# TRABALHO FINAL
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**MASKED HYPERTENSION: Review and analysis of a subpopulation of outpatients from the Hypertension Consultation of Hospital Santa Maria**

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**Summary**

Hypertension is defined as the level of Blood Pressure at which the benefits of treatment unequivocally outweigh the risks of treatment. In-office Hypertension is defined as Systolic Blood Pressure values above 140 mmHg measured at the office and/or Diastolic Blood Pressure ≥90mmHg.

Masked Hypertension is a condition defined by the patient having normal office blood pressure, with Blood Pressure values under 140/90 mmHg, and hypertension out of the office, with Blood Pressure values above 135/85 mmHg, measured through Ambulatory Blood Pressure Measurements or Home Blood Pressure Measurements.

Masked Hypertension has been associated with a greater risk of developing or evolving for sustained Hypertension in both young and older populations and with a risk for cardiovascular and chronic kidney disease comorbidities almost identical to sustained Hypertension.

In this work we analyzed several variables, related to Blood Pressure in-office and using Ambulatory Blood Pressure Measurements, from 2 samples, one group with Masked Hypertension and a Control group and compared them in between.

We concluded on the importance of Ambulatory Blood Pressure Measurements for the early diagnose of Mased Hypertension and how it should consensually be introduced in screening programs, especially for populations at higher risk of developing Hypertension.

**Sumário**

Hipertensão é definida como o nível de Pressão Arterial ao qual o benefício de tratamento inequivocamente ultrapassa os riscos. Hipertensão sustenida é definida como medicação em consultório de Pressão Arterial Sistólica superior a 140 mmHg e/ou Pressão Arterial diastólica ≥90mmHg.

Hipertensão Mascarada é uma condição definida por um paciente que apresenta valores normotensos em consulta, com valores inferiores a 140/90 mmHg, e hipertenso quando avaliado fora da consulta, com valores de Pressão Arterial

superiores a 135/85 mmHg, medidos através de Monitorização Ambulatória de Pressão Arterial ou avaliação da Pressão Arterial em domicílio.
A Hipertensão Mascarada tem sido associada a um risco aumento de desenvolver ou evoluir para Hipertensão sustenida, tanto em populações jovens como mais idosas e com um risco para comorbilidades cardiovasculares e doença renal crónica quase tão elevado como o da Hipertensão sustenida.
Neste trabalho analisamos várias variáveis, relacionadas com a Pressão Arterial em consulta e em Monitorização Ambulatória de Pressão Arterial, de 2 amostras, um grupo com Hipertensão Mascarada e um grupo Controlo e comparamo-las entre os mesmos.
Concluímos na importância da Monitorização Ambulatória de Pressão Arterial para o diagnóstico atempado de Hipertensão Mascarada e no benefício da sua introdução subsequente em programas de rastreio para populações em maior risco de desenvolver Hipertensão.

**Key-words**: Masked-Hypertension, Ambulatory Blood Pressure Measurements

**Index**


- Summary 3
- Index 5
- Introduction 7
    - Definition and Epidemiology
    - Pathophysiology
    - Risk Factors
    - Clinical Presentation
    - Blood Pressure Measurement Techniques
    - Diagnosis of Masked Hypertension
    - Assessment of Hypertension Mediated Organ Damage
    - Treatment
    - Prognosis
- Methods 22
- Results 25
- Discussion 33
- Conclusion 39
- Bibliography 43

## Introduction

### Definition and Epidemiology

Hypertension is defined as the level of Blood Pressure at which the benefits of treatment (either with lifestyle interventions or medication) unequivocally outweigh the risks of treatment, as documented by clinical trials.[1]

Despite increases in awareness and treatment, hypertension continues to be responsible for more combined years of life lost and years lived with disability than any other cause of morbidity and mortality.[2,3]

Hypertension can be classified in primary or secondary hypertension. Primary hypertension is also known as essential hypertension or idiopathic hypertension. Essential hypertension has no identified single etiology, but it is thought to be related with genetic factors, environmental factors, eating habits, sedentary lifestyle, and obesity.

Secondary hypertension is caused by another known medical condition. Generally, related with the cardiovascular, renal, or endocrine system. The prevalence of secondary hypertension is reported to be between 5–15% of the people with hypertension.[1]

Among the most common causes of Secondary Hypertension are Obstructive Sleep Apnea, Renal Parenchymal Disease, Atherosclerotic Renovascular Disease, Fibromuscular Dysplasia, Primary Aldosteronism, Phaeochromocytoma, Syndrome of Cushing, Thyroid pathology, Hyperparathyroidism, and Coarctation of the Aorta.[1]

There are several subtypes of Hypertension documented among the literature, namely Sustained Hypertension, Masked Hypertension and White Coat Hypertension.

In-office Hypertension is defined as Systolic Blood Pressure values above 140 mmHg measured at the office and/or Diastolic Blood Pressure $\geq$90mmHg. The latest consensus defines out-of-office daytime hypertension as Blood Pressure $\geq$135/85 mmHg, nighttime as Blood Pressure $\geq$120/70 mmHg and a 24 hour average as Blood Pressure $\geq$130/80 mmHg.[1,4]

Based on in-office Blood Pressure, the global prevalence of hypertension was estimated to be 1.13 billion in 2015, with a prevalence of over 150 million in central and eastern

Europe. The overall prevalence of hypertension in adults is around 30 - 45%. This high prevalence of hypertension is consistent across the world, irrespective of income status, i.e. in lower, middle, and higher income countries. Hypertension becomes progressively more common with advancing age, with a prevalence of more than 60% in people aged over 60 years. As population ages, adopts more sedentary lifestyles, and increases their body weight, the prevalence of hypertension worldwide will continue to rise.[4,5]

Masked Hypertension is a known condition defined by the patient having normal office blood pressure, with Blood Pressure values under 140/90 mmHg, and hypertension out of the office, with Blood Pressure values above 135/85 mmHg, measured through Ambulatory Blood Pressure Measurements or Home Blood Pressure Measurements.[6,7]

It is estimated that Hypertension affects 36% of the Portuguese population ad that 70% of the hypertensive population is not aware of their condition.[8]

About one-third of well-controlled in office hypertensive patients have uncontrolled masked hypertension.[7]

However, the term Masked Hypertension is appropriate to patients with hypertensive values in out-of-office measurements only when they are not under hypertensive treatment. To patients that present in-office normotensive values but out-of-office hypertensive values, who undertake hypertensive medication, should be assigned the term Masked Uncontrolled Hypertension.[4]

Masked hypertension can be found in approximately 15% of patients with a normal office Blood Pressure. The prevalence is greater in younger people, men, smokers, and those with higher levels of physical activity, alcohol consumption, anxiety, and a stressful working life. Obesity, diabetes, chronic kidney disease, family history of hypertension, and high–normal office Blood Pressure are also associated with an increased prevalence of masked hypertension.[1]

White Coat Hypertension is defined as the untreated condition in which Blood Pressure is elevated in the office but is normal when measured by Ambulatory Blood Pressure Measurement, Home Blood Pressure Measurement, or both.

Although the prevalence varies between studies, white-coat hypertension can account for up to 30 - 40% of people (and >50% in elderly populations) with an elevated office Blood Pressure. It is more common with ageing, in women, and in non-smokers. Its

prevalence is lower in patients with Hypertension Mediated Organ Damage, when office Blood Pressure is based on repeated measurements, or when a doctor is not involved in the Blood Pressure measurement. A significant white-coat effect can be seen at all grades of hypertension (including resistant hypertension), but the prevalence of white-coat hypertension is greatest in grade 1 hypertension.[1]

Hypertension can be classified in different grades according to Systolic and Diastolic Blood Pressure Measurements. The table 1 illustrates the classification of Hypertension according to the European Society of Hypertension.[1]

| **Classification** | Systolic Blood Pressure | | Diastolic Blood Pressure |
|---|---|---|---|
| **Optimal** | <120 mmHg | and | <80 mmHg |
| **Normal** | 120-129 mmHg | and/or | 80-84 mmHg |
| **High normal** | 130-139 mmHg | and/or | 85-89 |
| **Grade 1 Hypertension** | 140-159 mmHg | and/or | 90-99 |
| **Grade 2 Hypertension** | 160-179 mmHg | and/or | 100-109 mmHg |
| **Grade 3 Hypertension** | ≥180 mmHg | and/or | ≥110 mmHg |
| **Isolated Systolic Hypertension** | ≥140 mmHg | and | <90 mmHg |

Table 1: classification of Hypertension according to the European Society of Hypertension.

Blood pressure in humans presents a circadian variation profile with a morning increase, a small postprandial valley, and a deeper descent during night-time rest. Under certain conditions, the nocturnal decline in blood pressure can be reduced or even reversed (non-dipper), which is related to a significantly worse prognosis than a normal fall pattern (dipper).[9]

Blood Pressure values normally decrease during sleep time. A cut-off has been proposed to define patients as dippers if their nocturnal Blood Pressure falls by >10% of the daytime average Blood Pressure value and non-dippers if their Blood Pressure value doesn't fall or falls less than 10%. Among dippers we can subsequently scrutinize them between dippers and extreme dippers if the Blood Pressure falls by ≥30% of the daytime average during sleep time.[1]

Nonetheless, the 'dipping' status is often highly variable from day to day and thus is poorly reproducible. Recognized reasons for an absence of nocturnal Blood Pressure dipping are sleep disturbance, obstructive sleep apnea, obesity, high salt intake in salt-sensitive subjects, orthostatic hypotension, autonomic dysfunction, Chronic Kidney Disease, diabetic neuropathy, and old age.[1]

Pathophysiology

There are several factors associated with masked hypertension and masked uncontrolled hypertension such as environmental factor, genetics, and comorbidities.

In-office measures that occur after meals or significant food intake may be translated into a postprandial reduction of Blood Pressure. Thus, measurements that occur in such circumstances may lead to Masked Hypertension. Patients that face mental and physical stress at home or at work may present normotensive values at in-office evaluations and show hypertensive values when evaluated through Ambulatory Blood Pressure Measurements at the time of stressful circumstances.[4]

Sedentary and obese patients may record hypertensive values due to poor tolerance to physical activity and when evaluated at rest at the office present with normal Blood Pressure values. Individuals that smoke and have excessive alcoholic behavior are predisposed to have Masked Hypertension.[4]

Advanced age associated with a decrease baroreceptor activity and increase in Blood Pressure variability also results in a higher prevalence of Masked Hypertension, specially in males.

Shortened sleep time commonly starting at adolescence and obstructive sleep apnea have been shown to be associated with masked hypertension.[4]

Risk Factors

The risk for uncontrolled masked hypertension is even higher for patients with comorbidities such as chronic kidney disease. Masked Hypertension has been associated with a greater risk of developing or evolving for sustained Hypertension in both young and older populations and with a risk for cardiovascular and chronic kidney disease comorbidities almost identical to sustained Hypertension.[6,7]

It has been shown that masked hypertension is associated with an increase in aortic stiffness, renal injury and cardiovascular events and with symptoms of hypertension target-organ damage like left ventricular hypertrophy, increased pulse wave velocity and carotid intima and media thickness.[7]

The delay in making the diagnosis of masked hypertension might be associated with the elevated prevalence of target organ damage in patients with masked hypertension.[6]

Both masked hypertensive patients and masked uncontrolled patients have evidence of persistent target organ damage comparable to what is observed in patients with sustained hypertension.[6]

The prevalence of Masked Hypertension varies deeply on each population characteristics however the common use of antihypertensive medication increases the incidence of Masked Uncontrolled Hypertension.[7]

Several studies conducted with minority populations in the U.S.A showed that people of African and South-Asian inheritance had higher rates of Masked Hypertension along with greater left ventricular mass compared with normotensives as well as three times the odds of left ventricular hypertrophy. Multiple analysis reached the consensus that male gender, smoking, diabetes, and hypertensive treatment were predictors of Masked Hypertension.[4,10]

In a study conducted in children with Chronic Kidney Disease, Left Ventricular Hypertrophy was four times more frequent in the presence of Masked Hypertension as compared with those with normal Ambulatory Blood Pressure Measurements. In a different study of Chronic Kidney Disease patients almost 60% had Masked Hypertension diagnosed only through an Ambulatory Blood Pressure Measurement.[10]

Clinical Presentation

Hypertension is primarily a silent condition that can present itself as asymptomatic until target organ damage appears. In patients with Hypertension Mediated Organ Damage, we often find dizziness, facial flushing, headache, fatigue, epistaxis, and nervousness among the most common symptoms.

A 4$^{th}$ heart sound heard trough cardiac auscultation is one of the first signs to be detected in hypertensive heart disease.

Hypertension Mediated Organ Damage refers to structural or functional changes in arteries or end circulation organs, such as the heart, brain, eyes and kidneys, caused by an elevated Blood Pressure and is a signal of pre-clinical or asymptomatic cardiovascular disease.[1]

Hypertension Mediated Organ Damage is more frequent in severe or long term Hypertension but it is not unheard of to be found in less severe scenarios. It can be reversed by antihypertensive treatment, especially if initiated early in the process but longer the duration of hypertension more irreversible the damages become despite improvements in Blood Pressure control.[1]

Among the most common Hypertension Mediated Organ Damage we can found hypertensive cardiopathy, arterial thickness, hypertensive nephropathy, hypertensive retinopathy, and hypertensive cerebrovascular disease.[1]

Hypertensive cardiopathy is related with chronic increased left ventricular workload resulting in left ventricular hypertrophy, impaired left ventricular relaxation, left atrial enlargement, increased risk of arrythmias, especially Atrial Fibrillation, and an increased risk of Heart Failure with preserved Ejection Fraction and Heart Failure with reduced Ejection Fraction.[1]

Arterial thickness is most commonly seen in major blood vessels such as the internal carotid artery and femoral artery. Trough ultrasound techniques it is possible to detect thickness of the intima-media layer and/or the presence of atherosclerotic plaques in the arterial walls.

Large artery stiffening is the most important pathophysiological determinant of isolated systolic hypertension and age-dependent increase in pulse pressure. Carotid-femoral pulse wave velocity is the gold standard for measuring large artery stiffness. Stenotic aortic plaques have a strong predictive value for myocardial infarction and stroke.[1]

Hypertensive nephropathy is the second most important cause of Chronic Kidney Disease after Diabetes Mellitus. The diagnosis of hypertension induced renal damage is based on detecting reduced renal function and/or detecting albuminuria. A progressive reduction in estimated glomerular filtration rate and increased albuminuria indicates progressive loss of renal function and are both independent and additive predictors of increased cardiovascular risk and progression of renal disease.[1]

Hypertension may also be the presenting characteristic of asymptomatic primary kidney disease or a consequence of Chronic Kidney Disease presenting as Hypertension. The interaction between hypertension and Chronic Kidney Disease is complex and increases the risk of adverse cardiovascular and cerebrovascular outcomes. The pathophysiology of Chronic Kidney Disease associated hypertension is multifactorial with different mechanisms contributing to hypertension.[1,11]

Chronic Kidney Disease increases Blood Pressure through several mechanisms, including impaired sodium excretion and premature vascular ageing, which subsequently reduce baroreceptor sensitivity, increase sympathetic nervous tone, and activate the renin-angiotensin-aldosterone system. Underlying intrinsic kidney diseases such as glomerulonephritis can also cause hypertension.[3]

Hypertensive retinopathy is a consequence of arteriolar narrowing that leads to retinal hemorrhage, microaneurysms, hard exudates, cotton wool spots, and papilloedema.

Hypertension increases the prevalence of brain damage, of which transient ischemic events and strokes are the most severe acute clinical manifestations. In the asymptomatic phase of Hypertension, brain damage can be detected by magnetic resonance imaging as white matter hyperintensities, silent microinfarcts, lacunar microinfarctions, microbleeds, and brain atrophy. White matter hyperintensities and silent infarcts are associated with an increased risk of ischemic events and cognitive decline due to degenerative and vascular dementia.[1]

Although Intraparenchymal Hemorrhage accounts for less than 20% of cases of stroke, it continues to be associated with the highest mortality of all forms of stroke and substantial morbidity rates.[12]

Intraparenchymal Hemorrhage is classified between primary and secondary. Primary Intraparenchymal Hemorrhage accounts for 78 to 88% of cases of Intraparenchymal Hemorrhage and refers to the rupture of damaged small arterioles, most commonly secondary to either Hypertension or Cerebral Amyloidangiopathy. Secondary Intraparenchymal Hemorrhage is mostly secondary to coagulopathy cerebral venous thrombosis, Moyamoya Disease, Vasculitis, tumors, hemorrhagic conversion of ischemic stroke, rupture of mycotic aneurysm or vascular malformation, such as an arteriovenous malformation, arteriovenous fistula, or cavernous malformation.[12]

Hypertension is the primary risk factor for Intraparenchymal Hemorrhage. Hypertension induces degenerative changes in the small, arteriolar perforators which are thought to increase the likelihood of rupture of these blood vessels. Hence hypertensive hemorrhage has a tendency to occur in the deep brain structures supplied by these vessels (basal ganglia, thalamus, brainstem, and deep cerebellum).[12]

Blood Pressure Measurement Techniques

Blood Pressure can be assessed using different techniques, devices, and time frames. Auscultatory or oscillometer semiautomatic or automatic sphygmomanometers are the preferred method for measuring Blood Pressure in-office. These devices should be validated according to standardized conditions and protocols. Blood Pressure should initially be measured in both upper arms, using an appropriate cuff size for the arm circumference. If the Blood Pressure is substantially higher in one of the arms, the highest value should be considered and the respective arm should be used for posterior assessments. A consistent and significant Systolic Blood Pressure difference between arms (for example a difference superior to 15 mmHg) is associated with an increased cardiovascular risk, associated to atheromatous vascular disease, aortic dissection, and aorta coarctation.[1]

Automatic in-office multiple Blood Pressure readings improve the reproducibility of Blood Pressure assessments, and if the patient is seated alone and unobserved, the white coat influence can be substantially reduced or eliminated. Additionally, the Blood Pressure values are lower than those obtained by conventional office Blood Pressure measurements and are similar to those provided by ambulatory blood pressure monitoring or home blood pressure monitoring.[1]

Out-of-office Blood Pressure assessments refers to the use of either Home Blood Pressure Measurement or Ambulatory Blood Pressure Measurement, the latter usually over a 24 h period of assessment. It provides a larger number of Blood Pressure measurements than conventional in-office Blood Pressure in conditions that better represent daily routines and situations.[1]

Home Blood Pressure Measurement is the average of all Blood Pressure readings performed with a semiautomatic, validated Blood Pressure monitor, for at least 3 days

and preferably for 6–7 consecutive days before a consultation with a doctor, with readings in the morning and the evening, taken in a peaceful location after 5 minutes of rest, with the patient seated with their back and arm supported. Two measurements should be taken at each measurement session, performed 1 to 2 minutes apart from each other.

Ambulatory Blood Pressure Measurement provides the average of Blood Pressure readings over a defined period, most commonly a 24 hour period. The device is typically programmed to record Blood Pressure at 15 - 30 minutes intervals, and average Blood Pressure values are usually provided for daytime, night-time, and 24 hours. A diary of the patient's activities and sleep time can also be recorded. A minimum of 70% reliable and trustworthy Blood Pressure assessments are required for a valid Ambulatory Blood Pressure Measurement session.[1]

Home Blood Pressure Measurement and Ambulatory Blood Pressure Measurement better illustrate the patients' Blood Pressure on an environment closer to their daily routines and lifestyle, hence demonstrating a major advantage at the diagnosis of white coat hypertension and masked hypertension.[1]

Diagnosis of Masked Hypertension

Blood Pressure can be highly variable, consequently, the diagnosis of hypertension should not be based on a single set of Blood Pressure evaluation at a single doctor consultation, unless the Blood Pressure is substantially increased (e.g. grade 3 hypertension) and there is clear evidence of target organ damage. For all others, repeat Blood Pressure evaluations at follow-up doctors' consultations have been a long-standing strategy to confirm a persistent elevation in Blood Pressure, as well as for the classification of the hypertension status. Out-of-office Blood Pressure evaluations represent an alternative strategy to repeated office Blood Pressure evaluations to confirm the diagnosis of hypertension.[1]

A particular challenge is the identification of masked hypertension which is more likely in people with Blood Pressure in the high–normal range, with normal Blood Pressure but target organ damage mediated by hypertension, and normal Blood Pressure but high

total cardiovascular risk. For these out-of-office Blood Pressure evaluations should be considered to exclude masked hypertension.[1]

In-office measurements of Blood Pressure have been effective at detecting and initiating treatment for Sustained Hypertension however they fail to detect the outliers of white-coat hypertension, masked hypertension, and masked uncontrolled hypertension.

Although Home Blood Pressure Measurements have the advantage of detecting extra outliers when compared to in-office automatic Blood Pressure Measurements it has not the same specificity nor sensitivity as Ambulatory Blood Pressure Measurements according to a Chinese study comparing Home Blood Pressure Measurements with Ambulatory Blood Pressure Measurements where the first method failed to identify 25% of patients with Masked Hypertension confirming the superiority of Ambulatory Blood Pressure Measurement over Home Blood Pressure Measurement. Hence the recommendation from the British NICE (National Institute for Health and Care Excellence) of an Ambulatory Blood Pressure Measurement to confirm a clinical diagnosis or a conventional automatic Blood Pressure Measurement diagnose before initiating antihypertensive treatment.[4]

The US Preventive Services Task Force also supports the use of Ambulatory Blood Pressure Measurement as method of choice for detecting both outliers of White Coat hypertension and Masked Hypertension.[4,13]

The clinical indications for Ambulatory Blood pressure Measurements varies on their purposes.[14]

To diagnose White Coat Hypertension the indications are Stage 1 office hypertension, high variability of office blood pressure, to exclude pseudo-resistant hypertension, severely elevated office blood pressure without signs of target organ damage.[14]

To diagnose Masked Hypertension the indications are high-normal office blood pressure (130–139/85–89 mm Hg), normal office blood pressure with signs of target organ damage, normal office blood pressure in high-risk patients, risk factors for masked hypertension, i.e. diabetes, overweight and obesity, excessive alcohol intake, and smoking.[14]

Compared with in-office Blood Pressure, Home Blood Pressure Measurements values are usually lower, and the diagnostic threshold for hypertension is >_135/85 mmHg

(equivalent to in-office Blood Pressure ≥140/90 mmHg) when considering the average of 3–6 days of home Blood Pressure values.[1]

Compared with in-office Blood Pressure, Home Blood Pressure Measurements provide more reproducible Blood Pressure data and is more closely related to Hypertension Mediated Organ Damage, particularly Left Ventricular Hypertrophy.[1]

Ambulatory Blood Pressure Measurements values are, on average, lower than in-office Blood Pressure values, and the diagnostic threshold for hypertension is ≥130/80 mmHg over 24h, ≥135/85 mmHg for the daytime mean, and ≥120/70 for the night-time mean (all equivalent to in-office BP ≥140/90 mmHg).[1]

The criteria for the diagnosis of Hypertension using the different Blood Pressure Measurement techniques is summarized in table 2.

| **Category** | Systolic Blood Pressure | | Diastolic Blood Pressure |
|---|---|---|---|
| **In-office Blood Pressure** | ≥140 mmHg | and/or | ≥90 mmHg |
| **Ambulatory Blood Pressure** | | | |
| **Diurnal mean** | ≥135 mmHg | and/or | ≥85 mmHg |
| **Nocturnal mean** | ≥120 mmHg | and/or | ≥70 mmHg |
| **24h mean** | ≥130mmHg | and/or | ≥80 mmHg |
| **Home Blood Pressure** | ≥135 mmHg | and/or | ≥85 mmHg |

Table 2: Criteria for the diagnosis of Hypertension

The most recent guidelines for the management of arterial hypertension by the European Society of hypertension and the European Society of Cardiology recommend the use of out-of-office measurements techniques as an alternative strategy to repeated in-office Blood Pressure Measurements to confirm the diagnosis of Hypertension).[1]

Treatment

Lifestyle choices have a huge impact on the prevalence of certain diseases. When it comes to Hypertension a healthy lifestyle can prevent or delay the onset of hypertension and hence reduce the cardiovascular risk.[1]

Efficient lifestyle modifications can be sufficient to prevent or delay the use of medication in Grade 1 Hypertension and they are also helpful in amplifying the effect of antihypertensive medication but they should never be used to delay the start of antihypertensive medication in patients with Hypertensive Mediated Organ Damage or at a high level or cardiovascular risk.[1]

The recommended lifestyle modification strategies that have shown to reduce Blood Pressure are salt restriction, moderation of alcohol consumption, high consumption of fruits and vegetables, weight reduction and maintaining and ideal body weight, and regular physical activity. The biggest disadvantage of lifestyle modification strategies is the poor persistence and lack of consistency overtime.[1]

The majority of patients will need medication in addition to lifestyle modifications to achieve an optimal Blood Pressure. Recent Guidelines recommend the use of five major medication classes as antihypertensives; these are Angiotensin Converser Enzyme Inhibitors, Angiotensin II receptor blockers, beta-blockers, calcium channel blockers, and diuretics.[1]

From these pharmacological classes, 2 stand out for their addictive effect on Blood Pressure lowering. Both Angiotensin Converser Enzyme Inhibitors and Angiotensin II receptor blockers reduce albuminuria more than other pharmacological classes and are effective delaying the progression of Chronic kidney Disease. These are also effective in preventing or regressing Hypertension Mediated Organ Damage like Left ventricular hypertrophy and arteriolar remodeling.[1]

Masked Hypertension is common in people with dysmetabolic risk and asymptomatic target organ damage, hence the importance of Angiotensin Converser Enzyme Inhibitors and Angiotensin II receptor blockers in the treatment of Masked Hypertension in addiction to lifestyle modifications.[1]

## Assessment of Hypertensive Mediated Organ Damage

In order to assess the Hypertensive Mediated Organ Damage several screening tests can be taken upon on. Basic screening tests can help identify target organ damage before initiating more specific and sensitive tests.

Ambulatory Blood Pressure Measurements are a better predictor of Hypertension Mediated Organ Damage than in-office Blood Pressure. Additionally, 24h ambulatory Blood Pressure mean has been consistently shown to have a closer relationship with morbid or fatal events and is a more sensitive risk predictor than in-office Blood Pressure of Cardiovascular outcomes such as coronary morbid or fatal events and stroke.[1]

A 12-lead ECG screens for Left Ventricular Hypertrophy and other possible cardiac abnormalities and documents heart rate and cardiac rhythm. An Urine albumin: creatinine ratio can detect elevations in albumin excretion indicative of possible renal disease. A blood creatinine and estimated Glomerular Filtration Ratio can detect possible renal disease. A Fundoscopy can detect hypertensive retinopathy, especially in patients with grade 2 or 3 hypertension.[1]

More detailed screening can also be helpful such as Echocardiography to evaluate cardiac structure and function. A Carotid ultrasound is used to determine the presence of carotid plaque or stenosis, particularly in patients with cerebrovascular disease or vascular disease. An Abdominal ultrasound and Doppler studies are used to evaluate renal size and structure and exclude renal tract obstruction as possible underlying causes of CKD and hypertension, to evaluate abdominal aorta for evidence of aneurysmal dilatation and vascular disease, to examine adrenal glands for evidence of adenoma or phaeochromocytoma. A Renal artery Doppler study to screen for the presence of renovascular disease, especially in the presence of asymmetric renal size. Brain imaging to evaluate the presence of ischemic or hemorrhagic brain injury, especially in patients with a history of cerebrovascular disease or cognitive decline.[1]

Pulse Pressure is defined as the difference between the Systolic Blood Pressure and the Diastolic Blood Pressure, normal values for Systolic Blood Pressure and Diastolic Blood Pressure are estimated at 120 mmHg and 80 mmHg, respectively, producing an approximate value of 40 mmHg for average Pulse Pressure. A narrowed Pulse Pressure is defined as <25% of the Systolic Blood Pressure while a widened Pulse Pressure is defined as >100 mmHg, despite this Pulse Pressure should always be considered in the context of the patient's absolute SBP and DBP. The Pulse Pressure is used as an indirect marker or arterial stiffness and a narrowed Pulse Pressure is associated with worse cardiovascular outcomes.[15]

A Pulse Wave Velocity can estimate index of aortic stiffness and underlying arteriosclerosis. Carotid-femoral pulse wave velocity is the gold standard for measuring large artery stiffness. Reference values for pulse wave velocity are available in healthy populations and patients at increased Cardiovascular risk.[1]

A pulse wave velocity >10 m/s is considered a conservative estimate of significant changes of aortic function in middle-aged hypertensive patients.[1]

Central aortic Blood Pressure is often used as a superior predictor of cardiovascular risk compared to brachial Blood Pressure. Various techniques allow Central Blood Pressure to be derived from peripheral Blood Pressure Measurements using dedicated algorithms. Some studies and meta-analyses have shown that in hypertensive patients, Central Blood Pressure predicts Cardiovascular events and that there is a differential effect of antihypertensive drugs on central compared with brachial Blood Pressure, more specifically Calcium Channels Blockers and Angiotensin Converser Enzyme Inhibitors have a stronger effect reducing Central Blood Pressure than Beta-blockers.[1,16]

Carotid intima-media thickness is quantified by carotid ultra-sound, and/or the presence of plaques, and predicts cardiovascular risk. The carotid intima-media thickness is measured between the intimal-luminal and the medial-adventitial interfaces of the carotid artery wall represented as a double-line density on an ultrasound image.[1,17]

This holds true both for the intima-media thickness value at the carotid bifurcations (reflecting primarily atherosclerosis) and for the intima-media thickness value at the level of the common carotid artery (reflecting primarily hypertension-related hypertrophy). A carotid intima-media thickness >0.9 mm is considered abnormal, but the upper limit of normality varies with age. The presence of a plaque can be identified by an intima-media thickness $\geq$1.5 mm, or by a focal increase in thickness of 0.5 mm or 50% of the surrounding intima-media thickness value. The annual changes in intima-media thickness are small, and the differences between 25th and 75th percentiles are <1 mm, and therefore, a high degree of precision is required intima-media thickness measurement.[1,17]

Stenotic carotid plaques have a strong predictive value for both stroke and myocardial infarction, independent of traditional cardiovascular risk factors and confer superior

prognostic accuracy for future myocardial infarction compared with intima-media thickness.[1,17]

Prognosis

Masked Hypertension has overall cardiovascular risk equivalence to Grade 1 hypertension. Masked hypertension is frequently associated with target organ damage, such as Left Ventricular Hypertrophy and proteinuria—often long before a transition from Masked Hypertension to Sustained Hypertension happens.[4]

Starting antihypertensive treatment based only on in-office Blood Pressure assessments may have the effect of converting many patients with sustained hypertension into masked uncontrolled hypertension, rather than having the desired therapeutic goal of sustained normotension.[4]

Ambulatory Blood Pressure Measurement is the preferred diagnostic method of assessing out-of-office Blood Pressure during the start and duration of antihypertensive therapy. Home Blood Pressure Measurement can be a valuable supplement to Ambulatory Blood Pressure Measurement (or an alternative if the latter is not available). The two methods record Blood Pressure differently and tend to complement each other in confirming cardiometabolic risk, but Ambulatory Blood Pressure Measurement is the method of choice because it provides nighttime Blood Pressure assessments and may better define the overall risk of masked uncontrolled hypertension.[4]

Noteworthy undiagnosed and untreated masked hypertension and treated but uncontrolled masked hypertension represents two significant high-risk populations of public health concern.[4]

According to a Spanish Database, 31% of patients from a population who appeared to be controlled using conventional in-office Blood Pressure Measurements as follow-up were identified as having masked uncontrolled hypertension when monitored with Ambulatory Blood Pressure Measurement. Noteworthy nocturnal poor control of Blood Pressure was twice as common as daytime poor control of Blood Pressure according to Ambulatory Blood Pressure Measurements, and isolated nocturnal hypertension occurred in 24% of these patients.[18]

The common clinical characteristics of patients with Masked Uncontrolled hypertension were male sex, advanced age, obesity, smoking habits, diabetes, and longer history of hypertension.[4,18]

Evidence shows that patients identified with Masked Hypertension have increased risk of target organ damage and cardiovascular morbidity, approaching a similar risk to those with sustained hypertension.

Furthermore, the majority of people with Masked Hypertension have additional cardiometabolic risks, such as diabetes, obstructive apnea and Chronic Kidney Disease which require additional supervision besides antihypertensive medication.[4]

**Methods**

This work consists of a literature review focused on Masked Hypertension accompanied by a comparative study of a subpopulation of outpatients followed at the Hypertension Consultation of Hospital Santa Maria, that integrates Centro Hospitalar Lisboa Norte.

The literature review was conducted through PubMed library and Mendeley library using primarily the keywords “Masked Hypertension” and “Masked Uncontrolled Hypertension”. Furthermore, to complete the revision work, a smaller search was also conducted using the keywords “White-coat Hypertension”, “Secondary Hypertension”, and “Hypertensive Mediated Organ Damage”.

The selection of literature was reduced to guidelines, original articles, systematic-reviews, and meta-analysis and excluded clinical cases and narrative reviews. From the previous sample were used only literature published between 2014 and 2022. A total of 18 items were selected and reviewed for the analyses.

The subpopulation consisted in outpatients followed at the consultation of Hypertension of Hospital Santa Maria, due to Masked Hypertension and a control group of normotensive individuals.

To execute the analysis were gathered 96 individuals with Masked Hypertension and 95 individuals with normal Blood Pressure.

The data was collected by Professor Doctor Carlos Moreira and organized in a spreadsheet, forming a databased used for the purpose of this work.

The clinical examination for the Masked Hypertension group was conducted at the time of diagnose.

The study involves several parameters collected from both groups, including:

- Age,
- Body Mass Index (BMI),
-Systolic Blood Pressure (SBP) in-office,
-Diastolic Blood Pressure (DBP) in-office,
-Medium Blood Pressure (MBP) in-office,
-Pulse Pressure in-office,
-Heart Rate in-office,

-General Systolic Blood Pressure through Ambulatory Blood Pressure Measurements (SBP ABPM general),

-General Diastolic Blood Pressure through Ambulatory Blood Pressure Measurements (DBP ABPM general),

-General Medium Blood Pressure through Ambulatory Blood Pressure Measurements (MBP ABPM general),

-Heart Rate through Ambulatory Blood Pressure Measurements (HR ABPM),

-Daytime Systolic Blood Pressure through Ambulatory Blood Pressure Measurements (SBP ABPM daytime),

-Daytime Diastolic Blood Pressure through Ambulatory Blood Pressure Measurements (DBP ABPM daytime),

-Daytime Medium Blood Pressure through Ambulatory Blood Pressure Measurements (MBP ABPM daytime),

-Daytime Heart Rate through Ambulatory Blood Pressure Measurements (HR ABPM daytime),

-Nocturnal Systolic Blood Pressure through Ambulatory Blood Pressure Measurements (SBP ABPM nocturnal),

-Nocturnal Diastolic Blood Pressure through Ambulatory Blood Pressure Measurements (DBP ABPM nocturnal),

-Nocturnal Medium Blood Pressure through Ambulatory Blood Pressure Measurements (MBP ABPM nocturnal),

-Nocturnal Heart Rate through Ambulatory Blood Pressure Measurements (HR MAPA nocturnal),

-Aortic Systolic Blood Pressure (SBP aortic),

-Aortic Diastolic Blood Pressure (DBP aortic),

-Aortic Medium Blood Pressure (MBP aortic),

-Aortic Heart Rate (HR aortic),

-Wave pulse velocity (WPV),

-Interface between media and intima layer of the carotid artery (carotid media intima interface),

-Hemoglobin (Hb),

-Glycated Hemoglobin A1c (HbA1c),

-Cholesterol total,

-Cholesterol LDL,

-Cholesterol HDL,

-Triglyceride,

-Aspartate Aminotransferase (AST),

-Creatinine,

-Acid Uric.

To process the data, the software SPSS was used.It was constructed a table where the data analyzed were gathered presenting the specific variables according to sample and mean. The results are presented at table 3.

To better understand the data collected several tables were elaborated to able data observation differently. Table 4 presents the Age and Body Mass Index's Mean of both Control and Masked HTA group. Table 5 presents SBP in-office, SBP ABPM general, SBP ABPM daytime, SBP ABPM nocturnal and SBP aortic's Mean of both Control and Masked HTA group. Table 6 presents DBP in-office, DBP ABPM general, DBP ABPM daytime, DBP ABPM nocturnal and DBP aortic's Mean of both Control and Masked HTA group. Table 7 presents Carotid Media Intima Interface, Wave Pulse Velocity and Pulse Pressure in-office 's Mean. Table 8 presents Cholesterol Total, Cholesterol LDL and Cholesterol HDL's Mean. Table 9 presents Creatinine, Acid Uric and Glycated Hemoglobin A1c's Mean.

Afterwards were elaborated Tables containing the Pearson Correlation data regarding the variables in study, the results are presented in tables 10 to 22.

The final step of this work consisted in analyzing the graphics and its information, compare it with the most recent literature and draw the appropriate conclusions.

**Results**

| | Control (95) | Masked HTA (96) | |
|---|---|---|---|
| | Mean + Standard Deviation error | Mean \|Standard Deviation Error | P value |
| Age (years) | 59,0 ± 1,2 | 58,6 ± 1,2 | 0,813 |
| Body Mass Index (kg/$m^2$) | 26,7 ± 0,3 | 26,6 ± 0,4 | 0,886 |
| SBP in-office (mmHg) | 112,5 ± 1,3 | 117,1 ± 1,4 | 0,019 |
| DBP in-office (mmHg) | 83,0 ± 1,3 | 86,6 ± 1,4 | 0,065 |
| MBP in-office (mmHg) | 93 ± 1,3 | 96,7 ± 1,4 | 0,053 |
| Pulse Pressure in-offfice (mmHg) | 29,5 ± 0,3 | 30,5 ± 0,3 | 0,026 |
| Heart Rate in-office (bpm) | 67,9 ± 1,0 | 71,0 ± 1,2 | 0,046 |
| SBP ABPM general (mmHg) | 110,9 ± 1,2 | 141,6 ± 1,6 | 0,000 |
| DBP ABPM general (mmHg) | 80,6 ± 1,3 | 106,7 ± 1,7 | 0,000 |
| MBP ABPM general (mmHg) | 90,7 ± 1,2 | 118,4 ± 1,6 | 0,000 |
| HR ABPM general (mmHg) | 73,2 ± 1,2 | 73,6 ± 1,5 | 0,856 |
| SBP ABPM Daytime (mmHg) | 121,1 ± 1,2 | 150,7 ± 1,7 | 0,000 |
| DBP ABPM Daytime (mmHg) | 90,1 ± 1,2 | 101,0 ± 1,6 | 0,000 |
| MBP ABPM Daytime (mmHg) | 100,5 ± 1,2 | 117,5 ± 1,6 | 0,000 |
| HR ABPM Daytime (bpm) | 77,8 ± 1,0 | 78,2 ± 1,6 | 0,833 |
| SBP ABPM Nocturnal (mmHg) | 101 ± 1,3 | 110,6 ± 1,8 | 0,000 |

| | | | |
|---|---|---|---|
| **DBP ABPM Nocturnal (mmHg)** | 70,8 ± 1,4 | 71,5 ± 1,7 | 0,738 |
| **MBP ABPM Nocturnal (mmHg)** | 80,8 ± 1,3 | 84,5 ± 1,7 | 0,086 |
| **HR ABPM Nocturnal (bpm)** | 64,8 ± 1,1 | 76,4 ± 1,5 | 0,000 |
| **SBP aortic (mmHg)** | 96,4 ± 1,7 | 97,6 ± 1,3 | 0,0572 |
| **DBP aortic (mmHg)** | 66,1 ± 1,7 | 77,9 ± 1,3 | 0,000 |
| **MBP aortic (mmHg)** | 76,2 ± 1,7 | 84,4 ± 1,3 | 0,000 |
| **HR aortic (bpm)** | 62,8 ± 1,0 | 75,6 ± 1,5 | 0,000 |
| **WPV (m/s)** | 10,1 ± 0,1 | 12,1 ± 0,1 | 0,000 |
| **Carotid Media Intima Interface (mm)** | 0,8 ± 0,0 | 1,3 ± 0,0 | 0,000 |
| **Hemoglobin (g/dL)** | 13 ± 0,2 | 14,0 ± 0,2 | 0,000 |
| **Cholesterol Total (mg/dL)** | 159 ± 2,3 | 180,4 ± 2,1 | 0,000 |
| **Cholesterol HDL (mg/dL)** | 45,8 ± 0,9 | 48,9 ± 2,3 | 0,202 |
| **Cholesterol LDL (mg/dL)** | 86,2 ± 2,4 | 108,6 ± 2,2 | 0,000 |
| **Triglyceride (mg/dL)** | 134,8 ± 2,5 | 166,2 ± 2,6 | 0,000 |
| **AST (U/L)** | 18,9 ± 0,9 | 22,0 ± 1,3 | 0,049 |
| **Creatinine (mg/dL)** | 0,7 ± 0,0 | 1,1 ± 0,1 | 0,000 |
| **Hb A1c (%)** | 5,7 ± 0,0 | 5,8 ± 0,0 | 0,001 |
| **Uric Acid (mg/dL)** | 4,6 ± 0,2 | 5,8 ± 0,3 | 0,001 |

Table 3: Results from the variables in analyses.

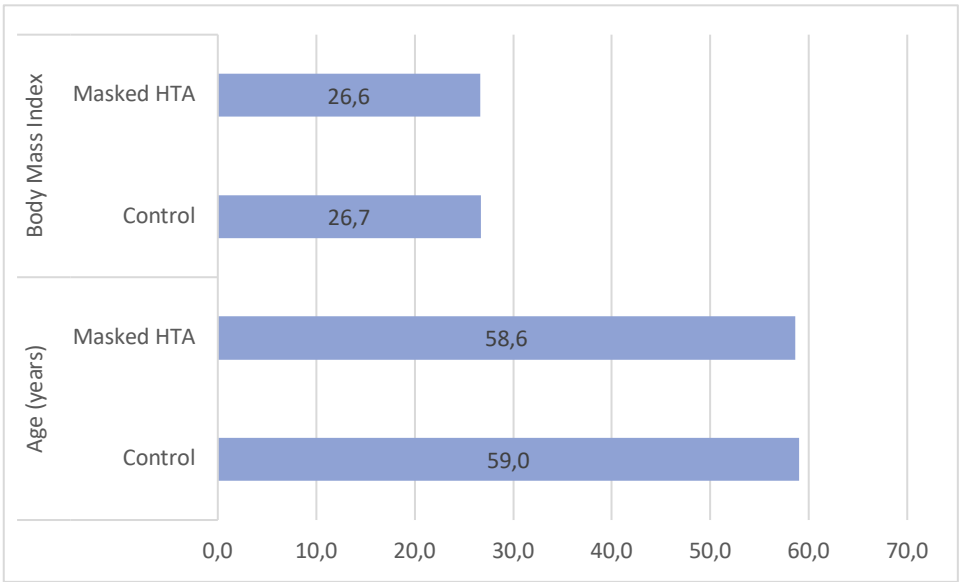


Table 4: Age and Body Mass Index's Mean of both Control and Masked HTA group.

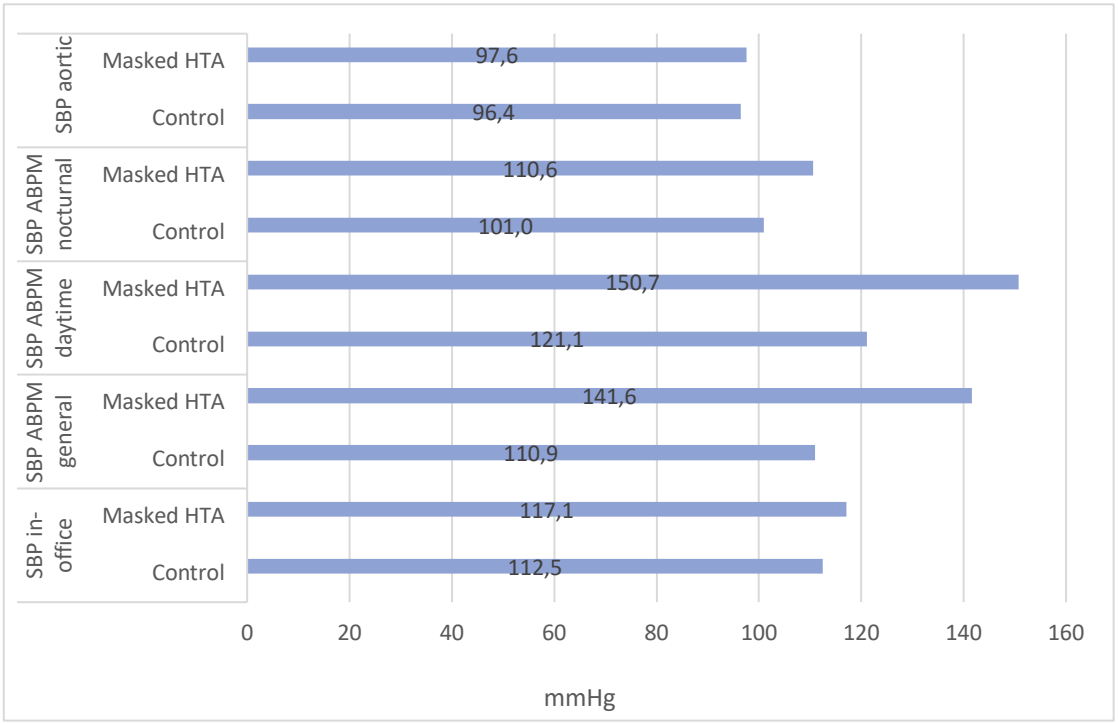


Table 5: SBP in-office, SBP ABPM general, SBP ABPM daytime, SBP ABPM nocturnal and SBP aortic's Mean of both Control and Masked HTA group.

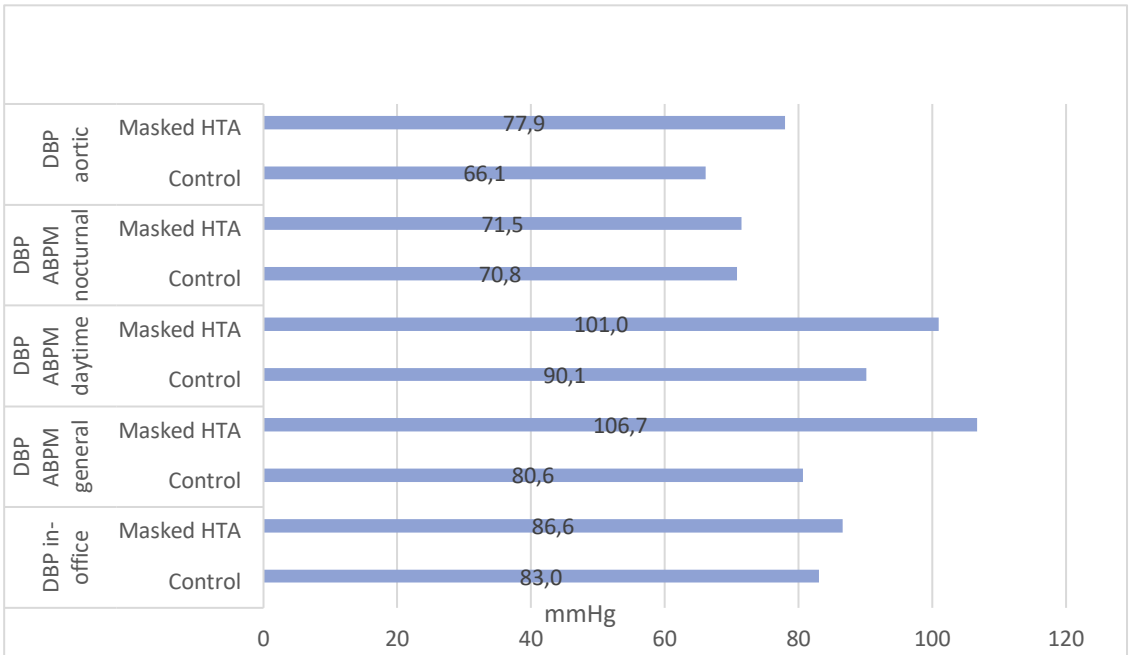


Table 6: DBP in-office, DBP ABPM general, DBP ABPM daytime, DBP ABPM nocturnal and DBP aortic's Mean of both Control and Masked HTA group.

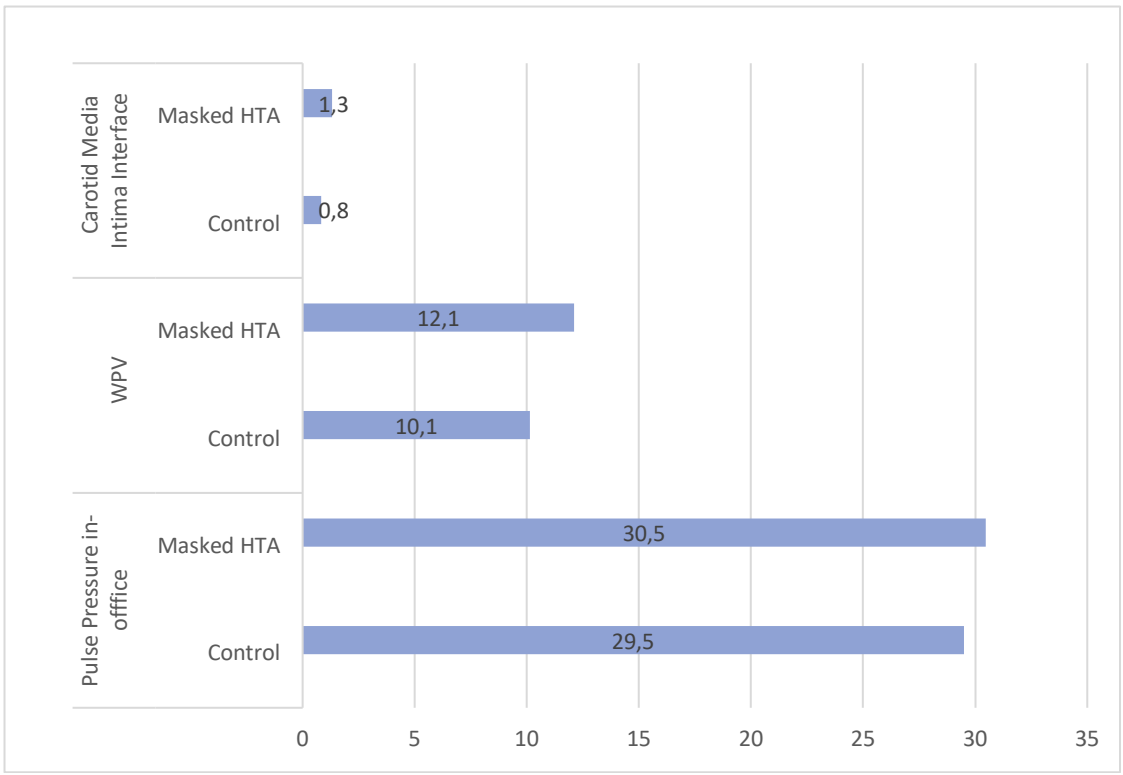


Table 7: Carotid Media Intima Interface, Wave Pulse Velocity and Pulse Pressure in-office 's Mean.

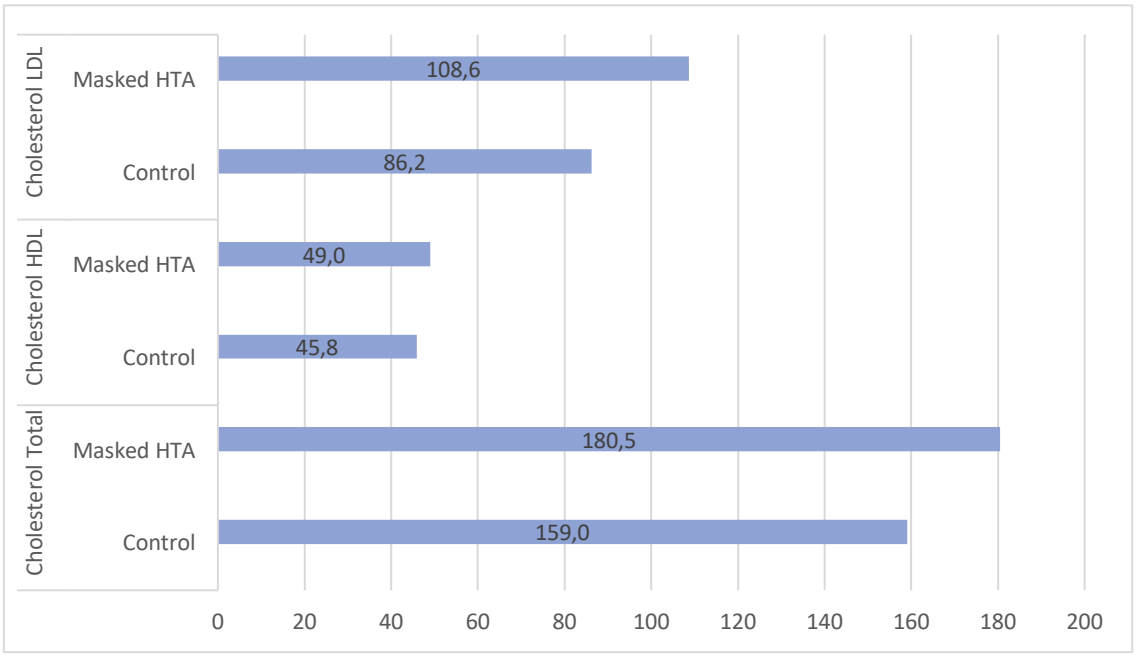


Table 8: Cholesterol Total, Cholesterol LDL and Cholesterol HDL's Mean.

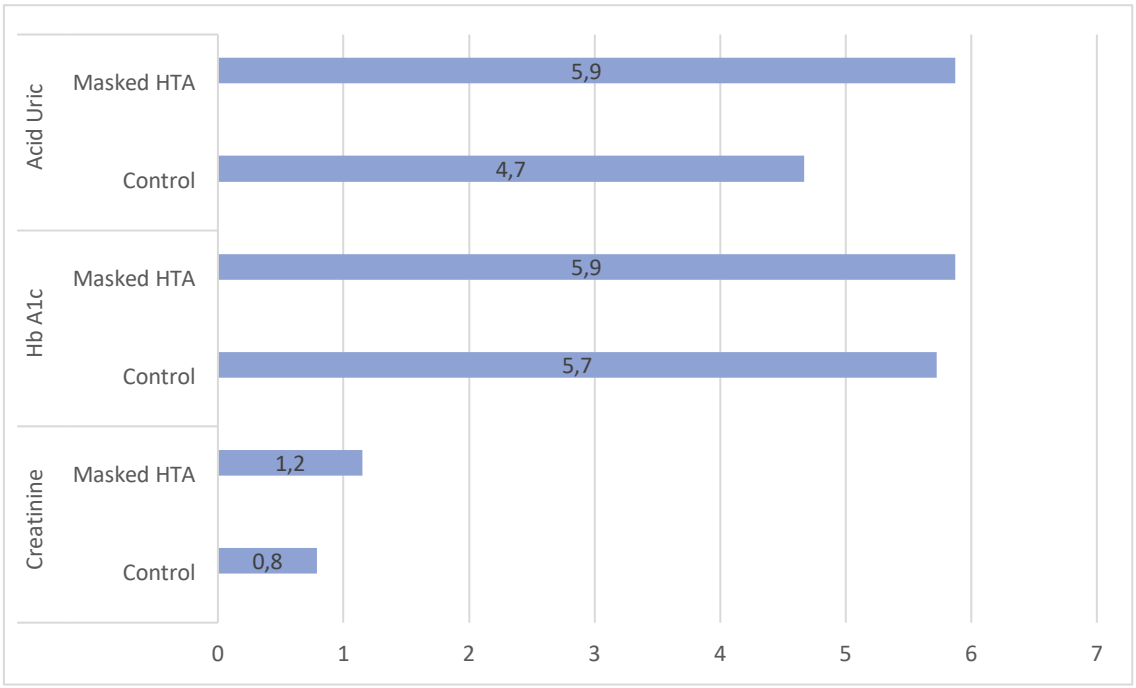


Table 9: Creatinine, Acid Uric and Hb A1c's Mean.

| Pearson Correlation | Age | Body Mass Index |
|---|---|---|
| SBP in-office | -0,112 | 0,124 |
| SBP ABPM general | 0,132 | 0,035 |

Table 10: Pearson Correlation of SBP in-office, SBP ABPM general, Age and Body Mass Index for the Control group.

| Pearson Correlation | Age | Body Mass Index |
|---|---|---|
| SBP in-office | -0,042 | 0,001 |
| SBP ABPM general | 0,187 | 0,116 |

Table 11: Pearson Correlation of SBP in-office, SBP ABPM general, Age and Body Mass Index for the Masked Hypertension group.

| Pearson Correlation | SBP in-office | SBP ABPM general | SBP ABPM daytime | SBP ABPM nocturnal | SBP aortic |
|---|---|---|---|---|---|
| SBP in-office | 1 | -0,120 | -0,093 | -0,13 | -0,098 |
| SBP ABPM general | -0,120 | 1 | 0,975 | 0,949 | 0,134 |
| SBP ABPM daytime | -0,093 | 0,975 | 1 | 0,973 | 0,104 |
| SBP ABPM nocturnal | -0,13 | 0,949 | 0,973 | 1 | 0,115 |
| SBP aortic | -0,098 | 0,134 | 0,104 | 0,115 | 1 |

Table 12: Pearson Correlation of SBP in-office, SBP ABPM general, SBP ABPM daytime, SBP ABPM nocturnal and SBP aortic for the Control group.

| Pearson Correlation | SBP in-office | SBP ABPM general | SBP ABPM daytime | SBP ABPM nocturnal | SBP aortic |
|---|---|---|---|---|---|
| SBP in-office | 1 | 0,063 | 0,068 | 0,073 | 0,109 |
| SBP ABPM general | 0,063 | 1 | 0,979 | 0,925 | 0,045 |
| SBP ABPM daytime | 0,068 | 0,979 | 1 | 0,936 | 0,024 |
| SBP ABPM nocturnal | 0,073 | 0,925 | 0,936 | 1 | 0,099 |
| SBP aortic | 0,109 | 0,045 | 0,024 | 0,099 | 1 |

Table 13: Pearson Correlation of SBP in-office, SBP ABPM general, SBP ABPM daytime, SBP ABPM nocturnal and SBP aortic for the Masked Hypertension group.

| Pearson Correlation | DBP in-office | DBP ABPM general | DBP ABPM daytime | DBP ABPM nocturnal | DBP aortic |
|---|---|---|---|---|---|
| DBP in-office | 1 | -0,098 | -0,029 | -0,109 | -0,063 |
| DBP ABPM general | -0,098 | 1 | 0,908 | 0,903 | 0,123 |
| DBP ABPM daytime | -0,029 | 0,908 | 1 | 0,888 | 0,116 |
| DBP ABPM nocturnal | -0,109 | 0,903 | 0,888 | 1 | 0,129 |
| DBP aortic | -0,063 | 0,123 | 0,116 | 0,129 | 1 |

Table 14: Pearson Correlation of DBP in-office, DBP ABPM general, DBP ABPM daytime, DBP ABPM nocturnal and DBP aortic for the Control group.

| Pearson Correlation | DBP in-office | DBP ABPM general | DBP ABPM daytime | DBP ABPM nocturnal | DBP aortic |
|---|---|---|---|---|---|
| DBP in-office | 1 | 0,048 | 0,026 | 0,039 | 0,095 |
| DBP ABPM general | 0,048 | 1 | 0,945 | 0,898 | 0,037 |
| DBP ABPM daytime | 0,026 | 0,945 | 1 | 0,899 | 0,073 |
| DBP ABPM nocturnal | 0,039 | 0,898 | 0,899 | 1 | 0,014 |
| DBP aortic | 0,095 | 0,037 | 0,073 | 0,014 | 1 |

Table 15: Pearson Correlation of DBP in-office, DBP ABPM general, DBP ABPM daytime, DBP ABPM nocturnal and DBP aortic for the Masked Hypertension group.

| Pearson Correlation | Carotid Media Intima Interface | Wace Pulse Velocity | Pulse Pressure in-office |
|---|---|---|---|
| SBP in-office | 0,174 | -0,044 | 0,115 |
| SBP ABPM general | -0,045 | -0,001 | -0,145 |

Table 16: Pearson Correlation of SBP in-office, SBP ABPM general, Carotid Media Intima Interface, Wave Pulse Velocity and Pulse Pressure in-office for the Control Group.

| Pearson Correlation | Carotida Media Intima Interface | Wace Pulse Velocity | Pulse Pressure in-office |
|---|---|---|---|
| SBP in-office | 0,105 | 0,246 | 0,068 |
| SBP ABPM general | 0,147 | 0,168 | 0,088 |

Table 17: Pearson Correlation of SBP in-office, SBP ABPM general, Carotid Media Intima Interface, Wave Pulse Velocity and Pulse Pressure in-office for the Masked Hypertension Group.

| Pearson Correlation | Cholesterol Total | Cholesterol LDL | Cholesterol HDL |
|---|---|---|---|
| SBP in-office | 0,112 | 0,093 | 0,029 |
| SBP ABPM general | 0,029 | 0,055 | 0,006 |

Table 18: Pearson Correlation of SBP in-office, SBP ABPM general, Cholesterol Total, Cholesterol LDL and Cholesterol LDL for the Control Group.

| Pearson Correlation | Cholesterol Total | Cholesterol LDL | Cholesterol HDL |
|---|---|---|---|
| PAS in-office | -0,009 | -0,092 | 0,044 |
| PAS MAPA general | 0,115 | 0,145 | 0,058 |

Table 19: Pearson Correlation of SBP in-office, SBP ABPM general, Cholesterol Total, Cholesterol LDL and Cholesterol LDL for the Masked Hypertension Group.

| Pearson Correlation | Creatinine | Acid Uric | Hb A1c |
|---|---|---|---|
| SBP in-office | -0,083 | -0,036 | 0,195 |
| SBP ABPM general | -0,025 | -0,028 | -0,158 |

Table 20: Pearson Correlation of SBP in-office, SBP ABPM general, Creatinine, Acid Uric and Glycated Hemoglobin A1c for the Control Group.

| Pearson Correlation | Creatinine | Acid Uric | Hb A1c |
|---|---|---|---|
| SBP in-office | -0,086 | 0,010 | -0,042 |
| SBP ABPM general | 0,061 | -0,003 | -0,076 |

Table 21: Pearson Correlation of SBP in-office, SBP ABPM general, Creatinine, Acid Uric and Glycated Hemoglobin A1c for the Masked Hypertension Group.

**Discussion**

As we can see represented in table 4, regarding the Body Mass Index there are no significant statistical differences between the control group (hereby group 1) and the Masked Hypertension group (hereby group 2). Despite no significant statistical differences being registered between group 1 and 2, both Body Mass Indexes fall on the category of over-weight or pre-obesity which mirrors the Portuguese population growing prevalence of obesity and overweight.

Regarding the Age there is no significant statistical difference between group 1 and 2.

According to table 10 and 11, the Pearson Correlation among Age and Body Mass Index, and Systolic Blood Pressure in-office and general Systolic Blood Pressure measured through Ambulatory Blood Pressure Measurements (ABPM) for both the Control and the Masked Hypertension group, is close to zero indicating that there is not a strong correlation among these variables. For both groups these variables present p values >0,05 attributing a weak statistical significance to this correlation.

As represented in table 5, regarding the Systolic Blood Pressure in-office, both groups present values considered optimal for Blood Pressure. The optimal in-office Systolic Blood Pressure is under 120 mmHg placing both groups on an optimal category classification of Blood Pressure.

Regarding the general Systolic Blood Pressure measured through ABPM we realize that group 2 presents values compatible with a diagnose of Masked Hypertension. The criteria for diagnose using the Ambulatory Blood Pressure Measurement is Systolic Blood Pressure above 130 mmHg, with group 2 presenting 142 mmHg which fits the criteria for Masked Hypertension while group 1 presenting 111 mmHg, values compatible with an optimal Blood Pressure just like evaluated in-office.

Regarding the daytime Systolic Blood Pressure measured through ABPM, the criteria for diagnose is Systolic Blood Pressure above 135 mmHg, with group 2 presenting a value of 151 mmHg, it is considered fit for the diagnose of Masked Hypertension while group 1 presents 121 mmHg values compatible with an optimal Blood Pressure according to the in-office evaluation.

Regarding the nocturnal Systolic Blood Pressure measured through ABPM, the criteria for diagnose is Systolic Blood Pressure above 120 mmHg, with group 2 presenting 111

mmHg and group 1 presenting 101 mmHg. Therefore, neither of the groups fits the criteria for Masked Hypertension according to the nocturnal evaluation of Systolic Blood Pressure measured through ABPM. The nocturnal measure was the only parameter related to Systolic Blood Pressure measured during a 24 hour period that didn't qualified group 2 to a diagnose of Masked Hypertension.

Regarding the aortic Systolic Blood Pressure, the reference values are considered normal when under 110 mm Hg. In this case, both groups present values under the reference value however group 2 presents a slightly more increased value, with 98 mmHg compared to the 97 mmHg of group 1.

According to table 12 and 13, the Pearson Correlation among general Systolic Blood Pressure measured ABPM, daytime Systolic Blood Pressure measured through ABPM and nocturnal Systolic Blood Pressure measured through ABPM, is close to 1, demonstrating a strong correlation among these variables.

A positive correlation value means that when one of the variables increases the other tends to increase as well in a linear relation. In this case there is a positive correlation regarding the increase in general Systolic Blood Pressure with daytime Systolic Blood Pressure and nocturnal Systolic Blood Pressure and also regarding the increase of daytime Systolic Blood Pressure with nocturnal Systolic Blood Pressure, this applies for both the Control and Masked Hypertension group. For both the Control and the Masked Hypertension group, the correlation amongst the Systolic Blood Pressure measurements is statistically significant, presenting a p value < 0,01.

The Pearson Correlation value among Systolic Blood Pressure in-office and general Systolic Blood Pressure measured through ABPM, daytime Systolic Blood Pressure measured through ABPM, nocturnal Systolic Blood Pressure measured through ABPM and aortic Systolic Blood Pressure, is close to zero indicating that there is not a strong correlation among these variables, this applies for both the Control and Masked Hypertension group. For both groups these variables present p values >0,05 attributing a weak statistical significance to this correlation.

As represented in table 6, regarding the Diastolic Blood Pressure in-office, both groups present values considered normal but not optimal for Blood Pressure. The optimal in-office Diastolic Blood Pressure is under 80 mmHg, normal is between 80 and 84 mmHg and high normal between 85 and 89 mmHg, with values above 90 mmHg being

considered Hypertension Grade 1, placing group 1 on a normal classification for Blood Pressure and group 2 on a high normal classification for Blood Pressure. High normal is often referenced as pre-hypertension grade emphasizing the risk of developing Hypertension, which among the Masked Hypertension group follows the literature which states that these individuals often present values qualified as high normal on in-office evaluations, suggestion that further studies with Ambulatory Blood Pressure Measurements may be beneficial for these individuals to allow early diagnose.

Regarding the general Diastolic Blood Pressure measured through ABPM we realize that both group present values compatible with a diagnose of Masked Hypertension.

The criteria for diagnose using the Ambulatory Blood Pressure Measurement is Diastolic Blood Pressure above 80 mmHg, with group 2 presenting 107 mmHg which fits the criteria for Masked Hypertension and group 1 presenting 81 mmHg, which is considered sufficient for the diagnose of Masked Hypertension.

Regarding the daytime Diastolic Blood Pressure measured through ABPM, the criteria for diagnose is Systolic Blood Pressure above 85 mmHg, with group 2 presenting a value of 101 mmHg and group 1 presenting a value of 90 mmHg, both groups are considered fit for the diagnose of Masked Hypertension.

Regarding the nocturnal Diastolic Blood Pressure measured through ABPM, the criteria for diagnose is Diastolic Blood Pressure above 70 mmHg, with both group 1 and 2 presenting 71 mmHg, both groups are considered fit for the diagnose of Masked Hypertension.

Regarding the aortic Diastolic Blood Pressure, the reference values are considered normal when under 80 mm Hg. In this case, both groups present values under the reference value however group 2 presents a significantly increased value compared to group 1, with 78 mmHg and 66 mmHg respectively.

According to table 14 and 15, the Pearson Correlation among general Diastolic Blood Pressure measured through ABPM, daytime Diastolic Blood Pressure measured through ABPM and nocturnal Diastolic Blood Pressure measured through ABPM, is close to 1, demonstrating a strong correlation among these variables. In this case there is a positive correlation regarding the increase in general Diastolic Blood Pressure with daytime Diastolic Blood Pressure and nocturnal Diastolic Blood Pressure and also regarding the increase of daytime Diastolic Blood Pressure with nocturnal Diastolic Blood Pressure,

this applies for both the Control and Masked Hypertension group. For both the Control and the Masked Hypertension group, the correlation amongst the Diastolic Blood Pressure measurements is statistically significant, presenting a p value < 0,01.

The Pearson Correlation value among Diastolic Blood Pressure in-office and general Diastolic Blood Pressure measured through ABPM, daytime Diastolic Blood Pressure measured through ABPM, nocturnal Diastolic Blood Pressure measured through ABPM and aortic Diastolic Blood Pressure, is close to zero indicating that there is not a strong correlation among these variables, this applies for both the Control and Masked Hypertension group. For both groups these variables present p values >0,05 attributing a weak statistical significance to this correlation.

As represented in table 7, Pulse Pressure, Wave Pulse Velocity and Carotid Media Intima interface are overall increased in group 2 compared with group 1. Regarding Carotid Media Intima Interface, the mean of group 2 is above 0.9 mm, the cut-off used as indication for abnormality in arterial stiffness whereas the mean of group 1 is under the cut-off indicating that the Masked Hypertension group has increased arteriosclerosis, with a higher cardiovascular risk and worst future cardiovascular outcomes.

Regarding Wave Pulse Velocity, both groups have increased Wave Pulse Velocities and above the cut-off of 10 m/s per which is considered to exist significant changes in aortic function including aortic stiffness and arteriosclerosis, considering that Wave Pulse Velocity is a gold standard measure to evaluate large vessels stiffness. Despite being both above recommended levels, group 1 is only slightly increased, with 10,1 m/s, while group 2 has a considerable increase, with 12,1 m/s, stating that the Masked Hypertension group has a higher prevalence of aortic stiffness and arteriosclerosis.

Regarding the Pulse Pressure, this is considered low when under 25% of the Systolic Blood Pressure. The values regarding the Pulse Pressure were considered for the in-office Blood Pressure measurements and therefore will be compared with the Systolic Blood Pressure in-office values. For group 1, the reference Pulse Pressure mean value translates in 28 mmHg and for group 2 translates in 29,5 mmHg. Hence, both groups present values of Pulse Pressure above 25% of the Systolic Blood Pressure values.

However, if considered the values of Systolic Blood Pressure measured through Ambulatory Blood Pressure Measurements, for group 1 the reference value of Pulse Pressure would be 27,5 mmHg and for group 2 it would be 35,25. This comparison would

put the control group with a desirable value of Pulse Pressure but the Masked Hypertension group with a value under the 25% of Systolic Blood Pressure recommended, consequently representing a narrowed Pulse Pressure associated with aortic stiffness and arteriosclerosis.

Considering these analysis focuses on the hidden consequences, such as late detected hypertension mediated target organ damage of Masked Hypertension, it is crucial to compare the values of Pulse Pressure with the Blood Pressure that individuals register during an entire 24 hour period other than during a medical consultation.

According to table 16 and 17, the Pearson Correlation among Carotid Media Intima Interface, Wave Pulse Velocity and Pulse Pressure in-office, and Systolic Blood Pressure in-office and general Systolic Blood Pressure measured through Ambulatory Blood Pressure Measurements, for both the Control and the Masked Hypertension group, is close to zero, in almost all variables, indicating that there is not a strong correlation among these variables and presenting a p values >0,05 which attributes a weak statistical significance to this correlation.

The exception falls on the correlation between the Wave Pulse Velocity and the Systolic Blood Pressure in-office of the Masked Hypertension group with a Pearson correlation of 0,246 and a p value <0,05, proving a statistical significance in this correlation.

As represented in table 8, regarding the Cholesterol Total neither group 1 nor 2 have values that fit the criteria for hypercholesterolemia however it is important to emphasize that the values of Cholesterol Total are significantly higher in group 2 compared with group 1, with 180 mg/dL and 159 mg/dL respectively. This places the Masked Hypertension group very close to the cut-off of 200 mg/dL for hypercholesterolemia.

Regarding the Cholesterol LDL, a similar scenery applies, with both groups presenting values according to the reference values but with the Masked Hypertension group with values very close to the maximum superior normal level, with 109 mg/dl and the Control group with 86 mg/dL.

Regarding the Cholesterol HDL there are no significant statistical differences between the 2 groups. Group 1 presents 46 mg/dL and group 2 presents 49 mg/dL, with both groups settling below the recommended values. For the purpose of this work, the

maximum superior normal level considered for Cholesterol LDL was under 110 mg/dL and for Cholesterol HDL was above 45 mg/dL.

According to table 18 and 19, the Pearson Correlation among Cholesterol Total, Cholesterol LDL and Cholesterol HDL, and Systolic Blood Pressure in-office and general Systolic Blood Pressure measured through Ambulatory Blood Pressure Measurements, for both the Control and the Masked Hypertension group, is close to zero, indicating that there is not a strong correlation among these variables. For both groups these variables present p values >0,05 attributing a weak statistical significance to this correlation.

As represented in table 9, regarding Glycated Hemoglobin A1c there is no significant statistical difference between group 1 and 2, and both groups have values considered within the reference interval with 5,7% and 5,8% respectively. For the purpose of this work, the reference interval for Glycated Hemoglobin A1c was 4 to 6.5%.

Regarding the Acid Uric, there is no significant statistical difference between group 1 and 2 and both groups have values considered within the reference interval with 4,6 mg/dL and 5,8 mg/dl respectively. For the purpose of this work, the reference interval for acid uric was 2,5 to 7 mg/dL.

Regarding the Creatinine, although both groups present values considered normal for the reference interval, there is a difference between both groups. Group 1 presents values considerably lower than group 2, with 0,79 mg/dL and 1,15 mg/dL respectively, with the Masked Hypertension group being closer to the maximum superior normal value. High levels of Creatinine are associated with renal function deterioration which can be found in Hypertensive Nephropathy and Chronic Kidney Disease, mirroring possible hypertension mediated target organ damage. For the purpose of this work, the reference interval for Creatinine was 0,6 to 1,3 mg/dL.

According to table 20 and 21, the Pearson Correlation among Creatinine, Acid Uric and Glycated Hemoglobin A1c, and Systolic Blood Pressure in-office and general Systolic Blood Pressure measured through Ambulatory Blood Pressure Measurements, for both the Control and the Masked Hypertension group, is close to zero, indicating that there is not a strong correlation among these variables. For both groups these variables present p values >0,05 attributing a weak statistical significance to this correlation.

**Conclusions**

With this analysis we were able to take several conclusions on the diagnose of Hypertension in Portugal. Firstly, using only Systolic Blood Pressure values from in-office evaluations increases the rate of undiagnosed hypertensive patients. As discussed prior according to the in-office Systolic Blood pressure evaluations both groups presented optimal Blood Pressure values which did not coincided with the results from the Ambulatory Blood Pressure Measurements, emphasizing the importance of further Blood Pressure studies on the population to allow a more effective screening for Hypertension, especially in population at higher cardiovascular risk.

It would be of great interest to have in possession the criteria which led the population on group 2 to undergo an Ambulatory Blood Pressure Measurement study and identify the common denominators such as clinical personal and family history, eating and exercise habits, lifestyle, and other potential risk factors for the development of masked Hypertension.

Secondly, the nocturnal Systolic Blood Pressure drops significantly in patients with Masked Hypertension, with all patients considered dipper or extreme dipper. Non-dippers have a worst prognosis compared to patients with dipper status, and are usually related to sleep disturbances, obstructive sleep apnea, obesity, high salt intake in salt-sensitive individuals, orthostatic hypotension, autonomic dysfunction, Chronic Kidney Disease, diabetic nephropathy, and old age. Some of these are common risk factors for the development of Masked Hypertension which could suggest that individuals with Masked Hypertension are more susceptible to present a non-dipper status however this does not come true. Noteworthy, the dipper and non-dipper status in highly variable and cannot be accurately evaluated in one single night of Ambulatory Blood Pressure monitorization. It would be interesting to conduct a further study where individuals with Masked hypertension are monitored with Ambulatory Blood pressure Measurements for a period of several days to inquire their dipper and non-dipper status more truthfully.

Thirdly, considering the data on Diastolic Blood Pressure Measurements simple conclusions were difficult to obtain. The in-office evaluations follow the most recent literature and show that high normal values of Blood Pressure in-office can be an indicative for further studies since individuals with Masked Hypertension often present borderline normal values of Blood Pressure in-office and reveal a Masked Hypertension

diagnose with an Ambulatory Blood Pressure Measurement evaluation. However, the Ambulatory Blood Pressure Measurements revealed values similar in both Control and Masked Hypertension group, where both classify for Masked Hypertension. Several reasons may be behind this, like Isolated Diastolic Hypertension or a non-dipping status population among the control group.

Considering the conclusions regarding the Wave Pulse Velocity, Pulse Pressure in-office and Carotid Media Intima Interface the results agree with the respective literature and show that Masked Hypertension individuals have greater arteriosclerosis, aortic stiffness, and higher cardiovascular risk with worst outcomes in case of cardiovascular events. Individuals with Masked Hypertension often present hypertension mediated target organ damage at the time of diagnose, due to delays in identifying the pathology conducing to more time for the disease and target organ damage to install. Hence the crucial importance of early diagnose since many hypertensive mediated target organ damage can be reversible if treatment initiated in early stages.

It would be interesting to pursuit a follow-up study on these patients from the Masked Hypertension group after starting antihypertensive medication, to evaluate not only if the Hypertension is well controlled but also to inquire if the hypertension mediated target organ damage were reverted at some level.

Considering the Cholesterol related criteria, the results confirmed the literature that states the higher cardiovascular risk that Masked Hypertension population has, despite not presenting values high enough to diagnose hypercholesterolemia, the comparison with the control group confirms the higher risk of developing hypercholesterolemia which directly contributes to a higher cardiovascular risk.

Considering the renal Function, the higher creatinine levels show a potential renal function deterioration which can be found in Hypertensive Nephropathy and Chronic Kidney Disease, mirroring possible hypertensive mediated target organ damage.

However, it is essential to emphasize that Creatinine is not the only criteria important to evaluate the deterioration of Kidney Function and it would be interesting to also have the values of albuminuria and albumin/creatinine ratio to complete the assessment of renal deterioration in Masked Hypertension individuals.

To summarize, this work allowed to conclude that the Portuguese reality of Hypertension, in specific Masked Hypertension, agrees with the most recent literature concerning the diagnose and the consequences of Masked Hypertension.

The importance of this work relies deeply on emphasizing the importance of introducing extra evaluation methods to the Health System to allow early diagnose of Masked Hypertension and avoid its consequences and to start treatment to revert them as early as possible. The Ambulatory Blood Pressure Measurements allows early diagnose of Masked Hypertension and should be consensually introduced in screening programs, especially for populations at higher risk of developing sustained Hypertension.

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