JOURNAL OF PHARMACEUTICAL ANALYSIS

MODIFIABLE NON-GENETIC FACTORS ASSOCIATED WITH ADHERENCE TO ANTIHYPERTENSIVE DRUG THERAPY

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1. Abstract

Background: Adherence to pharmacological treatment is considered a public health problem, so it is necessary to identify the factors and variables of each patient, to develop strategies that improve adherence.

Aims: to examine the relationship between adherence profiles and sociodemographic factors and their association with medication adherence in patients with hypertension.

Methods: Methods: Cross-sectional study in hypertensive patients from the HTA program at the Chía clinic, Colombia. Adherence to medications was assessed using the Morisky-Green (MMAS-4) instrument and the Bonilla (BT) test, and some variables from the clinical history. A descriptive and bivariate analysis was performed to determine the assessment between variables and adherence. The nonparametric Mann-Whitney U test was used for continuous variables, while the chi-square test was used for categorical variables. All tests were performed with an alpha level of 0.05 and a $p < 0.01$.

Results: Results: The sample consisted of 116 patients, the majority being over 60 years of age (71%), with a predominance of females (70%), with a high level of involvement in domestic responsibilities (50%), living in urban areas (61%), belonging to a low socioeconomic stratum (72%), with income below the Colombian minimum wage (equivalent to 323 dollars, 64%), with complete secondary education (58.77%). The majority are married (43%). Regarding TMG, the prevalence of non-adherence to treatment was 58.62%. In the case of TB, the prevalence of risk of

non-adherence was 65.62%. No significant association was found between the variables evaluated and lack of adherence.

Conclusion: The results indicate no notable correlation between the sociodemographic variables and the lack of adherence to treatment in hypertensive patients. However, a considerable proportion of hypertensive patients need to adhere to their treatment regimens. Consequently, further research is necessary to elucidate the underlying factors contributing to this non-adherence and to develop effective strategies to address these challenges.

2. Keywords: Hypertension; Medication Adherence; Modifiable Factors; Antihypertensives

3. Introduction

High blood pressure (hypertension) is a chronic disease that represents one of the most significant public health problems. According to the WHO, there are an estimated 1.13 billion people with hypertension worldwide, and most of them (about two-thirds) live in low- and middle-income countries. In addition, only 1 in 5 people with hypertension have the problem under control[1]. In the Americas, the prevalence of HTN is 36.3%; in the Colombian population, it is estimated at 24%; it is more common in men, with a proportion of 29%[2,3]. This condition is associated with a higher probability of coronary events, which are one of the leading causes of death[4]. The lack of medication adherence, the low effectiveness of some therapies, and the heterogeneity of patient responses to antihypertensive treatment may also be related to interindividual genetic variability. Recent studies indicate that the heterogeneity of patient responses to antihypertensive treatment is, at least in part, genetically determined, accounting for 30 to 50% of the interindividual variation in response to antihypertensive treatment[5]. The hereditary pattern of complex traits (non-Mendelian inheritance), multifactorial and polygenic, emerges because of the interaction between environmental risk factors and specific genetic susceptibility[6].

Non-modifiable risk factors are inherent to the individual, including sex, race, age, and heredity. In contrast, modifiable risk factors can be avoided, reduced, or eliminated[7]. Among the non-genetic factors that contribute to the development of hypertension, environmental and lifestyle factors have been identified as key influences. These factors can be social, familial, economic, an understanding of the illness, behavioral treatment, and even those surrounding the health system. Conversely, the patient's context and recognition of their potential limitations must be considered. It may be necessary for them to adhere to the established treatment plan. One of the most significant challenges currently facing clinical pharmacology is the substantial interindividual variability observed in the response to medications, both in effectiveness and toxicity. Additionally, more knowledge should be given regarding the medication and its use (adherence). Adherence is the extent to which an individual's behavior in following prescribed treatment (pharmacological treatment, psychotherapy, lifestyle changes, etc.) aligns with the recommendations agreed upon with a healthcare provider[8]. It is concerning that only 54% of hypertensive adults in developed countries are adherent to treatment and that the rate of blood pressure (BP) control may be even lower, with only one-third of adults achieving target BP despite targeted therapy; this is by the guidelines[3]. The control of blood pressure levels through non-pharmacological measures, such as modifications in lifestyle and antihypertensive pharmacological treatment, can reduce the

progression to cardiovascular diseases, which can result in premature mortality, disability, and significant economic and social costs[9].

In addition, when HTN is treated with multitherapy (including diuretics, beta-blockers (BB), angiotensin II converting enzyme inhibitors (ACEI), angiotensin receptor antagonists (ARB), calcium channel blockers (ACa), and alpha-blockers (alpha B)[9,10] a lack of control and poor adherence to pharmacological treatment has been demonstrated, In the best-case scenario, 50% of patients benefit from one of the available medications and achieve the treatment goal[11]. Therefore, despite the wealth of information in the literature that identifies initial pharmacologic and non-pharmacologic treatment, many patients still need more blood pressure control. According to the WHO, there are five factors. The main ones related to adherence are socioeconomic factors, factors related to the health system and its professionals, factors related to the treatment, the pathology, and the patient[12]. Investigations that allow for the primary identification of risk factors that subsequently promote person-centered activities and interventions with the integration of health professionals based on precision from a multifactorial approach with the integration of genetic and non-genetic factors facilitate a closer approach to the needs of patients and, therefore offer interventions with greater possibilities of success by jointly considering strategies that optimize therapeutic efficacy and compliance. In addition to the biological and hereditary factors contributing to an individual's risk for chronic disease, lifestyle habits, and economic interests must be considered as potential triggers for conditions such as high blood pressure[13]. These modifiable factors, which can be addressed through lifestyle modifications and other interventions, are in addition to the previously mentioned risk factors. In addition, two fundamental aspects that significantly influence health must be considered: the patient's compliance and adherence to a prescribed therapeutic regimen[14]. The objective of the present study is to analyze adherence to pharmacological treatment and the modifiable non-genetic factors that can influence the antihypertensive pharmacological therapeutic response of patients attending primary care outpatient clinics.

4. Participants and Methods

A cross-sectional study with an analytical component was carried out where adherence to antihypertensive pharmacological treatment and its association with modifiable non-genetic risk factors that can influence the antihypertensive pharmacological therapeutic response was determined in patients who attended an outpatient clinic in a primary care entity in the municipality of Chía Cundinamarca Colombia; located in the central savanna 10 km north of Bogotá, with a population of 160,435 inhabitants, being the fourth most populated municipality in Cundinamarca. A sample size was calculated using simple random sampling in the epidemiological software EPIDAT version 4.2. The data from the high-risk account were taken as a reference, and the latest statistics were used, which estimated that in Colombia, the number of hypertensive patients diagnosed and controlled in 2021 was 4,890,174. A 95% reliability level and a 5% precision were established for the Chía municipality estimate, which included at least 116 patients diagnosed with primary arterial hypertension and currently undergoing first-line antihypertensive treatment (ACEI, ARA, CA, BB, thiazides). The inclusion criteria were as follows: older adults diagnosed

with primary arterial hypertension who were attending the HBP primary care program at the Chía Clinic and who had been under treatment for a minimum of one month with a medical indication for the consumption of oral antihypertensive drugs. Additionally, they had to be on the first line of treatment and have previously consented to participate in the study. Patients with other chronic pathologies or disability that prevented them from following treatment and responding appropriately to the study scales, as well as institutionalized and bedridden individuals, such as pregnant women and women with preeclampsia, were excluded from the study. Data collection was conducted at the clinical institution when patients were scheduled to attend the HTA program by research assistants who had undergone prior training.

Instruments previously validated in similar studies were employed to assess treatment adherence. The Morisky-Green test (MGT) 4-item version (MMAS-4) (Table 1) comprises four questions that evaluate various aspects of the patient's behavior about medication adherence. These questions aim to assess the frequency and consistency with which a patient adheres to medical instructions regarding their medication. Each question is answered with a binary response of "yes" or "no." A score is assigned based on the response provided. The total score may vary, but a higher score typically indicates reduced adherence to the treatment regimen. The second instrument is as follows: The "actors that influence adherence to pharmacological and non-pharmacological treatments" instrument, as proposed by Bonilla and De Reales (BT), has been modified by Ortiz and comprises 24 items distributed across four dimensions: socioeconomic, related to the provider, related to therapy, and related to the patient. The following demographic variables were included: age, sex, place of residence, socioeconomic stratum, membership status, occupation, education, family support, marital status, and income. Medical diagnoses, consumption, frequency, and habits in taking antihypertensive medications were also taken from the clinical history. The procedure carried out to collect the data is presented in (Figure 1).

Question	**Score**	
1. Do you ever forget to take your medications to treat your illness?	Si= 0	No= 1
2. Do you take your medications at the prescribed times?	Si= 0	No= 1
3. When you feel well, do you stop taking your medication?	Si= 0	No= 1
4. If it ever makes you feel sick, do you stop taking it?	Si= 0	No= 1

Table 1: Morisky Green Medication Adherence Scale (MMAS-4)[34]

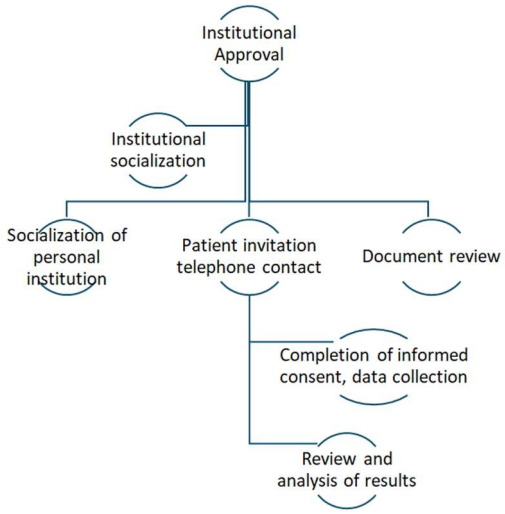

Figure 1: Flowchart for methodological development and data collection.

5. Analysis of data

A descriptive analysis was conducted, employing measures of central tendency, such as the mean and median, and dispersion, including the standard deviation and interquartile range, for the quantitative variables. For qualitative variables, both absolute and relative frequencies were calculated. A bivariate analysis was conducted to ascertain the relationship between the variables of interest. The nonparametric Mann-Whitney U test was employed for quantitative variables, while the chi-square test was utilized for categorical variables. All established hypothesis tests were conducted with an alpha level of 0.05. The data were processed and analyzed using Jamovi statistical software, version 2.3.

6. Results

(Table 2) presents a summary of the sociodemographic characteristics of the participating population. Of the 114 patients interviewed, the population over 60 years of age was the most represented (71%), predominantly female (70%), engaged in domestic activities (50%), residing in urban areas (61%), and belonging to a socioeconomic stratum classified as low. It was composed mainly of women (70%) who resided in urban areas (61%) and who belonged to a low socioeconomic stratum (72%). Additionally, 64% of the population had an income less than the Colombian minimum wage, equivalent to 323 dollars. Regarding education, 58.77% of the population had completed secondary schooling. Most of the population was married (43%), had functional independence (80%), and was engaged in clinical activities without requiring assistance (81.0%) or support from a caregiver (61%). Many patients (78.45%) are affiliated with a contributory social security system. The most prevalent morbidities were related to the osteoarticular (33.02%), endocrine (27.6%), and cardiovascular (24.11%) systems. The population surveyed reported at least one additional health problem beyond HTN (Table 3).

Variables	Quantities (n=116)	%	SD
Age (years)			
Between 20 and 39	7	5,3 %	16.1
Between 40 and 59	27	23,7 %	
≥60	82	71,1 %	
Gender			
Masculine	35	30 %	0.46
Feminine	79	70 %	
Residence			
Urban	70	61 %	0.48
Farm	44	39 %	
Housing stratum			
Stratum 1	1	0,8 %	
Straturm 2	82	72 %	
Stratum 3	30	26,4 %	
Stratum 4	1	0,8 %	
Type of coverage in Unified Health System			
Contributory	89	78 %	0.41
Subsidized	25	22 %	
Occupation/Profession			
Employee	21	18.2 %	1.19
Freelancer	20	17.2 %	
Student	3	2.6 %	
Housewife	56	50 %	

Other	14	12 %	
Monthly household income (n. minimum wages)			
More than 3 minimum wages	1	0,8 %	0.69
Between 1 and 3 minimum wages	10	8.7 %	
1 minimum wage	30	26.5 %	
Less than 1 minimum wage	73	64 %	
Marital Status			
Married	49	43 %	1.39
Separated	6	5.3 %	
Single	25	22 %	
Common-law marriage	13	11.3 %	
Widower	21	18.4 %	
Help to get around			
Always need someone's help	6	5 %	0.72
Need help frequently	17	15 %	
Doesn't need help	93	80 %	
Caregiver support			
Yes	41	39 %	0.48
No	71	61 %	
Education			
Does not know	3	2.6 %	1.70
Complete primary education	22	18.7 %	
Complete high school	67	58.7 %	
Technical/technological	10	8.7 %	

University	11	9.6 %
Postgraduate degree	2	1.7 %

Table 2: Distribution of sociodemographic and economic variables of the users of the Chia clinical hypertension program.

Medical diagnoses	**Quantities (n=116)**	**%**
Endocrine		
Hypothyroid	9	10.64
Hyperthyroidism	3	3.57
Diabetes mellitus type II	12	13.36
Osteoarticular		
Osteoarthritis	14	16.07
Arthritis	5	5.36
Osteoporosis	7	8.04
Epicondylitis	2	1.79
Rotating Cuff	2	1.79
Cardiovascular		
Acute myocardial infarction	2	1.79
Stroke	3	3.57
Pericarditis	2	1.79
Heart disease	7	8.04
Hyperlipidemias	8	8.95
Gastrointestinal		
Gastritis	8	8.95
Irritable bowel	2	1.79
Respiratory		
COPD	4	4.43
Others	17	19.69

Table 3: Frequency of medical diagnoses of users.

Regarding pharmacological therapy, 54% of the participants were receiving monotherapy, while 46% were receiving polypharmacy. The antihypertensive drugs most used in the ARAII group were losartan (87.1%), followed by hydrochlorothiazide (16.1%) and amlodipine (7.8%) (Table 4). The combination of losartan and hydrochlorothiazide was the most frequently used multitherapy, followed by adding amlodipine. Using the MGT scale, it was found that 58.6% of the population is not adherent; if we look in detail at the patient's responses to the four questions

of the MGT, the most negative responses relate to questions 3 and 1, reaching values of 81.9% and 46.5%, respectively, according to (Table 5). In the analysis of the sociodemographic characteristics of the patients as possible interfering factors in the adherence to the pharmacological treatment, according to MGT, there was no significant association between them and non-adherence ($p<0.01$) according to (Table 6), that is to say, that the variables evaluated are probably independent, however, we found that the female sex, who live in urban areas, of socioeconomic stratum 3, of home occupation, with low economic income are those who present a more significant lack of adherence to the treatment, in addition it was found that the patients are not adherent to the treatment regardless of the type of health regimen they have.

Treatment and medication	**Counts**	**%**	**Cumulative %**
Amlodipine	4	3.45%	3.45 %
Carvedilol	4	3.45%	6.90 %
Enalapril	2	1.72%	8.62 %
Hydrochlorothiazide	2	1.72%	10.34 %
Losartan	101	87.07%	97.41 %
Other	2	1.72%	99.14 %
Valsartan	1	0.86%	100 %
Polytherapy			
Losartan + Hydrochlorothiazide	28	38.88%	38.88%
Losartan + Amlodipine	10	13.88%	52.76%
Losartan + Metropolol	7	9.22%	61.98%
Losartan + Verapamil	4	5.55%	67.53%
Others	23	31.94%	100.00 %

Table 4: Antihypertensive pharmacological management used by users.

Question	**Si n= 116 (%)**	**No n= 116 (%)**
1. Do you ever forget to take your medications to treat your illness?	62 (46.55)	54 (53.45)
2. Do you take your medications at the prescribed times?	94 (81.03)	22 (18.97)

3. When you feel well, do you stop taking your medication?	95 (81.09)	21 (18.1)
4. If it ever makes you feel sick, do you stop taking it?	36 (31.03)	80 (68.93)

Table 5: Frequency of responses to the Morisky-Green test among patients using antihypertensive medications.

Variables	**Adherent N=116 (%)**	**Non-adherent N= 116 (%)**	**Test**	***p*-value**
Age (years)				
Between 20 and 39	3 (4.41)	4 (10.42)		
Between 40 and 59	10 (20.83)	17 (32.20)	X^2	0.181
≥60	22 (32.20)	60 (87.27)		
Gender				
Masculine	11 (22.92)	26 (38.24)	X^2	0.081
Feminine	37 (77.08)	42 (61.76)		
Residence				
City	26 (54.17)	46 (67.65)	X^2	0.141
Farm	22 (45.83)	22 (32.35)		
Housing stratum				
Stratrum 1	0 (0.0)	1 (1.47)		
Stratrum 2	38 (79.17)	45 (66.18)	X^2	--
Stratum 3	9 (18.75)	21 (30.88)		
Stratum 4	1 (1.47%)	1 (1.47%)		
Type of coverage in Unified Health System				
Contributory	38 (79.17)	53 (77.94)	X^2	0.874
Subsidized	10 (20.83)	15 (22.06)		

Occupation/Profession				
Employee	11 (22.92)	10 (14.71)		
Freelancer	7 (14.58)	13 (19.12)		
Student	1 (2.08)	3 (4.41)	X^2	--
Housewife	24 (50.0)	33 (48.53)		
Other	5 (10.42)	9 (13.24)		
Monthly household income (n. minimum wages)				
More than 3 minimum wages	1 (2.08)	0 (0.0)		
Between 1 and 3 minimum wages	5 (10.42)	5 (7.35)	X^2	--
1 minimum wage	11 (29.92)	19 (27.94)		
Less than 1 minimum wage	31 (64.58)	44 (64.71)		

Table 6: Level of adherence measured by the Morisky-Green Test (MMAS-4) characteristics of patients who use some antihypertensive medication.

The analysis of the Bonilla test shows that 30.1% of the population is in a situation of non-adherence, followed by 65.5% of patients at risk of non-adherence; this characteristic is a risk component in generating potential for non-adherence, as shown in (Table 7). From the bivariate analysis to determine the association of variables and the interpretation of adherence from the two methods, 45.7% of the population presents non-adherence to pharmacological treatment. In contrast, the risk of non-adherence to treatment is 67.9%, which is more relevant considering that these patients can easily have poor adherence to treatment (Table 8). However, the data do not show a statistically significant association, so it is necessary to carry out further studies with more participants.

Variable	Counts	% of Total	Cumulative %
Non-adherence situation	35	30.17%	30.17 %
At risk of non-adherence	76	65.52%	95.69 %
Advantage for adherence	5	4.31%	100.00 %

Table 7: Frequency of adherence classification by the Bonilla test (BT) of patients who use some antihypertensive medication.

	Batalla (BT) Classification			
Morisky interpretation	**Non-adherence situation**	**At risk of non-adherence**	**Advantage for adherence**	**Total**
Adherent	19	26	3	48
	54.29 %	34.21 %	60.00 %	41.38 %
Non-adherent	16	50	2	68
	45.71 %	65.79 %	40.00 %	58.62 %
Total	35	76	5	116
	100.00 %	100.00 %	100.00 %	100.00 %

Table 8: Analysis of variables and adherence to antihypertensive treatment related to the Morisky and Batalla tests.

7. Discussion

Recognizing that effective personalized pharmacological treatment depends not only on genetic knowledge and individualized prescription but also on the patient's compliance with the therapeutic regimen, counseling is also recommended by health professionals, especially those who have direct and frequent contact, such as nurses and doctors. Through counseling, a relationship of trust is established with the patient to support free and informed decision-making, co-responsibility, and personal conviction[15]. The results of the present study show the need to strengthen the accompaniment of patients to generate greater adherence, a condition confirmed by similar studies[16-19]. From a population and public health perspective, prevention represents a crucial strategy for the early detection of hypertension and the significant reduction of its progression. This is based on the associated diseases, their morbidity and mortality, and the personal, family, social, and economic problems hypertension produces. The results of this study identified several key characteristics, including age, gender, and income level, which align with the findings of previous research conducted by Guimarães *et al*. [20], Aquino *et al*. [21], and Recalde *et al*. [22].

One of the most significant challenges currently facing clinical pharmacology is the considerable interindividual variability observed in the response to medications, both in terms of efficacy and toxicity[5]. Clinical experience demonstrates that administering the same medication to different patients at the recommended doses can result in disparate responses[5], which in turn influences each patient's individual response. This phenomenon[23], coupled with the realities of polypharmacy and the discontinuation of medications in the first year of treatment by 16 to 50%[24], has a considerable impact on adherence to treatment. Several studies have assessed the impact of sociodemographic factors on adherence to antihypertensive treatment. These studies have demonstrated that age, gender, the quantity of antihypertensive drugs taken, and socioeconomic status are associated with adherence or non-adherence to treatment[25]. Some authors have proposed that older patients may

demonstrate superior adherence due to their heightened awareness of the significance of treatment for their health and the comorbidities they often present[25,26]. However, the findings of the present investigation indicate that adherence levels range from low to non-adherence. The findings indicate that the older population does not present favorable conditions for adherence [25,27], which may be related to older patients' cognitive level and capacity for self-care[25,28]. The provision of support and motivation for self-care could lead to improved results.

Implementing self-care practices and formulating action plans to guide and facilitate the adoption of healthy habits and pharmacological treatments is paramount in ensuring compliance with treatment regimens for hypertension and other asymptomatic chronic diseases. One of the most significant challenges in the management of hypertension and other asymptomatic chronic diseases is the low level of therapeutic compliance observed among patients. It is estimated that only 55.5% of patients adhere to their prescribed treatment plan. Since hypertension is an asymptomatic disease, healthy lifestyle habits are crucial for its management and readily detectable. Prevention efforts are primarily centered on raising awareness and implementing health education programs[29]. As Salles mentions[30], various studies yielded results indicating the identification of specific needs in patients who exhibited non-adherence and a lack of continuous follow-up to attend the indicated consultations. Some studies even recommended conducting home visits to ascertain the reasons for absences and provide encouragement to continue treatment. The nursing interventions documented in the review conducted by Georgiopoulos demonstrate the implementation of several assessment tools[31], including the Moriski Scale, electronic monitoring of medications, home blood pressure monitoring, urinary tests, and educational interventions. As a result of the findings, there was a notable improvement in therapeutic compliance, compliance with established schedules, and control of blood pressure levels in more patients. Additionally, systolic levels were reduced by a significant margin, exceeding 10 mmHg. Furthermore, using the fewest number of tablets, as Parati *et al*. [32] reported, in treating HTN improves compliance with treatment. However, this needs to be evident in the results of the present investigation, as 54% of patients use monotherapy (losartan), yet adherence levels are low or insufficient at 58%.

A comparison of the adherence rates found in this study with those reported in the MGT and BT studies reveals a correlation between the lack of adherence to antihypertensive treatment and the differing methodologies employed. The findings of da Silva *et al.* [33] indicate a need for more adherence to the MGT test and adherence to the BT. These findings indicate that individuals may have inadequate attitudes toward medication administration and limited knowledge about their disease. This may contribute to a need for recognition of the role of medication in disease progression. Consequently, there is a need for strategies that enhance education and promote the significance of adherence to treatment and lifestyle modifications. Adherence to antihypertensive treatment is paramount for the effective management of high blood pressure. This condition affects millions of people worldwide and can have serious health consequences if not adequately controlled. Medication adherence is not merely a matter of taking the appropriate doses at

designated times; rather, it encompasses a long-term dedication to the treatment plan, even when the symptoms of the disease may not be readily apparent. The study results demonstrate that the factors influencing medication adherence are complex, mainly when considered collectively. These factors include the therapeutic regimen, the side effects of the medications, economic and logistical barriers to obtaining the medications, and psychological and social factors. Therefore, health professionals must collaborate with patients to identify and address these factors, aiming to improve adherence to treatment.

The findings of studies such as this demonstrate a need for further research. In order to develop effective interventions and improve treatment adherence, it is essential to conduct studies with more robust methodological designs and larger samples. Preventing complications related to hypertension not only reduces human suffering but also results in a reduction in the costs associated with more intensive treatments and hospitalizations. From a broader perspective, pharmacological adherence confers benefits not only on the individual patient regarding improved blood pressure control but also in economic and public health terms. Studies such as this present an apparent reality, but proposals with methodological designs and larger samples are needed to provide alternatives for intervention and change to improve adherence. Preventing complications of hypertension not only reduces human suffering but also the costs associated with more intensive treatment and hospitalization. From a broader perspective, medication adherence benefits the individual patient by improving blood pressure control and has economic and public health implications.

8. Conclusion

The present study revealed no significant correlation between adherence to antihypertensive pharmacological therapy and the sociodemographic characteristics examined. However, factors such as age, sex, profession, and economic level have been identified as potential contributors to poor adherence to treatment. The diagnostic evaluation of the Morisky scales (MMAS-4 version) and Bonilla indicates that they are sensitive instruments for detecting patients who comply or do not comply with the therapeutic regimen. They also effectively estimate the probability of adherence and knowledge about the disease. However, further studies are needed to increase the population size and allow for a more comprehensive characterization of the factors contributing to low adherence. This will enable the development of more effective education and health strategies in the population that promote the importance of adherence to treatment and improvements in lifestyle.

9. Author Contributions

DMB and MZR-M were involved in the conceptualization and design of the project, the collection and analysis of data, and the interpretation of results. YM contributed to the collection of data and the recruitment of patients. ACV provided input on the study's design and assisted with data

analysis. DMB and MZR-M drafted the manuscript, and all authors performed a critical review and approved the final version for publication.

Ethical Considerations

The Comité Institucional de Ética en Investigación-Universidad El Bosque has approved this research project (Acta No. 012-2021, June 22, 2021).

Funding

No public or private sector entities funded this research.

Acknowledgments

The authors would like to thank the students for their contributions. We want to express our gratitude to the following students from the Nursing program at Universidad El Bosque: Arango Ardila Jesus David, Bello Cogua Rosa María, Castro Galvis Laura Camila, Daza Esquivel Danna Vanessa, Gamboa Santofimio Angie Katherine, Niño Duran Jorge Esteban, Solano Camberos Angie Pamela, and Vera Beltrán Vanessa Johanna. We would also like to express our gratitude to the nursing students who assisted with data collection and recruitment of participants and completed their degree work within the framework of this study. We would particularly like to acknowledge nurse Carolina Malaver and the administrative staff of the clínica Chia for their invaluable support in developing the study. Finally, we would like to thank David Andrade Fonseca from the Faculty of Nursing at Universidad El Bosque for his guidance and expertise in data analysis.

Conflicts of Interest

The authors declare no conflicts of interest.

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