Epidemiologic features and Management of Hypertension in Tunisia, the results from the NAtional TUnisian REgistry of HyperTension (NaTuRe HTN) about 25890 patients

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Abstract

Background

Hypertension is the leading cause of morbi-mortality in low, middle as well as high incomes countries. Tunisia is a developing country with a high cardiovascular profile and the prevalence of hypertension has widely increased during the last decades. Thus, we conducted this national survey on hypertension to analyze the profile of the Tunisian hypertensive patient and to assess the level of blood pressure control.

Methods

Nature HTN is an observational multicentric survey, including hypertensive individuals and consulting their doctors during the period of the study. The primary endpoint of our study was uncontrolled hypertension defined by a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Our objective is to assess the predictors of uncontrolled hypertension in our population.

Results

Three hundred twenty one investigators from all the Tunisian governorates participated in the study. We enrolled 25890 patients with a female predominance (Sex ratio 1.21) and an average age 64.4 ± 12.2 year-old. Most of individuals were treated in the public sector (74%), 39.4% of patients were diabetic, 25.8% were obese, 44.6% were overweight and 14% were smokers. Hypertension was controlled in 51.7% of cases if we consider 140/90 as BP target and only in 18.6% if we consider 130/80 as a target. The independents predictors of uncontrolled blood pressure were male sex (OR=1.09, 95%CI [1.02-1.16]), age > 65 year-old (OR=1.07, 95% CI [1.01-1.13], diabetes (OR=1.18, 95% CI [1.11-1.25], Smoking (OR=1.15, 95% CI [1.05-1.25]), Obesity (OR=1.14, 95% CI [1.07-1.21]), management in public sector (OR=1.25, 95% CI [1.16-1.34]) and Heart rate >80bpm (OR=1.59, 95% CI [1.48-1.71]). Contrarily, high educational level (OR=0.9, 95% CI [0.84-0.97], absence of history of coronary disease (OR=0.86, 95% CI [0.8-0.93]), salt restriction (OR=0.48, 95% CI [0.45-0.51]), drug compliance (OR=0.57, 95% CI [0.52-0.61]) and regular physical activity (OR=0.77, 95% CI [0.71-0.84]) are strong predictors of blood pressure control.

Conclusion

Nature HTN showed a remarkable improvement of blood pressure control amongst Tunisian people. The control remains low in patients with high cardiovascular profile and those treated in the public sector. A national health program based on therapeutic education, regular control and continuous giving much support to the public institutions is needed to decrease the hypertension burden affection rate in our population.

Background

Hypertension is the most common chronic disease in the world with a prevalence ranging between 30 and 50%, and it is considered to be the leading cause of morbi-mortality in adults especially in low and middle income countries [1–5]. The prevalence is higher in the elderly and exceeds 60% in people aged > 60 years [3]. Given the widespread of sedentary lifestyles and obesity, the prevalence of hypertension worldwide will continue to rise. It is estimated that the number of hypertensive people will increase by 15–20% by 2025, reaching close to 1.5 billion [2]. Several recent epidemiological studies demonstrated that high blood pressure is under diagnosed in the 5 continents of the world and despite the development of the therapeutic arsenal, the control of hypertension does not seem to improve in most countries [4, 6–10]. In Tunisia, a middle income developing country, the latest epidemiological data related to hypertension dates back to 2012, from the national survey “TAHINA Study” [11]. The lifestyle of Tunisian people has widely changed in last years with an increase of sedentarity, overweight and obesity, diabetes and dyslipidemia... Tunisia is considered as a high cardiovascular risk country [12] and the world health organization as well as other international organizations estimate that the Tunisian

epidemiologic situation will worsen in next years [13]. The main reason why we envisioned the need for a national multi-centric survey to analyze the epidemiologic profile of hypertension in Tunisia and to assess the level of blood pressure control as well as the predictor of uncontrolled hypertension.

Patients And Methods

Nature HTN registry is an observational multi-centric national study, conducted in all the governorates of Tunisia, in both public and private health sectors. Patients were included between 15 April 2019 and 15 May 2019 (Ramadan in between). Different investigators ensured the enrollment and the clinical examination: Cardiologists, General doctors as well others specialists as Nephrologists, Endocrinologists and Internists. We included all patients with known or new diagnosed hypertension, who consulted their doctors during the enrollment period.

Inclusion Criteria

We included during the office visits, patients with a history of or newly diagnosed elevated blood pressure and older than 18 year-old, after signing a consent form.

Except when hypertension is severe (e.g. grade 3 and especially in high-risk patients), the diagnosis of new hypertension was confirmed according to the ESC/ESH guidelines as either Out-of-office Blood Pressure (BP) measurement above the recommended thresholds or repeated office BP measurements on more than one visit above 140 mmHg for the systolic pressure and /or 90 mmHg for the diastolic pressure [14].

Exclusion Criteria

We excluded from the study, patients undergoing hemodialysis, pregnant women, those classified as white coat hypertension patients and those who refused to sign the consent form.

Clinical evaluation and data collection

During the office visit, the physician had to complete the case report form of the registry after patient's interrogation and examination.

Information's on socio-demographic characteristics including age, gender, education level, health insurance, smoking, diabetes, pulmonary diseases, hypothyroidism, moderate renal failure history (defined by an MDRD creatinine clearance < 60ml / min [15]), coronary disease as well as history of stroke were collected.

The interview-included questions related to drug compliance and salt intake as well as sport practice. The physical activity was considered as regular when it was performed at least 30 minutes three times a week [14].

On physical exam, we measured weight and height to assess body mass index ($BMI = \text{weight}/\text{height}^2$). Obesity is operationally defined as a BMI exceeding 30 kg/m² and is subclassified into moderate (BMI:30–34.9), morbid (BMI:35–39.9) and severe (BMI $\geq$ 40) [16]. Blood pressure measurements were conducted using a standardized auscultatory or oscillometric sphygmomanometer after at least 15 min of rest. Two separate readings were taken at least three minutes apart and we considered the average of the two measurements. In patients with asymmetric blood pressure between the two arms, we considered the higher pressure.

We checked on electrocardiogram whether the patient had a sinus rhythm or atrial fibrillation and we searched for left ventricle hypertrophy (LVH) based on the definition recommended by the ESC/ESH guidelines (Sokolow–Lyon index > 35 mm, or R in aVL $\geq$ 11 mm) [14]. We searched for LVH also on echocardiographic findings (if the patient underwent echocardiography during the last year).

We noted also the last biology tests, performed during the last six months before the office visit, especially creatinine, glycaemia, cholesterol and kaliemia as well as microalbuminuria (if performed during the last year).

To assess control blood pressure, we evaluated only patients with diagnosed hypertension for more than 6 months. The primary endpoint in our study was the rate of hypertension control.

Uncontrolled hypertension was defined according to the ESC/ESH guidelines as an average systolic blood pressure(SBP) above 140mmHg and/or an average diastolic blood pressure (DBP) above 90mmHg [14].

A validation of the study protocol and the consent form by a national ethic committee was also obtained.

The data collected, were managed by the Clinical Suite platform (Dacima Software), which complies with international standards including US Food and Drug Administration 21 Code of Federal Regulations Part 11, US Health Insurance Portability and Accountability Act, International Conference on Harmonisation, and Medical Dictionary for Regulatory Activities. The Clinical Suite platform allowed us to track the data entered and to check for inconsistencies and missing data. A steering committee was set up to monitor patient inclusions, verify data sources, perform the audit trail, and prepare the statistical analysis plan for the study.

We confirm that all methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the ethic committee of the Hospital of the Internal Security Forces. An informed written consent was obtained from all subjects. In case of illiterate participants informed consent was obtained from legal guardians.

Statistical analysis

All statistical analyses were achieved using the SPSS 23.0 (SPSS, Chicago, IL, USA) statistical package. Continuous variables were presented as means value $\pm$ standard deviation in case of Gaussian distribution and as medians as well as extremes values in case of non-Gaussian distribution.

Among patients with old hypertension more than 6 months, we distinguished two groups according to the hypertension control (controlled group versus uncontrolled group). The comparison between the two groups was achieved by Student's t-test and Chi2 test for continuous variables and categorical variables, respectively. Univariate logistic regression analyses were used to determine crude odds ratio with the 95% approximate confidence intervals as estimators of the non-control of hypertension for various characteristics of the study population. To assess the predictors of hypertension non control, we performed a multivariate logistic regression model. The significance threshold was set at $p < 0.05$.

Results

The Nature HTN registry concerned 25890 hypertensive patients, enrolled by 321 investigators from all the Tunisian governorates. The case report form was completed by Cardiologists in 71% of patients, general practitioner in 25% and others specialists in 4%. The patients were managed in public as well as private sector but the majority of patients were followed in public centers (78%). The hypertension was newly diagnosed in 2286 patients (8.8%) and in the medical history/record of more than six months in 23601 persons.

The majority of patient (16565, 64%) were included during Ramadan, especially for private sector.

The epidemiologic and clinic characteristics of the overall population are summarized in Table 1.

Table 1
Epidemiologic and clinic characteristics of the population according to the sex and the management sector

	All population	Female	Male	p (male vs female)	Public	Private	p (public vs private)
N	25890	14166	11700		20192	5698	
Age (years)	64.00(18–118)	64(18–118)	64(18–108)	0.059*	64(18–118)	65(18–101)	0.4
Median (min-max)		64.5 ± 12.2	64.2 ± 12.2		64.46 ± 12.2		
Mean ± SD	64.4 ± 12.2					64.19 ± 12.1	
Age > 65 yo (%)	12662(49.3)	6982(49.7)	5673(48.8)	0.1	9860 (49.1)	2802 (50.1)	0.4
Ramadan Inclusion (%)	16565 (64)	9155(64.6)	7403(63.3)	0.02	13173 (35.2)	3392(59.5)	< 10 ⁻³
Education level	5527(21.3)	4261(30.1)	1262(10.8)	< 10 ⁻³	4527(22.4)	1000(17.6)	< 10 ⁻³
Illiterate (%)	5475(21.1)	3124(22.1)	2346(20.1)		4384(21.7)	1091(19.1)	
Primary school (%)	4493(17.4)	1880(13.3)	2612(22.3)		3139(15.5)	1354(23.8)	
Secondary school (%)	2428(9.4)	825(5.8)	1600(13.7)		1439(7.1)	989(17.4)	
University school (%)	7967(30.8)	4076(28.8)	3880(33.2)		6703(33.2)	1264(22.2)	
Unprecised (%)							
Health insurance coverage	762(2.9)	399(2.8)	363(3.1)	< 10 ⁻³	434(2.1)	328(5.8)	< 10 ⁻³
Private insurance (%)	18453(71.3)	9806(69.2)	8632(73.8)		14165(70.2)	4285(75.2)	
National insurance (%)	5052(19.5)	3114(22)	1936(16.5)		4724(23.4)	328(5.8)	
State Medicare (%)	790(3.1)	408(2.9)	382(3.3)		520(2.6)	270(4.7)	
None insurance (%)	833(3.2)	439(3.1)	387(3.3)		346(1.7)	487(8.5)	
Unprecised (%)							
Smoking (%)	3630(14)	391(2.8)	3236(27.7)	< 10 ⁻³	3021(15)	609(10.7)	< 10 ⁻³
Diabetes (%)	10204 (39.4)	5621(39.7)	4583(39.2)	0.4	8185(40.5)	2029 (35,6)	< 10 ⁻³
Obesity (%)	6979 (25.8)	4927 (34.7)	2065 (17.6)	< 10 ⁻³	5207 (25.9)	2590 (46.3)	< 10 ⁻³

**mann-whitney nonparametric test*

ABPM: Ambulatory blood pressure monitoring, ACE: Antagonist of conversion enzyme, ARB: Angiotensin Receptor Blockers, BMI: Body mass Index, CCB: Calcium Channels Blockers, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic Blood Pressure, EKG: electrocardiogram, HTN: hypertension, LVH : Left Ventricle Hypertrophy, SD: Standard Deviation, SBP: systolic Blood Pressure, SMBP: Self measured Blood Pressure, TTE: Transthoracic echocardiography, yo: year-old

	All population	Female	Male	p (male vs female)	Public	Private	p (public vs private)
Corpulence	11539(44.6)	5984(42.2)	5546(47.4)	< 10 ⁻³	9454(46.8)	2085(36.6)	< 10 ⁻³
overweight (%)	5182(20)	3509(24.8)	1671(14.3)		3946(19.5)	1236(21.7)	
moderate obesity (%)	461(1.8)	375(2.6)	85(0.7)		302(1.5)	959(2.8)	
morbid obesity (%)	1354(5.2)	1043(7.4)	310(2.6)		959(4.7)	395(6.9)	
severe obesity (%)							
BMI (Kg/cm ²)	27.5(13.7–72.2)	28.3(14–70)	27.07 ± 3.93	< 10 ^{-3*}	27.3(14–72)	29(13.7–66.9)	< 10 ^{-3*}
Median (min-max)	28.1 ± 4.57	29.01 ± 4.57			27.9 ± 4.3	29.08 ± 5.13	
Mean ± SD							
Newly diagnosed HTN (%)	1475(5.7)	705(5.1)	770(6.8)	< 10 ⁻³	953(4.7)	522(9.2)	< 10 ⁻³
Moderate Renal Failure (%)	1524(5.9)	672(4.7)	851(7.3)	< 10 ⁻³	1305(6.5)	219(3.8)	< 10 ⁻³
Hypothyroidism (%)	1384(5.3)	1136(8)	248(2.1)	< 10 ⁻³	1034 (5.1)	350 (6.1)	0.002
Apnea syndrome	469(1.8)	257(1.8)	211(1.8)	0.02	276(1.4)	193(3.4)	< 10 ⁻³
Confirmed (%)	843(3.3)	499(3.5)	343(2.9)		505(2.5)	338(5.9)	
Suspected (%)							
COPD (%)	519(2)	137(1)	382(3.3)	< 10 ⁻³	380(1.9)	139(2.4)	0.008
Stroke history (%)	1707(6.6)	796(5.6)	910(7.8)	< 10 ⁻³	1311(6.5)	396(6.9)	0.2
Coronary disease (%)	4797(18.5)	1742(12.3)	3048(26.1)	< 10 ⁻³	3941(19.8)	856(15)	< 10 ⁻³
SBP (mmHg)	135(80–260)	135(80–260)	140(85–250)	< 10 ^{-3*}	140(80–260)	134.5(80–260)	0.1*
Median (min-max)	138.8 ± 19.6	138.5 ± 19.7	139.2 ± 19.4		138.9 ± 19.7	138.6 ± 19	
Mean ± SD							
DBP (mmHg)	80(40–140)	80(40–140)	80(40–140)	0.005*	80(40–140)	80(40–140)	0.6*
Median (min-max)	79.03 ± 11.1	78.8 ± 10.9	79.3 ± 11.3		78.9 ± 11.2	79.4 ± 10.7	
Mean ± SD							

**mann-whitney nonparametric test*

ABPM: Ambulatory blood pressure monitoring, ACE: Antagonist of conversion enzyme, ARB: Angiotensin Receptor Blockers, BMI: Body mass Index, CCB: Calcium Channels Blockers, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic Blood Pressure, EKG: electrocardiogram, HTN: hypertension, LVH : Left Ventricle Hypertrophy, SD: Standard Deviation, SBP: systolic Blood Pressure, SMBP: Self measured Blood Pressure, TTE: Transthoracic echocardiography, yo: year-old

	All population	Female	Male	p (male vs female)	Public	Private	p (public vs private)
HTN History > 6 months	23601(91.1)	13058 (55.3)	10543(44.7)	$< 10^{-3}$	18613(95.1)	4988(90.5)	$< 10^{-3}$
Controlled HTN (Target < 140/90 mmHg) (%)	12206 (51.7)	6825 (52.4)	5371 (50.9)	0.032	9361(50.3)	2845(57)	$< 10^{-3}$
Controlled HTN (Target < 130/80 mmHg) (%)	4386(18.6%)	2486(19.1)	1896(18)	0.033	3357(18)	1029(20.6)	$< 10^{-3}$
Heart rate (bpm)	74(40–150)	74(40–150)	73(40–150)	$< 10^{-3*}$	74(40–150)	70(40–150)	$< 10^{-3}$
Median (min-max)	73.8 ± 11	74.1 ± 11.1	73.5 ± 10.9		74.3 ± 10.8	72.2 ± 11.8	
Mean ± SD							
Heart rate > 80bpm (%)	4878(19.2)	2754(19.8)	2120(18.5)	0.009	3895(19.6)	983(17.8)	0.003
LVH on EKG or TTE (%)	3377(13)	1399(9.9)	1482(12.7)	$< 10^{-3}$	2125(10.5)	758(13.3)	$< 10^{-3}$
Atrial fibrillation (%)	1914(7.4)	1130(8)	783(6.7)	$< 10^{-3}$	1527(7.6)	387(6.8)	0.05
Recent lab tests < 6 months	14737(56.9)	8202(57.9)	6521(55.7)	$< 10^{-3}$	10302(77.8)	4435(51)	$< 10^{-3}$
Fasting Glucose (g/l)	1,1(0.5–3.9)	1.15(0.6–3.97)	1.1(0.6–3.9)	0.8*	1.129(0.6–3.9)	1.1(0.6–3.8)	$< 10^{-3*}$
Median (min-max)	1,3 ± 0.5	1.8 ± 6.1	1.6 ± 3.7		1.6 ± 2.5	1.9 ± 7.6	
Mean ± SD							
Creatinine (µmol/l)	81(30–700)	76(30–681)	89(32–700)	$< 10^{-3*}$	80(30–700)	85(30–663)	$< 10^{-3*}$
Median (min-max)	92.6 ± 50.7	85 ± 45.5	102 ± 55.11		93.1 ± 53.7	90.5 ± 38.5	
Mean ± SD)							
CreatininClearance (ml/min)	88.4(7-287)	96.4(7.62–287.3)	79.7(7.3–246)	$< 10^{-3*}$	89.2(7.3–287)	85(7.8–262)	$< 10^{-3*}$
Median (min-max)	90.4 ± 33.5	98.5 ± 35.3	80.3 ± 28		91 ± 34.6	88 ± 29	
Mean ± SD							

**mann-whitney nonparametric test*

ABPM: Ambulatory blood pressure monitoring, ACE: Antagonist of conversion enzyme, ARB: Angiotensin Receptor Blockers, BMI: Body mass Index, CCB: Calcium Channels Blockers, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic Blood Pressure, EKG: electrocardiogram, HTN: hypertension, LVH : Left Ventricle Hypertrophy, SD: Standard Deviation, SBP: systolic Blood Pressure, SMBP: Self measured Blood Pressure, TTE: Transthoracic echocardiography, yo: year-old

	All population	Female	Male	p (male vs female)	Public	Private	p (public vs private)
Total Cholesterol (g/l)	1.8(1–5)	1.8(1–5)	1.7(1–5)	$< 10^{-3*}$	1.8(1–5)	1.8(1–5)	0.6*
Median (min- max)	1.9 ± 0.6	1.96 ± 0.6	1.84 ± 0.6		1.8 ± 0.4	1.9 ± 0.7	
Mean ± SD							
K⁺ (mmol/l)	4.1(2.4-7)	4.1(2.5– 6.8)	4.1(2.4-7)	$< 10^{-3*}$	4.1(2.45-7)	4.1(2.5– 6.8)	0.005
Median (min- max)	4.1 ± 0.4	4.15 ± 0.4	4.1 ± 0.4		4.1 ± 0.48	4.1 ± 0.42	
Mean ± SD							
Microalbuminuria test during the last year (%)	4042 (15.6)	2226(15.7)	1814(15.5)	0.6	2190(10.8)	1852 (32.5)	$< 10^{-3}$
Positive Microalbuminuria (% among people who got the test)	1365(33.8)	652(29.3)	713(39.3)	$< 10^{-3*}$	910(41.6)	455(24.61)	$< 10^{-3}$
Drug treatment							
No drug (%)	4037(15.6)	2170(15.3)	1862(15.9)	0.3	3032(15)	1005(17.6)	$< 10^{-3}$
Monotherapy (%)	12042(46.5)	6626(46.8)	5408(46.2)		9794(48.5)	2248(39.5)	
Biotherapy (%)	6614(25.5)	3646(25.7)	2961(25.3)		5032(24.9)	1582(27.8)	
tritherapy or more (%)	3197(12.3)	1724(12.2)	1469(12.6)		2334(11.6)	863(15.1)	
Antihypertensive drugs							
ACE (%)	11770(45.5)	6420(45.3)	5341(45.6)	0.5	9251(45.8)	2519(44.2)	0.03
ARB (%)	5587(20.6)	3012(21.3)	2569(22)	0,17	3156(15.6)	2431(42.7)	$< 10^{-3}$
CCB (%)	8028(31.0)	4392(31)	3630(31)	0.9	6306(31.2)	1722(30.2)	0.14
Diuretics (%)	5514(21.3)	3061(21.6)	2446(20.9)	0.17	4304(21.3)	1210(21.2)	0.8
Betablockers (%)	5734(22.1)	3172(22.4)	2554(21.8)	0.27	4445(22)	1289(22.6)	0.3
Salt restriction (%)	13891(53.7)	7837(55.3)	6043(51.6)	$< 10^{-3}$	10789(53.4)	3102(54.4)	0.1
ABPM (%)	656(2.5)	352(2.5)	304(2.6)	0.5	314(1.6)	342(6)	$< 10^{-3}$
SMBP (%)	1630(6.3)	868(6.1)	762(6.5)	0.2	1053(4.1)	577(10.1)	$< 10^{-3}$
<i>*mann-whitney nonparametric test</i>							
<i>ABPM: Ambulatory blood pressure monitoring, ACE: Antagonist of conversion enzyme, ARB: Angiotensin Receptor Blockers, BMI: Body mass Index, CCB: Calcium Channels Blockers, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic Blood Pressure, EKG: electrocardiogram, HTN: hypertension, LVH : Left Ventricle Hypertrophy, SD: Standard Deviation, SBP: systolic Blood Pressure, SMBP: Self measured Blood Pressure, TTE: Transthoracic echocardiography, yo: year-old</i>							

	All population	Female	Male	p (male vs female)	Public	Private	p (public vs private)
Drug compliance (%)	19539(75.5)	10874(76.8)	8651(73.9)	$< 10^{-3}$	15326(75.9)	4213(73.9)	0.002
Physical activity (%)	3845(14.9)	1598(11.3)	2243(19.2)	$< 10^{-3}$	2748(13.6)	1097(19.3)	$< 10^{-3}$
<i>*mann-whitney nonparametric test</i>							
<i>ABPM: Ambulatory blood pressure monitoring, ACE: Antagonist of conversion enzyme, ARB: Angiotensin Receptor Blockers, BMI: Body mass Index, CCB: Calcium Channels Blockers, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic Blood Pressure, EKG: electrocardiogram, HTN: hypertension, LVH : Left Ventricle Hypertrophy, SD: Standard Deviation, SBP: systolic Blood Pressure, SMBP: Self measured Blood Pressure, TTE: Transthoracic echocardiography, yo: year-old</i>							

The mean age of our population was 64.0 ± 12.3 years (extremes: 18–108 years); the half of our patient (49.3%) were aged more than 65 year-old. There was a female predominance (sex ratio = 1.22). About 21.3% of the population was illiterate and only 9.4% got a university education. The rate of illiteracy was higher in women than in men (30.1% in female versus 10.8% in male). The majority of the model had a national health insurance (71.3%), a private insurance was more frequently noted in patients treated in private sector (5.8% versus 2.1%). The most associated risk factors were diabetes in 39.4 % and obesity in 25.8 %. Overweight or obesity were noted in 70.4%. The mean BMI of the population study was 28.1 ± 4.57 , it was significantly higher in women than in man ($p < 0.001$), and obesity was more prevalent in female patients than in male (34.8% versus 17.6%). One patient out of four had a history of cardiovascular events (coronary disease or/ and strokes), it means at very high cardiovascular risk.

The mean SBP during the visit office was 138.8 ± 19.6 mmHg and the mean DBP was 79.03 ± 11.1 mmHg. Using the cut-point of 140/90 mmHg as a BP target, 51.8 % of our patients had a controlled BP, but using the lower cut off recommended by the ACC/AHA of 130/80 mmHg, only 18.6% were controlled. Both DBP and SBP were significantly higher in man compared to women, but there were no significant differences between the private and the public sector. Women were also more likely to present atrial fibrillation (8% versus 6.7%, $p < 0.001$) and hypothyroidism (8% versus 2.1%, $p < 0.001$). Female patients were significantly more controlled than male (52.3% versus 50.9%, $p = 0.032$); Generally the male gender was found as an independent predictor of uncontrolled hypertension. In fact women were significantly more compliant to drug intake (76.6% versus 73.9%, $p < 10^{-3}$) and to salt restriction (55.3% versus 51.6%, $p < 10^{-3}$). Contrarily, men performed physical activities more frequently ($p < 10^{-3}$).

The patients who were treated in the public sector were more frequently smokers (15% versus 10.7%, $p < 10^{-3}$) and diabetics (40.5% versus 35.6%, $p < 10^{-3}$) compared to those treated in the private sector, but they performed less BP out office measurement. Moreover, they had less frequent physical activities (13.6% versus 19.3%, $p < 10^{-3}$). Thus, the rate of BP control was better in private sector (57% versus 50.3%, $p < 10^{-3}$ when we consider 140/90 mmHg as target).

The mean number of prescribed drug was 1.49 ± 0.6 , but 46.5% were on monotherapy and only 37.8 % received two antihypertensive treatments or more. The percentage of multiple drugs (2 or more) was higher in the private sector (42.9% versus 36.5%). An Antagonist of Conversion Enzyme (ACE) or an Angiotensin Receptor Blockers (ARB) were used in two patients out of three. The ACE class was more frequently prescribed in the public sector whereas the ARB class was more frequently used in the private sector.

On univariate analysis, patients with uncontrolled hypertension were significantly older, more frequently diabetic, obese and smokers. They were followed in the public sector, with more frequent history of strokes, and moderate renal failure

antecedents. These patients had also higher pulse rate (74.9 ± 11.4 bpm versus 72.5 ± 10.5 bpm, $p = < 0.001$). They practiced less frequently sport (11.5% versus 18.1%, $p < 0.001$) and are less compliant to the drug intake and the salt restriction.

Control of BP was better during the holly month (Ramadan), among 15239 hypertensive patients included during this month, with HTN history > 6 months, 53.3% individuals were in target.

Contrariwise, patients with controlled hypertension had more frequently a history of coronary diseases than others (19.9% versus 18.8%, $p = 0.033$), underwent more frequently electrocardiogram and echocardiography control and showed less frequently left ventricle hypertrophy (Table 2).

Table 2

Comparison of patients with controlled blood pressure to those with uncontrolled blood Pressure, based on univariate analysis

	Patients with Know hypertension > 6 months	Controlled BP (< 140/90)	Uncontrolled BP ($\geq$ 140/90 mmHg)	p
N	23601	12206	11395	
Age (years)	65(18–118)	65(18–118)	65(18–104)	0,022*
Median (min-max)	65.07 $\pm$ 11.9	64,94 $\pm$ 12,15	65.2 $\pm$ 11.6	
Mean $\pm$ SD				
Male (%)	10543(44.7)	5371(50.9)	5172(49.1)	0.032
Female (%)	13058 (55.3)	6835 (52.34)	6223 (47.6)	
Sex Ratio (F/M)	1.23	1.23	1.27	
Public sector (%)	18613 (78.9)	9361(76.7)	9252 (81.2)	$< 10^{-3}$
Ramadan inclusion (%)	15239 (64.6)	8132(66.6)	7107 (62.4)	$< 10^{-3}$
Education level	7182(30.4)	3688(30.2)	3494(30.7)	$< 10^{-3}$
Unprecised (%)	5236(22.2)	2588(21.2)	2648(23.2)	
Illiterate (%)	5111(21.7)	2548(20.9)	2563(22.5)	
Primary school	4041(17.1)	2217(18.2)	1824(16)	
Secondary school	2031(8.6)	1165(9.5)	866(7.6)	
University school				
Secondary/University education	6072(25.7)	3382(27.7)	2690(23.6)	$< 10^{-3}$

*mann-whitney nonparametric test

ABPM: Ambulatory blood pressure monitoring, ACE: Antagonist of conversion enzyme, ARB: Angiotensin Receptor Blockers, BMI: Body mass Index, CCB: Calcium Channels Blockers, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic Blood Pressure, EKG: electrocardiogram, HTN: hypertension, LVH: Left Ventricle Hypertrophy, SD: Standard Deviation, SBP: systolic Blood Pressure, SMBP: Self measured Blood Pressure, TTE: Transthoracic echocardiography, Yo: year-old,

	Patients with Know hypertension > 6 months	Controlled BP ($< 140/90$)	Uncontrolled BP ($\geq 140/90$ mmHg)	p
Health insurance coverage	624(2.6)	331(2.7)	293(2.6)	$< 10^{-3}$
Private insurance	17021(72.1)	9012(73.8)	8009(70.3)	
National insurance	4746(20.1)	2275(18.6)	2471(21.7)	
Indigent				
None				
unprecised				
	620(2.6)	296(2.4)	324(2.8)	
	590(2.5)	292(2.4)	298(2.6)	
History of HTN	1240 (5.3)	177 (3.7)	690 (5.7)	$< 10^{-3}$
< 1 y (%)	5922 (25.1)	1 138 (24.0)	3280 (26.9)	
1 to 5 y (%)	6293 (26.7)	1 434 (30.3)	3225 (26.4)	
5 to 10 y (%)	4620 (19.6)	1 486 (31.4)	2261 (18.5)	
10 to 15 y (%)	3187 (13.5)	503 (10.6)	148 (12.1)	
> 15 y (%)				
Smoking (%)	3226(13.7)	1525(12.5)	1701(14.9)	$< 10^{-3}$
Diabetes (%)	9730(41.2)	4738(38.8)	4992(43.8)	$< 10^{-3}$
Obesity (%)	6475(28.9)	3178 (27.4)	3297 (30.5)	$< 10^{-3}$
BMI	27.5(13–72)	27.4(13.7–67)	27.6(14.6–72)	$< 10^{-3*}$
Median (min-max)	28,1 $\pm$ 4,5		28,4 $\pm$ 4,6	
Mean $\pm$ SD		27,9 $\pm$ 4,5		
Moderate Renal Failure (%)	1479(6.3)	692(5.7)	787(6.9)	$< 10^{-3}$
Hypothyroidism (%)	1289(5.5)	679(5.6)	610(5.4)	0.4
Confirmed Apnea syndrome (%)	443(1.9)	201(1.6)	242(2.1)	0.004

**mann-whitney nonparametric test*

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	Patients with Know hypertension > 6 months	Controlled BP ($< 140/90$)	Uncontrolled BP ($\geq 140/90$ mmHg)	p
COPD (%)	502(2.1)	248(2)	254(2.2)	0.3
Stroke history (%)	1608(6.8)	765(6.3)	843(7.4)	$< 10^{-3}$
Coronary disease (%)	4579(19.4)	2433(19.9)	2146(18.8)	0.033
Median Heart rate	73(40–150)	71(40–150)	75(40–150)	$< 10^{-3*}$
Mean Heart rate $\pm$ SD (bpm)	73.6 $\pm$ 11	72.4 $\pm$ 10,5	74.8 $\pm$ 11,3	
Heart rate > 80bpm (%)	4328(18.3)	1773(14.6)	2555(22.6)	$< 10^{-3}$
LVH on EKG or TTE (%)	2728(11.6)	1213(9.9)	1515(13.3)	$< 10^{-3}$
Atrial fibrillation (%)	1834(7.8)	970(7.9)	864(7.6)	0.3
Recent lab tests < 6 months	13799(58.5)	7331(60.1)	6468(56.8)	$< 10^{-3}$
Fasting Glucose (mg/dl)	1.1(0.5–3.9)	1.1(0.5–3.9)	1.2(0.5–3.9)	$< 10^{-3*}$
Median (min-max)	1.3 $\pm$ 0.5		1.9 $\pm$ 6.1	
Mean $\pm$ SD)		1.6 $\pm$ 4.4		
Creatinine (μmol/l)	82(30–700)	80(30–700)	83(32–681)	$< 10^{-3*}$
Median (min-max)	93.07 $\pm$ 51,3	90.7 $\pm$ 47,3	95.5 $\pm$ 55,2	
Mean $\pm$ SD)				
Creatinin clearance (ml/min)	87.9(7-287)	89(7.34–287)	86.5(7.8–264)	$< 10^{-3*}$
Median (min-max)	89.9 $\pm$ 33.5		88 $\pm$ 34	
Mean $\pm$ SD)		91.2 $\pm$ 32		
Total Cholesterol (mg/dl)	1.8(1–5)	1.8(1–5)	1.8(1–5)	0.01*
Median (min-max)	1.9 $\pm$ 0.6	1.8 $\pm$ 0.6	1.93 $\pm$ 0.6	
Mean $\pm$ SD)				
K⁺ (mmol/l)	4.1(2.4-7)	4.1(2–7)	4.1(2.5-7)	0.3*
Median (min-max)	4.1 $\pm$ 0.46	4.1 $\pm$ 0.45	4.1 $\pm$ 0.5	
Mean $\pm$ SD)				
Proteinuria (+)	1306(5.5)	616(10.7)	690(13.3)	$< 10^{-3}$

**mann-whitney nonparametric test*

ABPM: Ambulatory blood pressure monitoring, ACE: Antagonist of conversion enzyme, ARB: Angiotensin Receptor Blockers, BMI: Body mass Index, CCB: Calcium Channels Blockers, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic Blood Pressure, EKG: electrocardiogram, HTN: hypertension, LVH: Left Ventricle Hypertrophy, SD: Standard Deviation, SBP: systolic Blood Pressure, SMBP: Self measured Blood Pressure, TTE: Transthoracic echocardiography, Yo: year-old,

	Patients with Know hypertension > 6 months	Controlled BP ($< 140/90$)	Uncontrolled BP ($\geq 140/90$ mmHg)	p
Drug treatment				
No drug (%)	3202(13.6)	1583(13)	1619(14.2)	$< 10^{-3}$
Monotherapy (%)	10959(46.4)	6294(51.6)	4665(40.9)	
Bitherapy (%)	6318(26.8)	3131(25.7)	3187(28.0)	
Tritherapy or more (%)	3122(13.2)	1198(9.8)	1924(16.9)	
Hypertensive drug				
ACE (%)	10734(45.5)	5602(45.9)	5132(45)	0.18
ARB (%)	5265(22.3)	3033(24.8)	2232(19.6)	$< 10^{-3}$
CCB (%)	7324(31)	3739(30.6)	3585(31.5)	0.16
Diuretics (%)	5018(21.3)	2643(21.7)	2375(20.8)	0.12
Betablockers (%)	5239(22.2)	2726(22.3)	2513(22.1)	0.6
One single pill therapy (%)	1506 (6.3)	766 (3.2)	740 (3.4)	0.829
Salt restriction (%)	13294(56.3)	8189(67.1)	5105(44.8)	$< 10^{-3}$
ABPM (%)	493(2.1)	231(1.9)	262(2.3)	0.02
SMBP (%)	1464(6.2)	758(6.2)	706(6.2)	0.9
Drug compliance (%)	18824(79.8)	10566(86.6)	8258(72.5)	$< 10^{-3}$
Physical activity (%)	3524(14.9)	2210(18.1)	1314(11.5)	$< 10^{-3}$
<i>*mann-whitney nonparametric test</i>				
<i>ABPM: Ambulatory blood pressure monitoring, ACE: Antagonist of conversion enzyme, ARB: Angiotensin Receptor Blockers, BMI: Body mass Index, CCB: Calcium Channels Blockers, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic Blood Pressure, EKG: electrocardiogram, HTN: hypertension, LVH: Left Ventricle Hypertrophy, SD: Standard Deviation, SBP: systolic Blood Pressure, SMBP: Self measured Blood Pressure, TTE: Transthoracic echocardiography, Yo: year-old,</i>				

Based on multivariate analysis, predictors of uncontrolled hypertension were of male gender, old age > 65 yo, diabetic, obese, smokers, in public sector management, HR more than 80 bpm. Contrariwise, predictors of controlled hypertension were of high educational level (secondary/university), with a history of coronary disease, salt restriction, drug compliance and regular physic activity (Table 3 and Fig. 1).

Table 3
Multivariate analysis: Independent predictors of Uncontrolled Blood Pressure

	OR	95% CI	P value
Male sex	1.09	1.02–1.16	0.006
Age > 65 y o	1.07	1.01–1.13	0.017
University or secondary education	0.909	0.84–0.97	0.006
Diabetes	1.18	1.11–1.25	< 10 ⁻³
Smoking	1.15	1.05–1.25	0.001
Obesity	1.14	1.075–1.219	< 10 ⁻³
Coronary disease	0.86	0.8–0.93	< 10 ⁻³
Public sector	1.25	1.16–1.34	< 10 ⁻³
HR > 80bpm	1.59	1.48–1.71	< 10 ⁻³
Salt restriction	0.48	0.45–0.51	< 10 ⁻³
Drug compliance	0.57	0.52–0.61	< 10 ⁻³
Physical Activity	0.77	0.71–0.84	< 10 ⁻³
<i>Bpm: beat per minute, CI: Confidence Interval, HR: Heart Rate, OR: odds Ration, Yo: year-old</i>			

Discussion

Hypertension is the most prevalent cardiovascular factors worldwide and is the main cause of death even in developed country [17]. Recently a large meta-analysis of 2939 sudden cardiac deaths (SCD) among 418,235 participants from 18 studies, showed that hypertension is associated with a twofold increase in risk of SCD and a 28% increase of SCD per 20 mmHg increment in SBP [18]. Moreover, in a pooled dataset from 44 low-income and middle-income countries including 1100507 participants, the authors showed that only 10.3% of hypertensive patients achieved BP control [9]. All these indicators demonstrate that hypertension is a public health problem in developed as well as developing countries. Tunisia, is a mild incomes country, and during the last decade, the Tunisian lifestyle, eating habits and the population ageing have widely changed; there has been an increase in cardiovascular risk factor [19]. Recently a national cross sectional Tunisian study “ATERA”, including 11 955 individuals showed that the prevalence of high blood pressure has increased to 50%, that of diabetes to 18% and that of obesity to 31% [20]. Face to these dramatic epidemiologic indicators, the Tunisian Society of Cardiology and Cardiovascular surgery, aimed to evaluate the cardiovascular profile of hypertensive patients and to assess the BP control, through a national flash study. In our knowledge, Nature HTN is the largest national survey of Hypertension in Africa. The most important findings of this registry is that the profile risk of the Tunisian has changed remarkably. In 2012, ben Romdhane et al published the results of TAHINA project, which was a Tunisian national survey including 8007 patients, aged between 35 and 70 years and examined across home visits. When comparing the results of TAHINA and Nature HTN among hypertensive patients, we found that the prevalence of illiterate people has decreased from 43–21.3%. Surprisingly, we found that the prevalence of diabetes among hypertensive people has deacreased from 62–39.4%, that of tobacco from 22–14% and that of obesity from 46–25% [11]. All these findings demonstrate that nowadays, the diagnosis of hypertension was made early before the development of diabetes and other comorbidities. That's why the rate of diabetic among hypertensive patients has decreased. This finding goes along with the improvement of the educational

level between the two studies, certainly the Tunisian citizen 's awareness of blood pressure risks, and management methods has evidently increased.

The second important finding of our registry is the improvement of BP control; in 2005, Ben Romdhane et al had conducted a Tunisian cross-sectional survey on 1837 adults, aged between 40–69 years old, only 13.2% of hypertensive individuals were controlled [7]. Then, hypertension control increased to 24.1% in the TAHINA project (2012) and recently we demonstrated in NATURE HTN that BP was controlled in 51.9% of our population when we consider 140/90 as a target. This rate is close to the rate achieved in many developed countries. Control of hypertension remains elusive nationally, despite widespread availability of effective therapies.

In fact, control hypertension remains a health problem in not only low and middle incomes countries but also even in high incomes countries. Ikeda et al, in a comparative analysis of national surveys in 20 countries, showed that hypertension was treated in 13.8–80.5% of hypertensive patients in the different countries but was controlled only in 4.4 % to 59.1% [10]. Recently, Pan et al reported a control of 60% of hypertensive patients in Taiwan, but the prevalence of diabetes, obesity and smoking in this cohort were lower compared to our population [21].

In California, the implementation of a large-scale hypertension program has been associated with a significant increase in hypertension control compared to the others cities of US. The control rate increased from 55% in 2001 to 64% in 2009. Key elements of this program included a comprehensive hypertension registry, development and sharing of performance metrics, evidence-based guidelines, medical assistant visits for blood pressure measurement, and single-pill combination pharmacotherapy [22].

Recently the FLASH 2019 study, a national French study has showed a rate of 54% of BP control [23]. This rate was stable in between the different Flash studies (2009–2019), a therapeutic inertia was advanced to explain the lack of BP control improvement. The monotherapy kept downgrading in the different guidelines but Girerd et al reported that the rate of monotherapy has increased according to the different FLASH studies, changing from 44% in 2009 to 55% in 2019, and he related the cause to the difficulties of drug reimbursement during the last years.

In our population, the BP control has improved, the reimbursement of Stage II and III hypertension costs as well as the availability of generic molecules, the improvement of the education level of the Tunisian population has certainly contributed to this achievement. However, management of patients in public sector was found as an independent predictor of uncontrolled hypertension. Certainly, this could be explained in part by the discrepancy of drug availability between the two sectors, the quality of health insurance and the lack of one single pill in public sector. However, we it is worth considering that we found in our cohort that patients treated in public sector seem to be at higher cardiovascular risk with higher prevalence obesity, diabetes, smoking with a less frequently physical activity. All these factors were identified as predictors of uncontrolled hypertension in our population and were behind the bad control of BP in public sector. Moreover, patients treated in the private sector ,underwent more frequently out office measurement, they had lower heart rate, better follow up with more frequent lab test. We noted also that ARB Class was more frequently prescribed in private sector and this class is associated with better tolerance and persistence. In public sector, the majority of patients take their drugs from the hospital. ARB class was not available in public sector. All these findings should be considered by the health ministry to improve the conditions of management of hypertensive patients in public sector where patients with the highest cardiovascular profile were treated.

The reimbursement of stage I hypertension costs by the national security fund is another point to discuss and which is missing both, in private and public sector. There is an urgent need for a comprehensive integrated population-based intervention program to improve the growing problem of hypertension in Tunisia.

Heart rate was another strong predictor of uncontrolled BP in our population and this is could be related to the big prevalence of overweight and obesity as well as the low physical activity practice. One patient out of five has a heart rate >

80bpm in our model. Recently, the ESC/ESH guidelines classified this clinical finding among the factors influencing cardiovascular risk [14, 24]. The Nice guidelines recommended to downgrade beta-blockers use and to limit their use to the specific settings [25], but we thought that sympathetic activation is well involved in the physiopathology of hypertension in Tunisian people, as it was demonstrated by the high Heart rate in our population [26]. Therapeutic education should be highly considered and practicing sports to reduce BP level highly recommended. In developed countries, 60% of the population practice sport regularly [27], in our study only 14% performed a physical activity. Recently, Sata rosa et al showed that active life style improves heart rate variability as well as reduces oxidative stress in hypertensive people and it improves BP control [28]. On the other hand, Beta blockers should not be dismissed, and patients with high HR, definitely need this therapeutic class.

Patients with a history of coronary disease were more in target in our model and ischemic cardiomyopathy was even identified as a predictor of controlled blood pressure. Many previous studies have confirmed these findings [6, 7, 10, 29], in fact patients with coronary disease are more compliant to their drugs and generally receive at least two class (beta blockers and ACE or ARB), moreover they consult their doctors more frequently.

Limits Of The Study

The main limit of our registry that it included only confirmed patients and didn't aim to assess the prevalence of hypertension, the rate of undiagnosed and non-treated hypertensive patients. If all these groups were considered, the control rate would be lower.

On the other hand, the definition of hypertension control was based on office measurements, we did not complete with a systematic out office measurements to check the white blouse high blood pressure effect, therefore the rate of uncontrolled patients could be over-estimated in this registry.

Finally, this cross sectional study did not evaluate the clinical follow up and the impact of uncontrolled blood pressure on cardiovascular events.

Conclusions

Nature HTN is the largest national survey of hypertension in Tunisia, it would contribute to analyze the burden of hypertension in a developing country, and highlight the important gaps in the treatment of hypertensive individuals. Certainly, it may help to guide the implementation of future interventions and to write national guidelines. The most important finding of this registry is that the control of hypertension has remarkably improved over the last years, although a high cardiovascular risk of our population. Therapeutic education along with substantial support and interest to the public sector are important preventive measure that can contribute to the public health in Tunisia.

Declarations

Ethics approval and consent to participate

An ethical approval letter has been obtained from the ethic committee of the Hospital of the Internal Security Forces. A written consent was obtained from all subjects. In case of illiterate participants written consent was obtained from legal guardians.

Consent for publication

Not applicable

Availability of data and materials

Data cannot be shared publicly because of privacy concern. Indeed, data might reveal the identity and the location of participants included into the study. Data are available from the Tunisian Society of Cardiology and Cardiovascular Surgery Ethics Committee (contact via Résidence les pergolas, Rue du Lac Huron Appartement 201, Berges du Lac – Tunisie, Email: secretaire.stcccv@gmail.com; Tel: (+216) 71 965 432) for researchers who meet the criteria for access to confidential data. there were no administrative permissions required to access the raw data from.

Competing interests

Authors declare that they have no conflict of interest.

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Not applicable

Authors' contributions

Leila Abid was a principal investigator. Rania Hammami was a major contributor in writing the manuscript. Yosra Mejdoub performed statistical analyzes. The other authors were investigators, they included their patients. All authors read and approved the final manuscript.

Imen gtif is a co-author and an investigator.

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Figures

Figure 1

Forest Plot graph: Predictors of Blood pressure control according to the Multivariate regression analysis BP: Blood Pressure, bpm: beat per minute, CI: confidence Interval, HR: Heart rate, OR: odd ratio, Yo: year old