retention/reabsorption in the distal nephron, along with the development of hypertension. In addition, the authors found a relationship between the G allele and a greater BP lowering response to HCTZ compared to AA homozygotes.

Carey *et al*.[26] confirm that white hypertensive carriers of cumulative copies of the GC haplotype of the NEDD4L gene (for SNPs rs4149601 and rs292449, respectively) responded better to hydrochlorothiazide. These observations were not replicated in African Americans. Therefore, more research is needed to determine whether treatment decisions in patients with HT could be based on the analysis of this polymorphism.

They also demonstrated in the study by Loganathan *et al*.[27] that, in Americans and Europeans, systolic and diastolic responses of BP to HCTZ treatment were consistently higher in GACAA genotypes carriers than in homozygous GG genes carriers.

They found that, in Caucasian population, BP response to HCTZ monotherapy has also been found to be related to SNPs within the Adapter Protein SH2B 3 gene (SH2B3 — rs3184504), fibroblast growth factor 5 (FGF5 —Rs1458038) and Early Cell Factor B (EBF1 — rs45551053)[27].

The first SNP mentioned above was shown to be related to higher BP values and increased risk of HT in Caucasian individuals. Furthermore, CC genotype carriers responded better to antihypertensive drugs (especially atenolol) than to other genotypes (TT and TC)[27].

Variants affecting antihypertensive responses to HCTZ further revealed that rs2273359 within the EDN3 region significantly modulate the systolic BP (SBP) response to HCTZ27.

Oliveira-Paula *et al*.[28] observed improvements in BP in response to HCTZ treatment in GC genotype carriers compared with CC genotype carriers. The PEAR and PEAR-2 studies suggested that antihypertensive response to thiazide diuretics may be related to genetic variants of protein phosphatase 1, regulatory subunit 15A (PPP1R15A), dual specificity phosphatase 1 (DUSP1), and murine osteosarcoma viral oncogene homologue (FOS).

In those that responded best to HCTZ or chlorthalidone, an upregulation in the transcription of the aforementioned genes was observed. In turn, response to HCTZ treatment was evaluated in Caucasian individuals with SBP> 140 mmHg and diastolic BP (DBP)> 90 mmHg without prior treatment, revealed six variants that are predictive of the SBP response and five variants predictive of DBP[28].

The strongest effect on the SBP response was observed for polymorphisms within TET2 and two SNPs in CSMD1. CSMD1 belongs to the 13C-associated vacuolar protein family with the classification, whereas TET2 is involved in the aENaC gene transcription in the renal collecting duct[28].

Padmanabhan *et al*.[29] claim that genome and transcriptomic analyses revealed that the SNP rs10995 in the VASP gene (encoding vasodilator-stimulated phosphoprotein) is a functional SNP associated with hydrochlorothiazide responses; thus, the G allele for this SNP was shown to be related to increased BP response to hydrochlorothiazide and increased expression of the VASP messenger ribonucleic acid (mRNA).

Despite these difficulties, a simplified pharmacogenomic approach to ensure that hypertensive patients receive the most effective, efficient, and well-tolerated drug regimen would be helpful. This would result in fewer patient visits for medication readjustment and better compliance with its medical regimen.

Better BP control would lead to fewer cardiovascular and renal complications, as well as improved life quality and longevity of hypertensive patients.

Demonstration of such improved results in clinical trials would be a powerful stimulus to bring pharmacogenomics to clinical use in patients with HT and fulfill the promise of personalized medicine.

CONCLUSIONS

Genetic polymorphisms influence the response of diuretic antyhipertensives since they intervene in

salt sensitivity and plasma renin concentrations. Better antihypertensive responses are evidenced in individuals with AA + AG genotypes compared to GG carriers

AUTHORSHIP

EALE: conceptualization, project administration data curation, formal analysis, investigation. LRMD y MARA: writing-review & editing, original draft, investigation.

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Influencia de la genética y la genómica en el tratamiento con antihipertensivos diuréticos

RESUMEN

Introducción: la hipertensión arterial es considerada un problema de salud a nivel mundial. Varios estudios farmacológicos reportan efectos adversos asociados a la influencia del componente genético y genómico en los antihipertensivos basados en la utilización de los principios de la farmacogenética y farmacogenómica. Objetivo: describir la influencia del componente ge-

nético y genómico en el tratamiento con antihipertensivos diuréticos. Método: se realizó una revisión bibliográfica en el periodo de abril a mayo de 2021. Se utilizaron los recursos disponibles en PubMed/MEDLINE y SciELO. De 32 referencias encontradas mediante los descriptores en ciencias de la salud, se consultaron 29 referencias bibliográficas que cumplieron los criterios de selección. Desarrollo: las variantes genéticas que perjudican las interacciones fármaco-receptor o las señales intracelulares posteriores pueden cambiar la farmacodinamia y la eficacia del fármaco. Los efectos de los diuréticos se realizan a través de diferentes mecanismos, se han sugerido varios genes candidatos para influir en las respuestas individuales a estos fármacos. Se han observado mejoras en la presión arterial en respuesta al tratamiento con hidroclorotiazida en los portadores del genotipo GC en comparación con los portadores del genotipo CC. Conclusiones: los polimorfismos genéticos influyen en la respuesta de los antihipertensivos diuréticos, ya que intervienen en la sensibilidad a la sal y las concentraciones plasmáticas de renina. Se evidencian mejores respuestas antihipertensivas en individuos portadores de los genotipos AA+AG en comparación con los portadores de GG.

Palabras clave: Antihipertensivos; Diuréticos; Eventos adversos; Farmacogenética; Genes.