Glutathione S-transferase M1 and T1 Genes Deletion Polymorphisms and Blood Pressure Control Among Treated Essential Hypertensive Patients in Burkina Faso.

Herman Karim SOMBIE
CERBA/LABIOGENE, UFR/SVT, University Jospeh Ki-Zerbo, 01 P.O. Box. 364 Ouagadougou 01, Burkina Faso
Daméhan Tchélougou
CERBA/LABIOGENE, UFR/SVT, 01 P.O. Box. 364 Ouagadougou 01, Burkina Faso
Pegdwendé Abel Sorgho
CERBA/LABIOGENE, UFR/SVT, University Joseph Ki-Zerbo, 01 P.O. Box. 364 Ouagadougou 01, Burkina Faso
Jonas Koudougou Kologo
Saint Camille Hospital of Ouagadougou (HOSCO), 01 P.O. Box. 444 Ouagadougou 01, Burkina Faso
Abdoul Karim OUATTARA (ak.ouattara02@gmail.com)
CERBA/LABIOGENE, PO BOX: 364 Ouagadougou 01, Burkina Faso https://orcid.org/0000-0002-9767-0646
Sakinata Yaméogo
Laboratory of Molecular Biology and Genetics (LABIOGENE), UFR/SVT, 03 P.O. Box. 7021 Ouagadougou 03, Burkina Faso
Arsène Wendpagnangdé Zongo
Laboratory of Molecular Biology and Genetics (LABIOGENE), UFR/SVT, University Joseph Ki-Zerbo, 03 P.O. Box. 7021 Ouagadougou 03, Burkina Faso
Isabelle Touwendpoulimdé Kiendrébéogo
CERBA/LABIOGENE, UFR/SVT, University Joseph Ki-Zerbo, 01 P.O. Box. 364 Ouagadougou 01, Burkina Faso
Edwige Yelemkouré
CERBA/LABIOGENE, UFR/SVT, University Joseph Ki-Zerbo, 01 P.O. Box. 364 Ouagadougou 01, Burkina Faso
Enagnon Tiémoko Herman Donald Adoko
University Hospital Center Yalgado Ouedraogo (CHUYO), 01 P.O. Box. 676 Ouagadougou 01, Burkina Faso
Albert Théophane Yonli
CERBA/LABIOGENE, UFR/SVT, University Joseph Ki-Zerbo, 01 P.O. Box. 364 Ouagadougou 01, Burkina Faso
Florencia Wendkuuni Djigma
CERBA/LABIOGENE, UFR/SVT, University Joseph Ki-Zerbo, 01 P.O. Box. 364 Ouagadougou 01, Burkina Faso
Patrice Zabsonré
University Hospital Center Yalgado Ouedraogo (HOSCO), 01 P.O. Box. 676 Ouagadougou 01, Burkina Faso
Hassanata Millogo
University Hospital Center Yalgado Ouedraogo (HOSCO), 01 P.O. Box. 676 Ouagadougou 01, Burkina Faso
Jacques Simporé
CERBA/LABIOGENE, UFR/SVT, University Joseph Ki-Zerbo, 01 P.O. Box. 364 Ouagadougou 01, Burkina Faso

Research note

Keywords: Blood pressure control, Essential hypertension, GSTM1, GSTT1, Burkina Faso

Posted Date: October 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-89342/v1

Version of Record: A version of this preprint was published at BMC Research Notes on June 30th, 2021. See the published version at https://doi.org/10.1186/s13104-021-05658-w.

Abstract

Objective

Glutathione S-transferases have been associated with experimental resistance to some drugs. The present study investigated the factors associated with blood pressure control in patients with essential hypertension, especially the role of *GSTT1* and *GSTM1* genes polymorphisms. This cross-sectional study in Burkina Faso consisted of 200 patients with essential hypertension and under treatment.

Results

This cross-sectional study population consisted of 57.5 % (115/200) of patients with their hypertension under control. No statistically significant difference ($p > 0.05$) was found between controlled and uncontrolled (SBP and/or DBP) groups for anthropometric and biochemical parameters as well as for GSTT1 or GSTM1 gene polymorphisms. However, current alcohol consumption (OR = 3.04; CI = 1.88 - 6.13; $p < 0.001$), physical inactivity (OR = 3.07; CI = 1.71 - 5.49; $p < 0.001$), severity of hypertension (Grade III [OR = 3.79; CI = 2.00 - 7.17; $p < 0.001$]) and heart damage (OR = 3, 14; CI = 1.59 - 6.02; $p < 0.001$) were statistically more frequent in uncontrolled essential hypertension group than controlled group.

Introduction

Normalization of blood pressure (BP) in hypertensive patients significantly decreases the risk of stroke and heart disease and improves patients' quality of life [1].

However, the achievement rates of the BP target values (Systolic Blood Pressure [SBP] < 140 mmHg and Diastolic Blood Pressure [DBP] < 90 mmHg) remain low in the treated patients estimated at 37.1% worldwide in 2010 and less than 10% in Sub-Saharan Africa in 2013 [2, 3]. Black people are the more susceptible subgroup to hypertension and its complications [4], and are more exposed to uncontrolled hypertension or use of multiple drugs to control their BP [5]. It therefore becomes necessary to better understand the factors that affect control of hypertension in order to minimize their effects. Many studies have looked for factors associated with hypertension control but the contribution of genetic factors is less studied. Glutathione S-transferase (GST) plays a crucial role in the detoxification mechanisms of drugs and xenobiotics [6]. Studies in both humans and animals have shown that some polymorphisms that affect the expression of certain families of GST also affect the effectiveness of certain drugs [7-10]. These results suggest that GST could affect the bioavailability of certain drugs which acts as GST enzyme substrate. To date, no study to our knowledge has evaluated the link between GST and antihypertensive responses, although Glutathione S-transferases Mu1 deletion has been associated with resistant hypertension [11]. In this study we hypothesized that the active variants of Glutathione S-transferases Mu1 (*GSTM1*) and theta 1 (*GSTT1*) which have normal detoxification activity could reduce the bioavailability of certain antihypertensive drugs and therefore affect the control of BP in hypertensive patients.

Hence, we aim to determine the factors associated with blood pressure control among hypertensive patients in Burkina Faso, especially identify the contribution of *GSTM1* and *GSTT1* genes variants.

Methods

1.1. Study design

We conducted a cross-sectional study from July 15, 2017 to March 27, 2018, including 200 essential hypertensive patients followed in the cardiology department of Saint Camille Hospital of Ouagadougou (HOSCO), University Hospital Center Yalgado Ouédraogo (CHUYO) and the Medical Center of General Aboubacar Sangoulé Lamizana military Camp).

The study population consisted of subjects under antihypertensive treatments regardless of gender or social characteristics, aged from 18 to 70 years old.

Patients with secondary hypertension or no antihypertensive treatment, pregnant women and subjects not descendants from Burkina Faso were not included in this study.

Controlled blood pressure was defined as an average of SBP < 140 mmHg and DBP < 90 mmHg for all patients [12] during the last two consecutive medical visits under treatment.

1.2. Samples and data collection

A standardized questionnaire was used to collect socio-demographic, lifestyle, clinical and biological data (see questionnaire in *additional file 3*).

BP was measured using an electronic cuffed sphygmomanometer by cardiologist as described previously [15].

Body mass index (BMI) was used to classify patients as obese (≥ 30 kg/m^2), overweight (25-30 kg/m^2), normal weight (20-25 kg/m^2) and underweight (< 20 kg/m^2). We determined waist circumference (WC) and abdominal obesity in men was determined when WC ≥ 102 cm and in women when WC ≥ 88 cm [13]. Family history of hypertension was determined in participants with at least one close family member being hypertensive before the age of 60 years. From each patient, venous blood sample was taken in EDTA tube and anticoagulant-free tube. Sera were directly used for biochemical analysis using *CYANExpert 130 analyzer*, and blood pellet were stored at -20°C until DNA extraction.

1.3. DNA extraction and genotyping

The salting out method as described by Miller and *al.* in 1988 was used to isolate genomic DNA from peripheral white blood cells [14].

Genotyping of the *GSTM1* and *GSTT1* genes has been previously described [15]. Briefly we performed multiplex PCR with the GeneAmp PCR system 9700 (Applied Biosystem, USA) in a reaction volume of 25µL including 10µL of Master Mix AmpliTaq Gold® (Applied Biosystems, USA), 7µL of nuclease-free water, 5µL of DNA and 1µL of each primer pairs for each gene (*β-globin, GSTM1, GSTT1*). After amplification, PCR products were migrated on ethidium bromide-stained 3% agarose gel during 45 mn, bands were visualized under UV light at 312 nm using the Geneflash revelation device (*Additional file1*) and the generated data were interpreted as previously described [15].

1.4. Statistical analysis

We used Statistical Package for Social Sciences (20.0) and Epi Info (6.0) for data analyses. To determine sample size, we have taken into account following values: 95% of two-sided confidence level, 80% of power, odds ratio more than 2.2, ratio of controlled BP to uncontrolled BP 1.1, the proportion of controlled BP patients group having *GSTM1*-null and *GSTT1*-null about 50 %. We expressed quantitative variables and frequencies as mean ± standard deviation and percentage respectively and comparisons between groups were done with t-test and chi-squared test respectively. Difference was considered as statistically significant when $p < 0.05$.

Results

2.1. Characteristics of the study population

The ***table 1*** presents the general characteristics of the study population. The BP levels of participants under treatment allowed us to classify them into patients with controlled and uncontrolled hypertension. We showed that 115 (57.5%) had their BP under control.

Regarding the socio-demographic and biochemical data, there was no significant difference between the controlled and the uncontrolled group (all $p > 0.05$).

Of the 200 patients under antihypertensive treatments, 99 patients were under monotherapy, 65 patients under bitherapy and 36 patients under Tritherapy (data not shown). *Supplementary file 2*.

2.2. Influence of genetic variants of *GSTM1* and *GSTT1* on the control of blood pressure and essential hypertension.

The ***table 2*** presents and compares the frequencies of *GSTM1* and *GSTT1* variants between the controlled and uncontrolled SBP groups, between the controlled and uncontrolled DBP groups and between the controlled and uncontrolled hypertension group. We did not find any significant difference between those groups ($p > 0.05$).

2.2. Research of non-genetic factors associated with the control of essential hypertension

The ***Table 3*** presents and compares the frequencies of non-genetic factors that have been associated with hypertension control in previous studies. Our results showed that alcohol consumption (OR = 3.04; CI = 1.88 - 6.13; $p < 0.001$), physical inactivity (OR = 3.07; CI = 1.71 - 5.49; $p < 0.001$), the severity of essential hypertension (Grade III [OR = 3.79; CI = 2.00 - 7.17; $p < 0.001$]) and heart damage (OR = 3, 14; CI = 1.59 - 6.02; $p < 0.001$) were more frequent in uncontrolled essential hypertension group than controlled group and differences were significant.

Discussion

In this study, we investigate the factors associated with essential hypertension control in Burkina Faso. Our results showed that there was no significant difference between the controlled and the uncontrolled hypertension group by comparing the levels of biochemical parameters, suggesting that BP control is independent of blood glucose, cholesterol, triglycerides and creatinine levels.

In this study, there was no significant difference between the control rates of patients under monotherapy and bitherapy or tritherapy, unlike studies which have shown that monotherapy [16] or multi-drug therapy [17] was associated with the low control of hypertension.

However, we found that alcohol consumption, physical inactivity, the initial hypertension grade before medication and cardiac affections were associated with low control of essential hypertension. The influence of alcohol consumption on antihypertensive therapy has long been studied. Stewart *et al.,* showed that the reduction of alcohol consumption increase the antihypertensive drugs effect and that the management of alcohol consumption must be considered as a major component of antihypertensive therapy in alcoholics [18]. Concerning physical exercise, a number of studies have consistently demonstrated its beneficial effects on hypertension with reductions in SBP and DBP of up to 5-7 mmHg [19] and more frequent and long-term exercise leads to a more sustained reduction in BP, called exercise training response [20]. It is believed that the reduction in BP with physical activity is due to the attenuation of peripheral vascular resistance, which may be due to neurohormonal and structural responses [21]. Other mechanisms suggested in reducing BP through exercise include favorable changes in oxidative stress, inflammation, endothelial function, body mass, activity of the renin-angiotensin system, renal function, and insulin sensitivity [19]. Cardiac damages were found more in the uncontrolled group compared to the controlled group and this may be the cause or the effect of the poor control of blood pressure in essential hypertensive patients.

Our results also showed that there was no association between socio-demographic characteristics, residence areas and gender with BP control unlike other studies which have shown that women had a higher control rate than men in African countries [22]. Our results are similar to those reported in Tanzania by Maginga *et al.,* who showed that age, gender, educational level, marital status, professional status and residency did not affect the control of hypertension

[23]. However, unlike our study which found no association between obesity and the control of essential hypertension, that of Maginga *et al.,* showed that it was associated with a poor control rate.

Considering the genetic aspects, we investigated the influence of variants of the *GSTM1* and *GSTT1* genes on the control of essential hypertension. Genetic factors may influence the pharmacokinetics and pharmacodynamics (tissue or organ responsiveness) of drugs [24]. Studies have reported that in cancer cells, GST often show high levels of expression when compared to normal cells [25] and this may contribute to increase detoxification of anticancer drugs [26]. It have been also shown that GST Through their detoxification activity, might play an important role in the protection against the toxic effect of the antimicrobial agents which leads bacteria to become resistant to antibiotics [27].

In HIV treated patients, homozygous deletion of *GSTM1* and *GSTT1* have been associated with CD4+ count rising above 350 cells/mm3 suggesting that patients with homozygous deletion have slower disease progression and better drug response [28]. Among GST genes, *GSTM1* and *GSTT1* are the most investigated in studies exploring genetic and drug response and they have been described as polymorphic in humans [29]. The most common polymorphisms of the loci of the *GSTM1* and *GSTT1* genes consist in the complete deletion of these genes (*GSTM1*-null and *GSTT1*-null) [30]. Individuals who are homozygous for the null genotype of *GSTM1* or *GSTT1* lack the respective enzyme functions [31, 32] and may have lower xenobiotic and drug detoxification activity than subjects with active genotypes.

In this study, our results showed that neither *GSTM1* nor *GSTT1* was associated with the control of essential hypertension; this at first sight indicates an absence of association between the active variants of these two genes and the low disponibility and efficacy of antihypertensive drugs. Some studies estimate that other members of the GST enzyme family must have compensated for the absence of a functional enzyme in the double deletion subjects [33, 34], which leads to the same level of activity of GST both in the null and active genotype. In addition to not confirming our initial hypothesis, our results may also not support the hypothesis that expression of the *GSTM1* gene could protect against resistant hypertension [11].

Conclusion

In this study, the patient's lifestyle seems to be more determining in BP control under treatment than genetic factors studied. Especially alcohol consumption and physical inactivity are associated with a poor blood pressure control. In contrast, no association was found between *GSTM1* and *GSTT1* genes polymorphisms with systolic or diastolic blood pressure control in our study population. In addition, given the fact that an advanced disease stage, with or without cardiac complications, is also linked to a poor blood pressure control, an early diagnosis should be therefore encouraged for effective management and for better therapeutic responses.

Limitations

Our study could have certain limitations, in particular the small size of the study population and the lack of information on adherence to antihypertensive therapy. These observations could be taken into account in future studies.

Abbreviations

BMI	:	Body mass index
CERBA	:	Pietro Annigoni Biomolecular Research Center
DBP	:	Diastolic blood pressure
EDTA	:	Ethylenediaminetetraacetic
GSTM1	:	Glutathione S-transferases Mu 1
GSTT1	:	Glutathione S-transferasesTheta 1
HDL-c	:	High-density lipoprotein cholesterol
LABIOGENE	:	Laboratory of molecular biology and genetics
LDL-c	:	Low-density lipoprotein cholesterol
MD	:	Means difference
PCR	:	Polymerase chain reaction
ROS	:	Reactive Oxygen Species
SBP	:	Systolic blood pressure
SD	:	Standard deviation
SPSS	:	Statistical Package for theSocial Sciences
TC	:	Total cholesterol
WC	:	waist circumference

Declarations

1. Ethics approval and consent to participate

The present study has been approved by the ethics committee of CERBA/LABIOGENE and the National Ethics Committee for Health Research of Burkina Faso.CERS20186065, 6 June 2018, retrospectively registered. Free and written consent was obtained from all participants of this study. The anonymity and confidentiality of the patients were respected as stated in the IRB (Institutional Review Board) protocol.

2. Consent for publication

Not Applicable

3. Availability of data and materials

The dataset generated in this study is available from NCBI Nucleotide under the accession number LC517160.1.

4. Competing interests

The authors declare that they have no competing interests

4. Funding

This work was supported by West African Economic and Monetary Union (WAEMU) through the "*Programmed'appui et de développement des centresd'excellencerégionaux"* (PACERII) and "*Centre national de l'Information, de l'OrientationScolaire et Professionnelle, et des Bourses"*(CIOSPB) especially for researcher life stipend. Financial support for reagents and consumables was provided by Italian Episcopal Conference (CEI).

The funding bodies played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

6. Authors' contributions

Study concept and design: SHK, JKK, TD, HM and JS. Sampling and Laboratory analysis: HKS, APS, SY, ITK, AWZ, EY, ETHDA and JKK. Statistical analysis and interpretation of data: HKS, APS, ATY, DT. Drafting of the manuscript: APS, HKS, TD, AKO and JS. Critical revision of the manuscript for important intellectual content: AKO, HKS, DT, FWD, HM, JKK, PZ and JS. Administrative, technical, and material support: FWD, ATY, JKK and JS. Study supervision: JKK, HM, PZ and JS.

The Corresponding Author declares that the manuscript has been read and approved by all named authors and that the order of authors listed in the manuscript has been approved by all of us.

7. Acknowledgements

The authors wish to thank all participants in this study. A deep gratitude to all the staff of Saint Camille Hospital of Ouagadougou (HOSCO) and Biomolecular Research Center Pietro Annigoni (CERBA) for technical support.

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Tables

Table 1: General characteristics of the study population according to hypertension control

Parameters	Total *n* = 200 (100%)	Controlled HTA *n* = 115 (57.5%)	Uncontrolled HTA *n* = 85 (42.5%)	*p* value
Gender (M/F)	71/129	40/75	31/54	0.88
Age (years)	54.06 ± 10.89	54.16 ± 11.1	53.95 ± 10.70	0.89
SBP (mmHg)	137.54 ± 16.84	126.74 ± 8.55	150.61 ± 15.06	**< 0.001***
DBP (mmHg)	83.45 ± 14.40	78.77 ± 8.27	89.11 ± 17.87	**< 0.001***
BMI (Kg/m^2)	28.76 ± 6.38	29.14 ± 7.22	28.39 ± 5.32	0.40
WC (cm)	94.55 ± 13.17	94.17 ± 13.26	95.00 ± 13.13	0.66
Glucose (mM)	5.44 ± 0.96	5.58 ± 1.11	5.41 ± 1.01	0.51
HDL-c (mM)	1.56 ± 0.93	1.52 ± 0.47	1.61 ± 1.27	0.72
LDL-c (mM)	2.98 ± 1.00	2.82 ± 0.93	3.15 ± 1.05	0.19
Total Cholesterol (mM)	5.13 ± 0.99	4.88 ± 0.98	5.34 ± 0.97	0.1
Triglycerides (mM)	1.26 ± 0.94	1.13 ± 0.51	1.39 ± 1.23	0.28
Creatine (µM)	111.52 ± 94.42	101.47 ± 43.85	121.57 ± 126.48	0.40

*Values are expressed as mean ± standard deviation for continuous variables; the statistical analyzes were made by the t test or the chi-square test; *: significant difference between the groups (p < 0.05); SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; mM: millimolar; µM: micromolar.*

Table 2: Distribution of GSTM1 and GSTT1 genes variants according to control state of essential hypertension, SBP and DBP

Parameters	Genes -Variants	SystolicBlood Pressure (SBP)			Diastolic Blood Pressure (DBP)			Hypertension	
		Controlled *n*= 126 (%)	Uncontrolled *n* = 74 (%)	*p* value	controlled *n*= 152 (%)	uncontrolled *n*= 48 (%)	*p* value	Controlled *n*= 115 (%)	Uncontrolled *n* = 85 (%)
Monotherapy *n* = 110	*# GSTM1-active*	55 (74.32)	30 (83.33)		66 (76.74)	19 (82.14)		51 (76.12)	34 (79.07)
	GSTM1-null	19 (25.68)	6 (16.77)	0.34	20 (23.26)	5 (17.86)	1.00	16 (23.88)	9 (20.93)
	# GSTT1-active	28 (37.84)	10 (27.78)		31 (36.05)	7 (35.71)		27 (40.30)	11 (25.58)
	GSTT1-null	46 (62.16)	26 (72.22)	0.39	55 (63.95)	17 (64.29)	0.63	40 (59.70)	32 (74.42)
Bitherapy *n* = 55	*# GSTM1-active*	17 (60.71)	17 (70.83)		24 (61.54)	10 (64.71)		16 (57.14)	18 (66.67)
	GSTM1-null	11 (39.29)	7 (29.17)	0.56	15 (38.46)	6 (35.29)	1.00	12 (42.86)	9 (33.33)
	# GSTT1-active	14 (50.00)	9 (37.50)		16 (41.03)	7 (41.18)		11 (39.29)	12 (44.44)
	GSTT1-null	14 (50.00)	15 (62.50)	0.41	23 (58.97)	9 (58.82)	1.00	17 (60.71)	15 (55.56)
Tritherapy *n* = 35	*# GSTM1-active*	13 (61.91)	9 (64.28)		19 (70.37)	3 (45.45)		12 (60.00)	10 (66.67)
	GSTM1-null	8 (38.09)	5 (35.72)	1.00	8 (29.63)	5 (54.55)	0.11	8 (40.00)	5 (33.33)
	# GSTT1-active	7 (33.33)	8 (57.14)		10 (37.04)	5 (54.55)		7 (35.00)	8 (53.33)
	GSTT1-null	14 (66.67)	6 (42.86)	0.18	17 (62.96)	3 (45.45)	0.24	13 (65.00)	7 (46.67)
Total *n* = 200	*# GSTM1-active*	85 (67.46)	56 (75.68)		109 (71.71)	32 (69.64)		79 (68.70)	62 (72.94)
	GSTM1-null	41 (32.54)	18 (24.42)	0.26	43 (28.29)	16 (30.36)	0.58	36 (31.30)	23 (27.06)
	# GSTT1-active	49 (38.89)	27 (36.49)		57 (37.50)	19 (41.07)		45 (39.13)	31 (36.47)
	GSTT1-null	77 (61.11)	47 (63.51)	0.76	95 (62.50)	29 (58.93)	0.86	70 (60.87)	54 (63.53)
	#GSTM1(+)/GSTT1(+)	25 (19.84)	16 (21.62)		34 (24.34)	7 (14.58)		24 (20.87)	17 (20.00)
	GSTM1(-)/GSTT1(+)	24 (19.05)	11 (14.87)	0.63	23 (15.13)	12 (25.00)	0.11	21 (18.26)	14 (16.47)
	GSTM1(+)/GSTT1(-)	60 (47.62)	40 (54.05)	1.00	75 (49.34)	25 (52.08)	0.37	55 (47.83)	45 (52.94)
	GSTM1(-)/GSTT1(-)	17 (13.49)	7 (9.46)	0.59	20 (13.16)	4 (8.33)	1.00	15 (13.04)	9 (10.59)

*Values are expressed in numbers (percentages) and the comparison between groups was made using the chi-square test; *: significant difference between the groups (p < 0.05); #: reference; (+): active; (-): null.*

Table3: Bivariate analysis of non-genetic factors affecting blood pressure control in patients with essential hypertensive

Parameters	Controlled *n* =115 (%)	Uncontrolled *n* =85 (%)	OR	CI	*p* value
Sex					
Men/Women	40/75	31/54	0.92	0.51-1.16	0.88
Age					
≤ 45 years	22 (19%)	21 (25%)	1.38	0.70 - 2.73	0.38
46 - 55 years	44 (38%)	31 (36%)	0.92	0.51 - 1.65	0.88
56 - 65 years	28 (24%)	25 (30%)	1.29	0.68 - 2.43	0.42
≥ 66 years	21 (18%)	8 (9%)	0.46	0.19 - 1.10	0.10
Residence					
Rural/ Urban	31/84	15 /70	1.72	0.86-3.44	0.13
Behavioral factors					
Current alcohol use	34 (30%)	50 (59%)	3.04	1.88 - 6.13	< 0.001*
Current tobacco use	10 (8.6%)	7 (8%)	0.94	0.34 - 2.58	1
Low sodium diet	6 (5.2%)	7 (8%)	1.63	0.52 - 5.03	0.40
Lack of physical exercise	39 (34%)	52 (61%)	3.07	1.71 - 5.49	< 0.001*
Normal weight	35 (30%)	23 (27%)	0.84	0.45 - 1.57	0.63
Overweight and obesity	80 (70%)	62 (73%)	1.17	0.63 - 2.19	0.63
Central obesity	60 (52%)	48 (56%)	0.84	0.48 - 1.48	0.56
Grade hypertension					
Grade I	44 (39%)	14 (16%)	0.31	0.16 - 0.63	< 0.001*
Grade II	50 (43%)	32 (38%)	0.78	0.44 - 1.39	0.46
Grade III	21 (18%)	39 (46%)	3.79	2.00 - 7.17	< 0.001*
Personal history					
Heart involvement Yes/No	17/98	30/55	3.14	1.59 - 6.02	< 0.001*
Diabetes mellitus Yes/No	14/101	7/78	0.64	0.24 - 1.68	0.48
Asthma Yes/No	3/112	3/82	1.36	0.26 - 6.93	0.70
Taste Yes/No	6/109	6/79	1.37	0.42 - 4.43	0.76
Family history					
Hypertension Yes/No	70/45	56/29	1.24	0.69 - 2.22	0.55
Diabetes mellitus Yes/No	70/45	56/29	1.24	0.69 - 2.22	0.55
Treatment level					
Monotherapy	59 (51%)	40 (47%)	0.90	0.51 - 1.58	0.77
Bitherapy	35 (31%)	30 (35%)	1.21	0.67 - 2.18	0.54
Tritherapy	21 (18%)	15 (18%)	0.88	0.41 - 1.85	0.85
Professional status					
Household	45 (40%)	24 (32%)	0.61	0.33 - 1.11	0.13
Farmer	5 (4%)	2 (2%)	0.53	0.10 - 2.80	0.70
Official	24 (21%)	24 (32%)	1.49	0.77 - 2.86	0.24
Daily	1 (1)	1 (1%)	1.35	0.10-22.01	1
Unemployed	6 (5%)	5 (7%)	1.13	0.33 - 3.85	1
Retirement	9 (8%)	7 (9%)	1.05	0.37 - 2.96	1
trader	20 (17%)	14 (21%)	1.09	0.51 - 2.3	0.84
Other	5 (4%)	8 (13%)	2.28	0.72 - 7.25	0.24

*Values are expressed in numbers (percentages) and the comparison between groups was made using the chi-square test; *: significant difference between the groups ($p < 0.05$).*

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