

# **Blood glucose and nocturnal blood pressure in African and Caucasian men: the SABPA study**

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**Innovation through diversity**



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## **Affirmation by the authors**

The following researchers contributed to this study:

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Was involved in collecting and processing of cardiovascular data, namely pulse wave velocity and blood pressure as well as performing quality control regarding the correctness and completeness of each participant's questionnaires. Responsible for literature searches, statistical analyses, processing of cardiovascular data, design and planning of the manuscript.

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This is a statement from the co-authors confirming their individual role in the study and giving their permission that the article may form part of this dissertation.

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## **Summary**

### **Motivation**

Hypertension and type 2 diabetes mellitus are common in the black population of South Africa. The literature also shows that elevated blood glucose concentrations can lead to an increase in blood pressure and a blunted decline in nocturnal blood pressure. Therefore, the motivation for this study was to determine if blood glucose may play a role regarding the blunted nocturnal decline in blood pressure in African and Caucasian men.

### **Aim**

The aim of this study was to investigate the relationship between a blunted nocturnal decline in blood pressure and blood glucose in African and Caucasian men.

### **Methodology**

A comparative population study was performed that consisted of 202 school teachers (101 African and 101 Caucasian) between the ages of 25-60 years from the North West Province, South Africa. Subjects were excluded if their body temperature was elevated, had a dependence or abuse of psychotropic substances, were regular blood donors and/or vaccinated in the previous three months. Ambulatory systolic (SBP) and diastolic blood pressure (DBP) were measured. Blood samples from the antebachial vein were collected in sodium fluoride tubes to determine the serum glucose level and glycosylated hemoglobin A1c (HbA1c) percentage. Estimated average glucose (eAG) was determined from the percentage HbA1c by means of a regression formula. Means and proportions were compared by standard t-test and the chi-square test, respectively. Pearson correlations were used to determine unadjusted associations and multiple regression analysis to determine adjusted associations between variables.

### **Results and Conclusion**

African men had an elevated HbA1c ( $p < 0.001$ ), eAG ( $p < 0.001$ ), nighttime SBP ( $p < 0.001$ ) and DBP ( $p < 0.001$ ). These results remained similar when non-dipping African and Caucasian men were compared. The Africans also smoked more ( $p = 0.012$ ), consumed more alcohol ( $p = 0.049$ ),

had a higher percentage of non-dippers ( $p=0.054$ ), HIV infected subjects ( $p<0.001$ ) and a larger number of subjects that used anti-hypertensive medication ( $p=0.049$ ). The unadjusted analysis showed positive correlations between all the blood pressure measurements and serum glucose, HbA1c and eAG in the African non-dipper men. While in the non-dipper Caucasian men, only daytime SBP and nighttime SBP (22:00-06:00) correlated positively with serum glucose, HbA1c and eAG. Furthermore, when viewing the relationship between carotid intima-media thickness (CIMT) and the blood pressure measurements in the African population, only nighttime (00:00-04:00) SBP ( $r=0.581$ ,  $p<0.001$ ) and DBP ( $r=0.566$ ,  $p<0.001$ ) showed positive associations. After adjustments were made for age and body mass index the associations between the various blood pressure measurements and blood glucose disappeared in the non-dipper Caucasian men. However, in the non-dipper African men both nighttime (22:00-06:00) SBP and (00:00-04:00) SBP showed positive correlations with serum glucose, HbA1c and eAG. After full adjustments (age, BMI, smoking, alcohol intake, physical activity, C-reactive protein and baroreceptor sensitivity) were made, nighttime (00:00-04:00) SBP was the only measure of blood pressure that correlated positively with HbA1c ( $p=0.069$ ) and eAG ( $p<0.001$ ) in the non-dipper African men. No significant relationships were found for Caucasian men. Furthermore, to determine if the association between nighttime (00:00-04:00) SBP and eAG were independent of CIMT, we adjusted for CIMT. By doing so the positive association between SBP and eAG remained significant in the non-dipper African men ( $R^2=0.617$ ;  $\beta=0.438$ ;  $p=0.008$ ) and non-significant in the non-dipper Caucasian men ( $R^2=0.423$ ;  $\beta=0.169$ ;  $p=0.33$ ). However, the relationship between CIMT and eAG disappeared when we adjusted for SBP, suggesting that the SBP and eAG relationship drives CIMT.

In conclusion, the association between the early morning SBP (00:00-04:00) and the blood glucose in non-dipping African men suggests that the blunted decline in nocturnal blood pressure during the early morning hours is associated with chronically elevated blood glucose.

**Keywords:** glucose, glycosylated hemoglobin A1c, nocturnal blood pressure, non-dipping, ethnicity.

# **Afrikaanse titel: Bloedglukose en nagtelike bloeddruk in Afrika- en Koukasiese mans: die SABPA-studie**

## **Opsomming**

### **Motivering**

Hipertensie en tipe 2-diabetes mellitus is algemeen onder die swart bevolking van Suid-Afrika. Die literatuur toon ook aan dat verhoogde bloedglukosekonsentrasies kan lei tot verhoogde bloeddruk en 'n afgestompte daling in nagtelike bloeddruk. Die motivering vir hierdie studie was gevolglik om te bepaal of bloedglukose 'n rol kan speel in die afgestompte nagtelike daling in bloeddruk onder Afrika- en Koukasiese mans.

### **Doel**

Die doel van hierdie studie was om die verhouding tussen 'n afgestompte nagtelike daling in bloeddruk en bloedglukose by Afrika- en Koukasiese mans te ondersoek.

### **Metodologie**

'n Vergelykende populasiestudie is gedoen, wat bestaan het uit 202 onderwysers (101 Afrikane en 101 Koukasiërs) tussen die ouderdomme 25 en 60 jaar in die Noordwesprovinsie, Suid-Afrika. Deelnemers is uitgesluit indien hulle liggaamstemperatuur verhoog was, indien hulle afhanklik van psigotropiese substansie was of dit misbruik het, indien hulle gereelde bloedskenkers was en/of indien hulle in die voorafgaande drie maande ingeënt was. Ambulatories-sistoliese (SBP) en diastoliese bloeddruk (DBP) is gemeet. Bloedmonsters van die antebregiale aar is versamel in natriumfluoriedbuis, om die serumglukosevlak en glikosileerde hemoglobien A1c (HbA1c) persentasie te bepaal. Geraamde gemiddelde glukose (eAG) is bepaal vanuit die persentasie HbA1c deur middel van 'n regressieformule. Gemiddeldes en proporsies is vergelyk deur middel van onderskeidelik standaard t-toete en die chi-vierkanttoets. Pearson-korrelasies is gebruik om onverstelde verbande en veelvuldige regressie-analise te bepaal, sodat verstelde verbande tussen veranderlikes bepaal kon word.

## Resultate en Gevolgtrekking

Die Afrika-mans het 'n verhoogde HbA1c ( $p < 0.001$ ), eAG ( $p < 0.001$ ), nagtelike SBP ( $p < 0.001$ ) en DBP ( $p < 0.001$ ) gehad. Hierdie resultate het soortgelyk gebly wanneer nie-dalende Afrika- en Koukasiese mans vergelyk is. Die Afrikane het ook meer gerook ( $p = 0.012$ ), meer alkohol verbruik, 'n hoër persentasie nie-dalers ingesluit ( $p = 0.054$ ), 'n hoër persentasie MIV-besmette proefpersone ingesluit ( $p < 0.001$ ) en 'n groter aantal proefpersone ingesluit wat teen-hipertensiewe medikasie gebruik het ( $p = 0.049$ ). Die onverstelde analise het positiewe korrelasies getoon tussen al die bloeddrukmetings en serumglukose, HbA1c en eAG in die nie-dalende Afrika-mans. By die nie-dalende Koukasiese mans het slegs dag-SBP en nagtelike SBP (22:00-06:00) positief gekorreleer met serumglukose, HbA1c en eAG. Wat die verhouding tussen karotis intima-media dikte (CIMT) en die bloeddrukvlakke onder die Afrika-populasie betref, het ook slegs nagtelike (00:00-04:00) SBP ( $r = 0.581$ ,  $p < 0.001$ ) en DBP ( $r = 0.566$ ,  $p < 0.001$ ) positiewe verbande getoon. Nadat verstellings gemaak is vir ouderdom en liggaamsmassa-indeks, het die verbande tussen die verskillende bloeddrukmetings en bloedglukose verdwyn by die nie-dalende Koukasiese mans. By die nie-dalende Afrika-mans het nagtelike (22:00-06:00) SBP sowel as (00:00-04:00) SBP egter positiewe korrelasies getoon met serumglukose, HbA1c en eAG. Nadat volledige verstellings gemaak is (ouderdom, liggaamsmassa-indeks, rook, alkoholname, fisiese aktiwiteit, C-reaktiewe proteïen en baroreseptorsensitiwiteit), was nagtelike (00:00-04:00) SBP die enigste bloeddrukmeting wat positief gekorreleer het met HbA1c ( $p = 0.069$ ) en eAG ( $p < 0.001$ ) by die nie-dalende Afrika-mans. Geen beduidende verhoudings is gevind vir Koukasiese mans nie. Om vas te stel of die verband tussen nagtelike (00:00-04:00) SBP en eAG onafhanklik van CIMT is, is daar ook vir CIMT verstel. Na hierdie verstelling het die positiewe verband tussen SBP en eAG beduidend gebly vir die nie-dalende Afrika-mans ( $R^2 = 0.617$ ;  $\beta = 0.438$ ;  $p = 0.008$ ) en nie-beduidend vir die nie-dalende Koukasiese mans ( $R^2 = 0.423$ ;  $\beta = 0.169$ ;  $p = 0.33$ ). Die verhouding tussen CIMT en eAG het egter verdwyn nadat daar verstel is vir SBP, wat suggereer dat CIMT bepaal word deur die verhouding tussen SBP en eAG.

Samevattend suggereer die verband tussen die vroegoggend-SBP (00:00-04:00) en die bloedglukose by nie-dalende Afrika-mans dat die afgestompte afname in nagtelike bloeddruk in die vroeë oggendure verband hou met kronies verhoogde bloedglukose.

**Sleutelwoorde:** glukose, glikosileerde hemoglobien A1c, nagtelike bloeddruk, nie-dalend, etnisiteit.

## **Preface**

The *article format* was used for this dissertation. This is a format approved and recommended by the North-West University, consisting basically of a manuscript ready for submission to a peer reviewed journal. The manuscript is accompanied by an in-depth literature review as well as an interpretation of the results. The structured format of this information is as follows: Chapter 1 provides an introduction containing a short background, motivation, aim, objectives and hypotheses in order to clarify the purpose of the study and provide knowledge needed for the interpretation of the data. Chapter 2 is a complete literature overview of the topic. Chapter 3 is the article following the instructions of the *American Journal of Hypertension* containing the background, methodology, results and interpretation of the study. Lastly, Chapter 4 consists of a summary of the main findings, and recommendations to future studies. Appropriate references are presented at the end of each chapter, according to the style of the *American Journal of Hypertension*.

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## **List of abbreviations**

|        |  |
|--------|--|
| CIMT:  | Carotid intima-media thickness                                 |
| DBP:   | Diastolic blood pressure                                       |
| eAG:   | Estimated average glucose                                      |
| HbA1c: | Glycosylated hemoglobin A1c                                    |
| HIV:   | Human immunodeficiency virus                                   |
| SABPA: | Sympathetic activity and Ambulatory Blood Pressure in Africans |
| SBP:   | Systolic blood pressure  |
| T2D:   | Type 2 diabetes mellitus                                       |

# **CHAPTER 1**

## **INTRODUCTION**

## **Background**

Blood pressure follows a circadian rhythm that can be altered by both physiological and behavioral influences.<sup>1,2</sup> Previous studies investigated the influence of elevated blood pressure levels on the cardiovascular system and found that it is associated with an increased risk for cardiovascular and cerebrovascular events.<sup>3-5</sup> Some investigators suggested that an elevated nocturnal blood pressure may contribute more to a worsened cardiovascular outcome than daytime blood pressure.<sup>6</sup>

Individuals from African descent are more likely to have a non-dipping blood pressure pattern than individuals of European descent.<sup>7</sup> A non-dipping blood pressure pattern occurs when the nighttime blood pressure of an individual fails to decline with 10-20 percent of their average daytime blood pressure.<sup>8,9</sup> It has been found that a range of mechanisms could be the cause of this non-dipping pattern and that the mechanisms may differ between ethnic groups.<sup>2,6</sup> The mechanism that is usually associated with a non-dipping pattern is an impaired autonomic nervous system.<sup>10,11</sup> This not only has a direct influence on blood pressure regulation but also influences various other mechanisms, such as in insulin resistance, adding to their contribution to non-dipping.<sup>12</sup>

Type 2 diabetes mellitus is on the increase in the African population and it is known to be more common in individuals with hypertension.<sup>13,14</sup> Nielsen et al.<sup>15</sup> found that individuals with diabetes are also more likely to have a non-dipping blood pressure pattern. Glycosylated hemoglobin A1c (HbA1c) is widely accepted as the most reliable measurement to determine chronic hyperglycemia in diabetic patients, and it is suggested that moderate levels of HbA1c might already be associated with vascular complications.<sup>16</sup> It has also been reported that the contribution of hyperglycemia to cardiovascular disease is gradual and cumulative and is caused by decades of elevated blood glucose levels.<sup>16</sup> Elevated levels of blood glucose are associated with vascular changes such as the thickening of the walls of the carotid artery. This in turn causes an increase in blood pressure and is associated with the occurrence of cardiovascular disease.<sup>17,18</sup> Limited information exists regarding the influence of blood glucose on nocturnal blood pressure regulation.

## **Motivation**

Various mechanisms have been described that may lead to a blunted nocturnal decline of blood pressure. However, the main motivation for this study was to determine if blood glucose is associated with the blunted nocturnal decline in blood pressure of African and Caucasian men.

## **Aim**

The aim of this study is to investigate the possible relationship between a blunted nocturnal decline in blood pressure and blood glucose in African and Caucasian men.

## **Objectives**

The objectives of this study are to:

- Compare blood glucose and non-dipping prevalence between African and Caucasian men;
- Determine whether an association exists between nocturnal blood pressure and blood glucose in non-dipper African and Caucasian men.

## **Hypotheses**

- The prevalence of non-dipping nighttime blood pressure and elevated blood glucose levels are higher in African men compared to Caucasian men;
- Nocturnal blood pressure is associated with elevated blood glucose levels in non-dipping African and Caucasian men.

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# **CHAPTER 2**

## **LITERATURE STUDY**

## **INTRODUCTION**

Cardiovascular disease is becoming the major cause of mortality among the black African population of South Africa.<sup>1</sup> Recently it was indicated that black Africans are more frequently diagnosed with heart failure than any of the other ethnic groups.<sup>2</sup> This might be due to the increase in urbanization during the last decade, which resulted in non-communicable diseases to become more prevalent in this population group.<sup>2</sup> Differences between Africans and Caucasians have been established by several investigators, finding that Africans have higher daytime and nighttime blood pressures, a blunted nocturnal decline, higher rates of hypertension, increased levels of blood glucose and higher cardiovascular mortality rates than Caucasians.<sup>3,4</sup> Hypertension and type 2 diabetes mellitus (T2D) are the most common causes for cardiovascular morbidity and mortality in the black urban population.<sup>5</sup> These conditions are known to coexist in Africans and are causing a synergistic effect that contributes to a poor cardiovascular risk profile in diabetic patients.<sup>5-7</sup> Therefore, effective and appropriate control of blood pressure and blood glucose levels in this group are important to cause a reduction in cardiovascular morbidity and mortality.<sup>5</sup>

## **BLOOD PRESSURE**

Ambulatory blood pressure monitoring makes it possible to study the circadian variation of blood pressure in individuals.<sup>8</sup> It was found that blood pressure follows a reproducible circadian pattern that is characterized by a low pressure period during sleep followed by an early morning, post awakening surge and reaches a plateau period while a person is awake.<sup>9</sup> These blood pressure measurements showed that nocturnal blood pressure tends to decrease by 10 – 20 percent of an individual's average daytime blood pressure during sleep. Individuals with this decrease are known as dippers, whereas, when the nocturnal decline in blood pressure is less than 10 percent, the term non-dipper is applied.<sup>10</sup> A non-dipper pattern is seen as abnormal and previous investigators have established that non-dipping individuals are at an increased risk of being or becoming hypertensive,<sup>11</sup> developing target organ damage<sup>12</sup> and have an increased occurrence of cardiovascular<sup>13</sup> and cerebrovascular<sup>14</sup> events.

The circadian pattern of blood pressure is influenced by a number of factors.<sup>15</sup> Several previous investigators reported that daytime inactivity, poor sleep quality and obstructive sleep apnea are the reasons for a non-dipping profile in some individuals.<sup>16-18</sup> However, other investigators went further, and determined that the non-dipping pattern may rather be a result of an impaired autonomic nervous system activity, abnormalities in volume regulation, as well as functional and structural vascular alterations.<sup>19,20</sup> The impaired activity of the autonomic nervous system has been reported by the majority of investigators as the main factor associated with a non-dipping blood pressure profile.<sup>21</sup> This impaired autonomic nervous system activity is characterized by a disrupted sympathovagal balance, with increased sympathetic outflow.<sup>20,22</sup> Environmental factors such as smoking, alcohol consumption and sodium intake may also influence dipping in some individuals.<sup>23,24</sup> Therefore, this array of mechanisms make it difficult to determine the exact contributing mechanism/s to non-dipping.

### **Blood pressure and cardiovascular parameters**

Cardiac output and peripheral vascular resistance are involved in the determination of blood pressure and are known to be influenced by the increased activity of the sympathetic nervous system.<sup>25</sup> The cardiac output of an individual is normally decreased during the night due to a decrease in heart rate that leads to a decreased nocturnal blood pressure.<sup>26</sup> On the other hand, peripheral vascular resistance is usually increased or similar to daytime values at night. It has been suggested that the increase in peripheral resistance during the night exists due to a reduction in blood flow.<sup>27</sup> Previous studies tried to compare day-night changes in cardiac output and vascular resistance in dippers and non-dippers. However, they were unable to find consistent results because cardiac output and systemic vascular resistance are strongly influenced by changes in posture as well as daily activities.<sup>20,28</sup> Therefore, it was concluded that a non-dipping profile can be caused by a diminished nocturnal decrease in cardiac output, an exaggerated increase in systemic vascular resistance, or both.<sup>17</sup>

## **Blood pressure and baroreceptor sensitivity**

It is possible that the variability of blood pressure can originate from a varied baroreflex response.<sup>29</sup> Baroreceptor sensitivity is a representation of the arterial baroreflex function, and is mainly influenced by means of the autonomic nervous system and arterial distensibility.<sup>30,31</sup> According to La Rovere et al.<sup>32</sup> baroreflex function is a determinant of the neural regulation of the cardiovascular system. Therefore, it is seen as an established tool for the assessment of the autonomic nervous system. Baroreceptor sensitivity of an individual is augmented whenever sympathetic nervous system activity is increased, and attenuated when central arterial compliance is decreased.<sup>33</sup> The reduction of baroreceptor sensitivity is associated with impaired regulation of blood pressure, electrical instability of the myocardium and increased risk of cardiovascular disease and related mortality.<sup>34,35</sup> Therefore, it is possible that the increased sympathetic activity that is found in individuals with an impaired autonomic nervous system activity can influence the baroreceptor reflex to such an extent that a non-dipping blood pressure profile can occur.<sup>36</sup>

## **Blood pressure and the kidneys**

The kidneys are essential in the control of blood pressure. Previous investigators reported that an increase in blood pressure is associated with renal function impairment.<sup>37,38</sup> It has also been suggested that the non-dipping blood pressure profile of some individuals are associated with a high sodium intake and salt sensitivity.<sup>39,40</sup> Salt sensitive individuals' blood pressure varies with changes in sodium intake.<sup>41</sup> The prevalence of sodium sensitivity has been found to be higher in hypertensives than normotensives, Africans than Caucasians and in the elderly than the young.<sup>42</sup> Salt sensitivity is controlled by the kidneys and serves as an indicator for the loss of renal function reserve.<sup>43,44</sup> Normally sodium excretion declines at night. However, when daily sodium excretion is insufficient, sodium excretion increases at night to maintain overall sodium balance.<sup>45</sup> Nocturnal sodium excretion can only be increased by adjusting the nocturnal blood pressure upward to stimulate pressure-natriuresis during the night which leads to a non-dipping blood pressure pattern in these individuals.<sup>46</sup> The well-known salt sensitive state of Africans is believed to be caused by a reduced filtration capability of the glomerulus. This leads to an

elevation of the glomerular capillary pressure to excrete excess sodium, resulting in glomerular scarring, endothelial dysfunction and eventual renal failure.<sup>45</sup> In individuals that are still in the early phase of renal impairment, the non-dipping pattern will only be maintained until sufficient sodium is excreted into the urine and balance is achieved. However, as the renal impairment advances in these individuals, more time is needed to excrete sodium.<sup>47</sup> This ultimately leads to the shifting of the operating set point of pressure-natriuresis to a higher range throughout the day and night, resulting in overall sustained hypertension and a blunted decline in blood pressure.<sup>48</sup> It is this sustained increase in blood pressure which leads to increased occurrence of cardiovascular events in these individuals.<sup>42</sup>

### **Blood pressure and carotid intima-media thickness**

Carotid intima-media thickness (CIMT) is a validated measurement of subclinical atherosclerosis and is frequently seen in hypertensives as an established risk marker for cardiovascular disease.<sup>49-50</sup> Metoki et al.<sup>51</sup> reported that nighttime blood pressure, especially a blunted nocturnal decline in systolic blood pressure is closely associated with an increased CIMT. A small increase in CIMT is predictive of an increased risk for coronary heart disease and stroke.<sup>49</sup> The mechanisms by which hypertension predisposes individuals to vascular remodeling and structural changes include endothelial dysfunction, barotrauma caused by shear stress and increased smooth muscle proliferation with proteoglycan accumulation.<sup>52</sup> The vessel walls of the carotid artery are vulnerable to intermittent stress. Extensive oscillations in blood pressure increase the extent of the oscillatory shear stress in the carotid artery.<sup>53</sup> Oscillatory shear stress is associated with increased macrophage density of the atherosclerotic plaque that is seen as an indicator of plaque instability.<sup>54</sup> Furthermore, this type of shear stress also causes the activation of pro-oxidant processes with the increased activity of NADH oxidase and the stimulation of adhesion molecule expression, leading to redox sensitive gene expression that causes a severe increase in atherosclerotic alterations and propagation.<sup>55</sup>

## **Blood pressure and antihypertensive medication**

The goal of antihypertensive medication is to lower blood pressure to normal levels and in doing so prevent the occurrence of cardiovascular and cerebrovascular events in hypertensive individuals.<sup>56</sup> The influence of antihypertensive drug treatment on diurnal blood pressure variation was extensively researched in hypertensive individuals.<sup>57</sup> The time of day when treatment was administered had an influence on nocturnal blood pressure.<sup>58</sup> Some investigators suggested that a non-dipping pattern might be due to the intake of blood pressure lowering drugs during the morning, which only lowers the blood pressure during the day but not at night. However, this was not the case in all of the individuals and it was suggested that the individuals risk level should be considered.<sup>59</sup> The ingestion of medication during the morning seems to be an appropriate treatment choice for dipper individuals. However, this treatment strategy does not seem appropriate for non-dipping individuals. In non-dipping individuals evening drug administration seemed to be more adequate in terms of blood pressure control because, it resulted in a lower nocturnal blood pressure and a dipping pattern that led to a reduction in these individuals' cardiovascular risk.<sup>60</sup> Therefore, it is crucial to find the right drug and administration time for each individual because evidence has shown that effective and appropriate blood pressure control causes a remarkable reduction in cardiovascular and cerebrovascular events.<sup>39</sup> However, blood pressure management in Africans seems to be less adequate.<sup>61</sup> This might indicate a greater severity of their hypertension, inadequacy of drug therapy due to individual insensitivity to different drugs, or due to a lack of compliance.<sup>62</sup>

## **BLOOD GLUCOSE**

As described previously, black Africans have a high prevalence of hyperglycemia along with an increased risk cardiovascular disease.<sup>5,6</sup> Glycosylated hemoglobin A1c (HbA1c) represents the percentage of glycated hemoglobin and reflects the long term glycemic control of an individual.<sup>63,64</sup> It is seen as being more stable than conventional blood glucose measurements, with a lower measurement error.<sup>63</sup> In individuals with a normal erythrocyte lifespan, HbA1c is directly proportional to the level of glycemia during the preceding 2-3 months.<sup>65</sup> The concentration of HbA1c is a strong predictor of vascular complications and, therefore, the

improvement in glycemic control is crucial in the lowering of vascular disease, especially in diabetic patients.<sup>66,67</sup> The American Diabetes Association estimated that before the onset of T2D, a prediabetic state exists during which these individuals may already begin to develop vascular complications.<sup>68</sup> A prediabetic state exists when an individual's HbA1c level is between 5.7 and 6.4 percent.<sup>69</sup> These levels may be found in individuals as early as 10 years before the full onset of diabetes mellitus.<sup>68</sup> Ethnic disparities have been found in the Diabetes Outcome Progression Trial (ADOPT) and the Diabetes Prevention Program which reported that overall Africans had an HbA1c level of 0.4-0.7 percent greater than Caucasians.<sup>70,71</sup> Because, HbA1c is represented as a percentage and not as a standard unit such as acute glucose that is measured in mmol/L, patients with diabetes find it difficult to understand the meaning of their HbA1c results.<sup>72</sup> Therefore, HbA1c levels are also reported as an estimated average glucose (eAG) level in mmol/L.<sup>64</sup> This is determined from the percentage of HbA1c by means of a simple linear regression formula ( $eAG_{(mmol/L)} = 1.59 \times A1c - 2.59$ ).<sup>64,73</sup> However, it was found that this method results in values that are 1.5–2.0 percentage points lower than the current Glycohemoglobin Standardization Program values used in the United States of America which also leads to confusion.<sup>74</sup>

The physiological processes by which hyperglycemia contribute to cardiovascular disease is gradual and cumulative, occurring after sustained exposure to elevated blood glucose levels.<sup>75</sup> There are several possible mechanisms that may explain the direct relationship between chronically elevated blood glucose levels and coronary heart disease, for example the glucose can react with various different proteins, ultimately causing structural alterations and subsequently impair proteins and tissue function.<sup>75,76</sup> These alterations, as well as the formation of advanced glycation end-products may contribute to the long term cardiovascular complications in diabetic individuals. These include endothelial dysfunction, changes in arterial distensibility, plaque formation and atherosclerosis.<sup>77,78</sup>

### **Blood glucose and insulin resistance**

Previous studies have reported both the presence and the absence of insulin resistance in non-dippers.<sup>79,80</sup> Their explanation for the inconsistency was the heterogenic backgrounds of the individuals. Individuals from African descent might be more susceptible to insulin resistance because of the increased prevalence of T2D in this population group.<sup>81</sup> Chen et al.<sup>79</sup> showed that a higher fasting glucose, insulin/glucose ratio and lower postprandial levels of insulin may lead to the coexistence of insulin resistance and  $\beta$ -cell dysfunction in non-dipper individuals. The mechanism(s) for insulin resistance and  $\beta$ -cell dysfunction in non-dipper individuals are not yet fully understood.<sup>79</sup> It seems as if early insulin secretion from the  $\beta$ -cell is increased whenever the sympathetic activity is increased. However, it is also possible that chronic postprandial hyperglycemia might induce glucose toxicity to the  $\beta$ -cells that lead to the impaired insulin secretion.<sup>82,83</sup> Insulin usually has vascular protective effects. However, during an insulin resistant state, hyperinsulinemia occurs that is accompanied by various cardiovascular risk factors such as glucose intolerance, dyslipidemia, elevated inflammatory markers and endothelial dysfunction that cause injury to the cells in the arterial wall.<sup>84</sup>

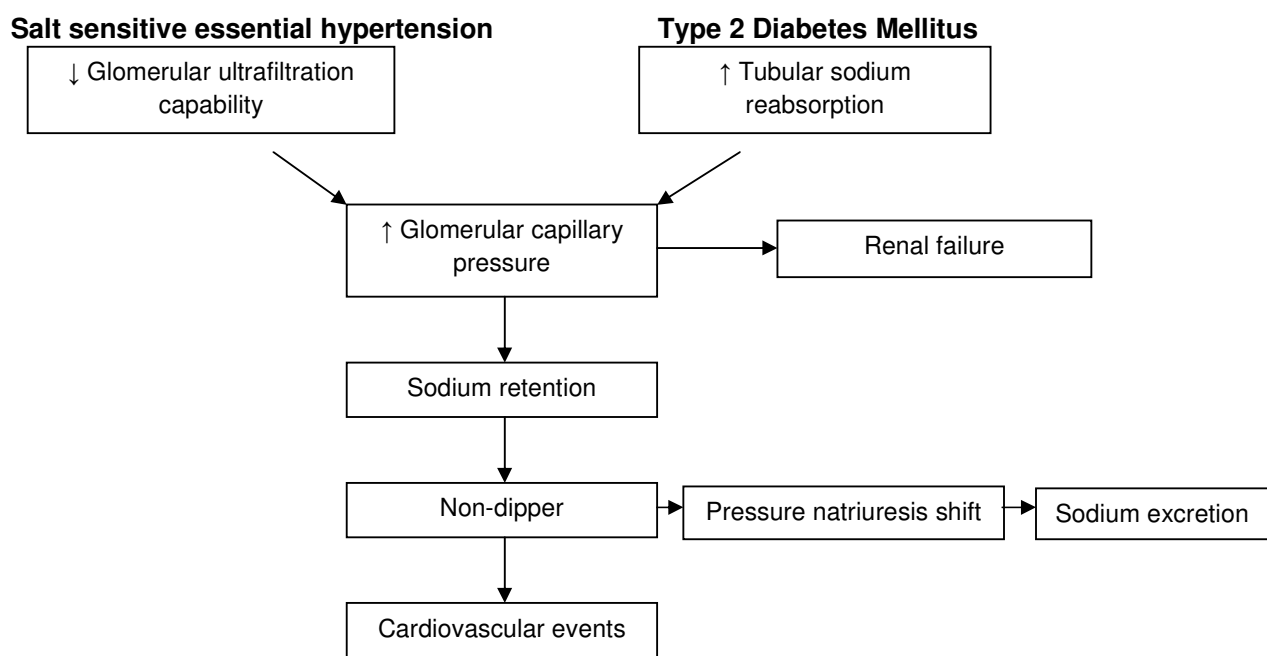
### **Blood glucose and baroreceptor sensitivity**

Investigators found a negative relationship between fasting plasma glucose, insulin resistance and baroreceptor sensitivity.<sup>36</sup> In individuals with increased blood glucose, the baroreceptor sensitivity might be influenced by concomitant hyperinsulinemia which increases sympathetic nervous system activity.<sup>36,85</sup> This resulting sympatho-excitatory effect leads to the withdrawal of parasympathetic activity and ultimately results in impaired baroreceptor function by decreasing baroreceptor sensitivity.<sup>33,85</sup> This in turn has an effect on the blood pressure regulation and can possibly lead to a non-dipping blood pressure pattern.<sup>36</sup>

### **Blood glucose and the kidneys**

The dipping pattern of blood pressure is blunted in patients with diabetes mellitus and has been considered a risk factor in the progression of autonomic neuropathy and nephropathy.<sup>86</sup> Therefore, non-dipper individuals, especially those with diabetes mellitus, are associated with a

rapid decline in renal function.<sup>87</sup> A person becomes salt sensitive when the ultrafiltration capability of the glomerulus is reduced as discussed previously or when the renal tubular reabsorption of sodium is enhanced as found in diabetic patients (Figure 1).<sup>45,93</sup> The mechanism in diabetic patients is similar to that found in hypertensive Africans. However, this time glomerular load is increased due to the increased tubular reabsorption of sodium. This elevates the nocturnal blood pressure of the individual that leads to a non-dipper blood pressure pattern.<sup>88</sup>



**Figure 1:** The kidney's connection with salt sensitivity and blood pressure.<sup>88</sup>

### **Blood glucose and carotid intima-media thickness**

Previous investigators have shown that raised blood glucose levels also aid in the progression of atherosclerosis and it was recently reported that CIMT is significantly associated with diabetic nephropathy.<sup>89,90</sup> Vitelli et al.<sup>91</sup> found that HbA1c levels in the absence of diabetes is associated with carotid intima-media thickening. Their data suggested that mild glycemia below the cut-off limit for T2D could be considered a risk factor for increased CIMT in non-diabetic individuals. Furthermore, it seems as if hyperglycemia and the potential generation of advanced glycation end-products in these individuals play an important role in the alterations of this artery.<sup>92</sup> It is

possible that the increased deposition of fibrous and calcific tissue in the arterial wall, in addition to impaired endothelial-dependent relaxation, may limit vessel wall expansion with plaque accumulation.<sup>93</sup> This impairment of compensatory remodeling of the artery appears to be prominent in diabetic patients treated with insulin.<sup>94</sup> The smooth muscle and fibrous tissue proliferation in response to insulin might increase the vascular stiffness of these patients and, therefore, further impair the ability of the arterial wall to expand in response to accumulation of plaque.<sup>89,95</sup>

### **Blood glucose and antihypertensive medication**

Individuals with both hypertension and T2D are at a high risk for cardiovascular disease, and it is estimated that 80 percent of these individuals will die from myocardial infarction, stroke or peripheral artery disease.<sup>96,97</sup> The reduction of blood pressure is known to reduce the risk of cardiovascular disease. Therefore, an aggressive treatment strategy is recommended for individuals with both hypertension and diabetes mellitus.<sup>56</sup> However, a recent study found that it is difficult to treat individuals who have both of these conditions with only 30 percent of their participants achieving their target blood pressure with intensive guidance.<sup>98</sup> In the subjects where blood pressure control was possible, the antihypertensive medication showed beneficial effects on hypertension related cardiovascular end-points such as the reduction of left ventricular hypertrophy and arterial stiffness that resulted in a lower risk for cardiovascular events.<sup>99</sup>

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# CHAPTER 3

## **Blood glucose and nocturnal blood pressure in African and Caucasian men: the SABPA study**

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# Blood glucose and nocturnal blood pressure in African and Caucasians: the SABPA Study

Running Head: Blood glucose and nocturnal blood pressure

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## **Abstract**

**Background:** Africans tend to have higher nocturnal blood pressure with a blunted nocturnal decline and elevated blood glucose levels when compared to Caucasians. Therefore, the aim of the study was to investigate if a relationship exists between a non-dipping pattern and blood glucose.

**Methods:** Nocturnal blood pressures and blood glucose levels of 41 non-dipping African and 28 non-dipping Caucasian men were investigated. Ambulatory systolic (SBP) and diastolic blood pressure (DBP) were measured and blood collected in sodium fluoride tubes from the antibrachial vein to determine serum glucose and glycosylated hemoglobin A1c (HbA1c) percentage. The estimated average glucose (eAG) was determined from HbA1c percentage with a regression formula.

**Results:** The African non-dippers had higher blood pressures ( $p < 0.001$ ) and elevated HbA1c ( $p = 0.037$ ) and eAG ( $p = 0.041$ ) levels compared to the Caucasians. In single, partial and multiple regression analyses nighttime (00:00-04:00) SBP correlated positively with HbA1c ( $p = 0.069$ ) and eAG ( $p < 0.001$ ) in the African men. No correlations were found in the Caucasian men. Sensitivity analysis confirmed that the association between nighttime SBP (00:00-04:00) and eAG was independent of carotid intima-media thickness in the African men ( $R^2 = 0.617$ ;  $\beta = 0.438$ ;  $p = 0.008$ ).

**Conclusion:** The blunted nocturnal decline in SBP during the early morning hours is associated with chronically elevated blood glucose in non-dipper African men.

**Key words:** glucose, glycosylated hemoglobin A1c, nocturnal blood pressure, ethnicity.

## Introduction

In Africa, cardiovascular disease is a major cause of death and disability, with the leading culprits being hypertension and diabetes mellitus.<sup>1</sup> These risk factors synergistically increase the population's risk of cardiovascular morbidity and mortality.<sup>1-3</sup>

In addition, to the soaring increase in the prevalence of hypertension in Africans, they also tend to have higher nighttime blood pressures with a blunted nocturnal decline.<sup>4,5</sup> A blunted nocturnal decline in blood pressure occurs when an individual's nighttime blood pressure fails to fall with more than 10 percent of their average daytime blood pressure, and is commonly referred to as non-dipping.<sup>6,7</sup> Individuals with a non-dipping pattern are known to present greater target organ damage, such as increased intima-media thickening and an increased occurrence of cardiovascular and cerebrovascular events.<sup>8-10</sup>

People from African descent are known to have elevated blood glucose levels that are accompanied by a non-dipping pattern and a worsened cardiovascular outcome.<sup>11,12</sup> It has been reported that as early as 10 years before the onset of diabetes mellitus, individuals may have prediabetes and that during this phase glycemic markers such as glycosylated hemoglobin A1c are already associated with cardiovascular disease.<sup>13,14</sup>

As mentioned above hypertension and type 2 diabetes are known to coexist in the African population and it seems that both of these risk factors are associated with the development of a non-dipping pattern.<sup>2,11,15</sup> The aim of this study is therefore, to investigate the relationship between nocturnal blood pressure and chronically elevated blood glucose to determine if these elevated blood glucose concentrations contribute to a non-dipping blood pressure, especially in high-risk groups such as Africans.

## **Materials and methods**

### **Study population**

The Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study was a comparative target population study involving educators between the ages of 25 – 60 years from the North West Province, South Africa. Participants of the present study consisted of 202 African (n=101) and Caucasian (n=101) men. The exclusion criteria were an elevated ear temperature, dependence or abuse of psychotropic substances, regular blood donors and/or individuals vaccinated in the previous three months. An informed consent form was signed by all the participants prior to the commencement of measurements. Furthermore, each participant completed a lifestyle questionnaire, which was used to determine their smoking and alcohol habits. The study complied with all applicable requirements of international regulations, in particular the Helsinki declaration of 1975 (as revised in 2008) for investigation of human participants. The Ethics Review Board of the North-West University (Potchefstroom Campus) approved the study.

### **Clinical Measurements**

A 24-hour ambulatory blood pressure measurement (ABPM) and electrocardiogram measurement were conducted during the working week. At approximately 08:00, an ABPM and two-lead electrocardiogram apparatus (Meditech CE120® Cardiotens, Budapest, Hungary) was attached to the participant's non-dominant arm at their workplace. The ABPM apparatus was programmed to measure blood pressure at 30 minute intervals during the day (08:00 – 22:00) and every hour during the night (22:00 – 06:00). The electrocardiogram apparatus recorded measurements every 5 minutes for 20 seconds. The participants continued with their daily activities and were asked to record any abnormalities such as nausea, headache, physical activity and stress on their ambulatory diary cards. Each participant's energy expenditure during the day was calculated with a physical activity meter (Actical® accelerometers, Montréal, Québec). Participants reported to the Metabolic Research Unit of the North-West University at 16:30 where they were informed of the procedures of the following day. They received a standardized dinner and had their last beverages (tea/coffee) and two biscuits at 20:30. They

were requested to go to bed at around 22:00. At 06:00, the ABPM apparatus was removed and followed by anthropometric measurements, a 5 minute resting Finometer measurement and blood sampling. The 24-hour blood pressure and electrocardiogram data were downloaded onto a database using the CardioVisions 1.9.0 Personal Edition software. The CardioVisions software (validated by the British Hypertension Society)<sup>16</sup> automatically calculated the participant's dipping status. The SonoSite Micromaxx ultrasound system (SonoSite Inc., WA, USA) and a 6-13 MHz linear array transducer were used to determine the carotid intima-media thickness (CIMT). Images from at least two optimal angles of the left and right common carotid artery were obtained. Following previously prescribed protocols,<sup>17</sup> these segments were imaged and measured. The images were digitised and imported into the Artery Measurement Systems automated software<sup>18,19</sup> for dedicated analysis of CIMT. A maximal 10 mm segment with good image quality was chosen for analysis. The program automatically identifies the borders of the intima-media of the near and far wall, and the inner diameter of the vessel, and calculates the CIMT and diameter from around 100 discrete measurements through the 10 mm segment. This automated analysis was capable of being manually corrected if not found appropriate on visual inspection. For the purpose of this study, far wall measurements were used. Intra-observer variability for the far wall was 0.04 mm between two measurements made 4 weeks apart on 10 subjects. Resting baroreceptor sensitivity was determined from the Finometer blood pressure measurements using software developed by Finapres Medical Systems (FMS, Amsterdam, The Netherlands).<sup>20</sup>

### **Anthropometric Measurements**

All measurements were taken in triplicate with calibrated instruments. Stature was measured to the nearest 0.1 cm with a stadiometer (Invicta Stadiometer, IP 1465, UK), body mass to the nearest 0.1 kg (Precision Health Scale, A & D Company, Japan)<sup>21</sup> and waist circumference to the nearest 0.1 cm.<sup>22</sup>

### **Biochemical Measurements**

A registered nurse collected blood samples with a sterile winged infusion set from the participants' antebrachial vein branches. Serum was stored at -80°C. Fasting blood glucose

samples were collected in sodium fluoride tubes and were determined by using a timed-end-point method (Unicel DXC 800, Beckman Coulter, Germany). The percentage of glycosylated haemoglobin (HbA1c) was determined by means of the turbidimetric inhibition immunoassay using Roche Integra 400 (Roche, Basel, Switzerland). The HbA1c percentage was used to calculate the estimated average glucose (eAG) by means of the following linear regression formula ( $eAG_{(mmol/L)} = 1.59 \times A1c - 2.59$ ) that reflects the average capillary glucose equivalent of the preceding 2-3 months.<sup>23,24</sup> Serum total cholesterol and high sensitivity C-reactive protein were determined with a sequential multiple analyser computer (Konelab 20i™, ThermoScientific, Vantaa, Finland; Roche, Basel, Switzerland).

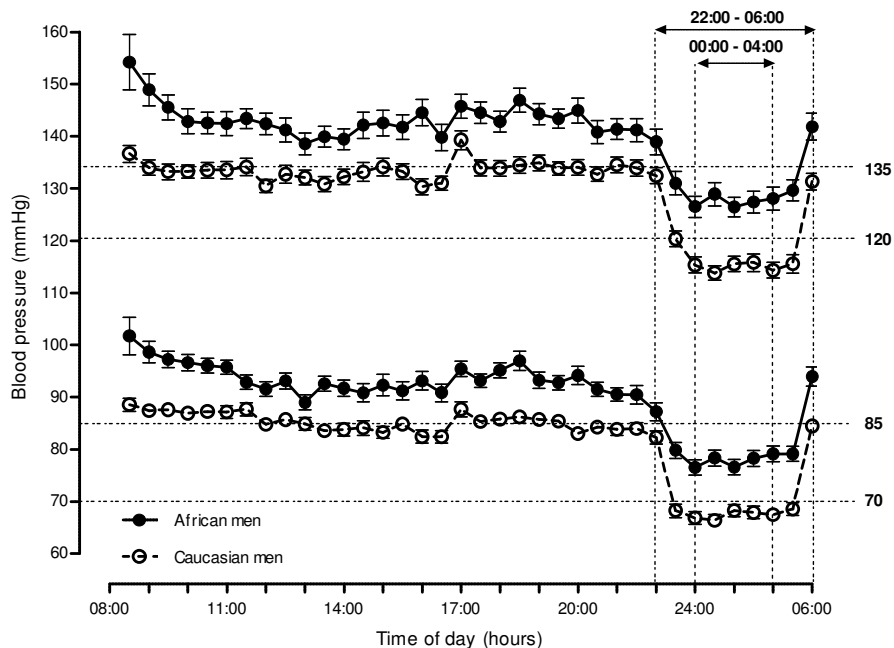
### **Statistical Analyses**

Statistica software v9.0 was used for database management and statistical analyses (Statsoft, Inc., 2008). Means and proportions were compared by a standard t-test and chi-square test, respectively. Mean values of glucose were plotted by tertiles of blood pressure to ensure that linear correlation techniques were appropriate. The distribution of serum glucose, HbA1c, eAG and physical activity were normalised by means of logarithmic transformation. The central tendency and spread of these variables were represented by the geometric mean and the 5th and 95th percentile intervals. Pearson correlations were used to determine unadjusted associations between variables. Partial correlations were performed by adjusting for age and body mass index, followed by multiple regression analyses. Covariates included in the model were age, body mass index, smoking, alcohol intake, physical activity, C-reactive protein and baroreceptor sensitivity. All p-values refer to two-sided hypothesis.

## Results

### Characteristics of the study population

Table 1 list the characteristics of the African and Caucasian men. No significant differences in age, body mass index (BMI), serum glucose, carotid intima-media thickness (CIMT) and physical activity were found between the African and Caucasian men. The African men had a significantly higher percentage of glycosylated hemoglobin A1c (HbA1c) ( $p<0.001$ ) and estimated average glucose (eAG) ( $p<0.001$ ). Furthermore, blood pressure measurements taken during the day and night, as well as the prevalence of non-dippers ( $p=0.054$ ) were higher in the African men (Table 1, Figure 1). The African men also smoked more ( $p=0.012$ ), consumed more alcohol ( $p=0.049$ ), had a higher percentage of non-dippers ( $p=0.054$ ) and HIV infected subjects ( $p<0.001$ ), and a larger number of subjects that used antihypertensive medication ( $p=0.042$ ). Due to the aim of this study, all subsequent analyses were performed in non-dipper African and Caucasian men.



**Figure 1:** Systolic and diastolic ambulatory blood pressure of the African and Caucasian men. Bars indicate standard error.

|                                    | African men (n=101) | Caucasian men (n=101) | P      |
|------------------------------------|---------------------|-----------------------|--------|
| Age, years                         | 43.2 ± 8.1          | 45.0 ± 11.1           | 0.19   |
| Body mass index, kg/m <sup>2</sup> | 27.6 ± 5.8          | 29.0 ± 5.2            | 0.060  |
| Waist circumference, cm            | 93.6 ± 15.5         | 101.5 ± 14.4          | <0.001 |
| <b>Biochemical Measurements</b>    |                     |                       |        |
| Total cholesterol, mmol/L          | 4.74 ± 1.17         | 5.58 ± 1.20           | <0.001 |
| Serum glucose, mmol/L              | 5.74 (4.34-9.96)    | 5.98 (5.00-7.40)      | 0.16   |
| Glycosylated hemoglobin A1c, %     | 6.09 (5.20-8.80)    | 5.66 (5.10-6.40)      | <0.001 |
| Estimated average glucose, mmol/L  | 7.10 (5.70-11.40)   | 6.41 (5.50-7.60)      | <0.001 |
| <b>Cardiovascular Measurements</b> |                     |                       |        |
| Daytime SBP, mmHg                  | 142.74 ± 15.80      | 133.7 ± 10.7          | <0.001 |
| Daytime DBP, mmHg                  | 93.15 ± 10.71       | 85.0 ± 8.3            | <0.001 |
| Nighttime SBP (22:00-06:00), mmHg  | 129.0 ± 18.0        | 116.9 ± 11.6          | <0.001 |
| Nighttime DBP (22:00-06:00), mmHg  | 78.7 ± 12.4         | 68.6 ± 8.3            | <0.001 |
| Nighttime SBP (00:00-04:00), mmHg  | 127.1 ± 17.1        | 115.3 ± 12.0          | <0.001 |
| Nighttime DBP (00:00-04:00), mmHg  | 77.6 ± 12.0         | 67.7 ± 8.4            | <0.001 |
| CIMT, mm                           | 0.70 ± 0.16         | 0.68 ± 0.15           | 0.30   |
| <b>Lifestyle</b>                   |                     |                       |        |
| Physical activity, kcal/day        | 3.42 (3.24-3.60)    | 3.54 (3.41-3.67)      | 0.75   |
| Non-dipper, n (%)                  | 41 (40.6)           | 28 (27.7)             | 0.054  |
| HIV infected, n (%)                | 13 (12.9)           | 0 (0)                 | <0.001 |
| Current smoking, n (%)             | 31 (30.7)           | 16 (15.8)             | 0.012  |
| Current drinking, n (%)            | 41 (40.6)           | 55 (54.5)             | 0.049  |
| <b>Intake of medication</b>        |                     |                       |        |
| Antihypertensive medication, n (%) | 19 (18.8)           | 9 (8.9)               | 0.042  |

**Table 1:** Characteristics of the study population

Values are arithmetic mean ± SD, geometric mean (5<sup>th</sup> to 95<sup>th</sup> percentile interval), or number of subjects (%). SBP, Systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima-media thickness.

When comparing the non-dipper African (n=41) and Caucasian (n=28) men (Table 2), similar results to Table 1 were obtained. HbA1c (p=0.037), eAG (p=0.041), and all blood pressure measurements (p<0.001) were significantly higher in the non-dipping African men.

**Table 2:** Characteristics of the non-dipper population

|                                    | African men<br>Non-dippers N=41 | Caucasian men<br>Non-dippers N=28 | P      |
|------------------------------------|---------------------------------|-----------------------------------|--------|
| <b>Biochemical measurements</b>    |                                 |                                   |        |
| Serum glucose, mmol/L              | 5.76 (4.31-10.50)               | 5.94 (4.90-7.40)                  | 0.63   |
| Glycosylated hemoglobin A1c, %     | 6.15 (5.30-9.60)                | 5.69 (5.10-6.40)                  | 0.037  |
| Estimated average glucose, mmol/L  | 7.19 (5.80-12.70)               | 6.46 (5.50-7.60)                  | 0.041  |
| <b>Cardiovascular measurements</b> |                                 |                                   |        |
| Daytime SBP, mmHg                  | 143.1 ± 17.1                    | 132.4 ± 12.6                      | 0.006  |
| Daytime DBP, mmHg                  | 93.3 ± 11.4                     | 84.4 ± 8.8                        | <0.001 |
| Nighttime SBP (22:00-06:00), mmHg  | 138.6 ± 18.8                    | 124.1 ± 12.8                      | <0.001 |
| Nighttime DBP (22:00-06:00), mmHg  | 84.8 ± 12.5                     | 72.8 ± 9.1                        | <0.001 |
| Nighttime SBP (00:00-04:00), mmHg  | 137.3 ± 16.5                    | 123.3 ± 13.7                      | <0.001 |
| Nighttime DBP (00:00-04:00), mmHg  | 83.8 ± 11.1                     | 71.6 ± 9.7                        | <0.001 |
| CIMT, mm                           | 0.69 ± 0.14                     | 0.70 ± 0.16                       | 0.73   |

Values are arithmetic mean ± SD, geometric mean (5<sup>th</sup> to 95<sup>th</sup> percentile interval) or number of subjects (%). SBP, Systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima-media thickness.

### Unadjusted Analyses

In non-dipper African men (Table 3), all the blood pressure measurements correlated positively with serum glucose, HbA1c and eAG. In the non-dipper Caucasian men, positive associations of daytime systolic blood pressure (SBP) and nighttime (22:00-06:00) SBP were found with serum glucose, HbA1c and eAG. However, only daytime diastolic blood pressure (DBP) and nighttime (22:00-06:00) DBP showed positive associations with serum glucose. In the African men, only nighttime (00:00-04:00) SBP ( $r=0.58$ ,  $p<0.001$ ) and DBP ( $r=0.57$ ,  $p<0.001$ ) showed a positive association with CIMT in this group (Figure 2).

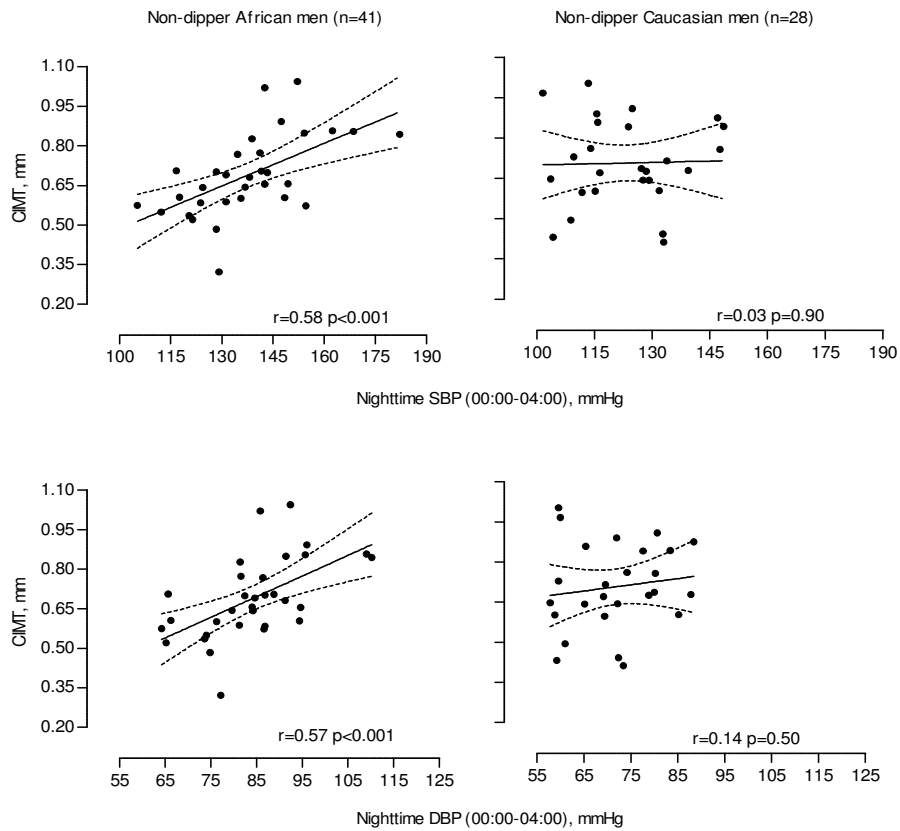
### Adjusted analyses

By adjusting for age and BMI (Table 3), the associations between the various blood pressure measurements and blood glucose disappeared in the non-dipper Caucasian men. However, in the non-dipper African men, daytime SBP, nighttime (22:00-06:00) SBP and nighttime (00:00-04:00) SBP showed positive associations with serum glucose, HbA1c and eAG. Daytime DBP, nighttime (22:00-06:00) DBP and nighttime (00:00-04:00) DBP correlated significantly with serum glucose while borderline significant associations were obtained with HbA1c and eAG.

**Table 3:** Regression analyses of various glucose measurements with several blood pressures and carotid intima-media thickness.

|   | Single regression       |         |                                |         |                                   |         |                           |         |                                |         |                                   |         |
|---|-------------------------|---------|--------------------------------|---------|-----------------------------------|---------|---------------------------|---------|--------------------------------|---------|-----------------------------------|---------|
|   | African men non-dippers |         |                                |         |                                   |         | Caucasian men non-dippers |         |                                |         |                                   |         |
|   | Serum glucose, mmol/L   |         | Glycosylated hemoglobin A1c, % |         | Estimated average glucose, mmol/L |         | Serum glucose, mmol/L     |         | Glycosylated hemoglobin A1c, % |         | Estimated average glucose, mmol/L |         |
| Daytime SBP, mmHg                             | r=0.538                 | p=0.000 | r=0.394                        | p=0.016 | r=0.392                           | p=0.018 | r=0.436                   | p=0.020 | r=0.466                        | p=0.012 | r=0.461                           | p=0.014 |
| Daytime DBP, mmHg                             | r=0.548                 | p=0.000 | r=0.341                        | p=0.039 | r=0.338                           | p=0.044 | r=0.432                   | p=0.022 | r=0.353                        | p=0.065 | r=0.355                           | p=0.064 |
| Nighttime SBP (22:00-06:00), mmHg             | r=0.536                 | p=0.000 | r=0.445                        | p=0.006 | r=0.444                           | p=0.007 | r=0.412                   | p=0.029 | r=0.428                        | p=0.023 | r=0.421                           | p=0.026 |
| Nighttime DBP (22:00-06:00), mmHg             | r=0.529                 | p=0.001 | r=0.324                        | p=0.051 | r=0.322                           | p=0.055 | r=0.446                   | p=0.017 | r=0.192                        | p=0.33  | r=0.185                           | p=0.35  |
| Nighttime SBP (00:00-04:00), mmHg             | r=0.521                 | p=0.003 | r=0.543                        | p=0.002 | r=0.540                           | p=0.003 | r=0.340                   | p=0.089 | r=0.378                        | p=0.057 | r=0.374                           | p=0.060 |
| Nighttime DBP (00:00-04:00), mmHg             | r=0.500                 | p=0.004 | r=0.374                        | p=0.045 | r=0.372                           | p=0.051 | r=0.326                   | p=0.10  | r=0.146                        | p=0.48  | r=0.139                           | p=0.50  |
| CIMT, mm                                      | r=0.279                 | p=0.090 | r=0.351                        | p=0.036 | r=0.357                           | p=0.035 | r=0.448                   | p=0.017 | r=0.269                        | p=0.17  | r=0.257                           | p=0.19  |
| Partial regression : Adjusted for age and BMI |                         |         |                                |         |                                   |         |                           |         |                                |         |                                   |         |
|   | African men non-dippers |         |                                |         |                                   |         | Caucasian men non-dippers |         |                                |         |                                   |         |
|   | Serum glucose, mmol/L   |         | Glycosylated hemoglobin A1c, % |         | Estimated average glucose, mmol/L |         | Serum glucose, mmol/L     |         | Glycosylated hemoglobin A1c, % |         | Estimated average glucose, mmol/L |         |
| Daytime SBP, mmHg                             | r=0.467                 | p=0.006 | r=0.334                        | p=0.052 | r=0.339                           | p=0.050 | r=0.160                   | p=0.44  | r=0.327                        | p=0.10  | r=0.325                           | p=0.11  |
| Daytime DBP, mmHg                             | r=0.485                 | p=0.004 | r=0.312                        | p=0.072 | r=0.313                           | p=0.072 | r=0.137                   | p=0.51  | r=0.152                        | p=0.46  | r=0.158                           | p=0.44  |
| Nighttime SBP (22:00-06:00), mmHg             | r=0.468                 | p=0.006 | r=0.398                        | p=0.020 | r=0.401                           | p=0.019 | r=0.152                   | p=0.46  | r=0.272                        | p=0.18  | r=0.268                           | p=0.19  |
| Nighttime DBP (22:00-06:00), mmHg             | r=0.463                 | p=0.007 | r=0.308                        | p=0.077 | r=0.312                           | p=0.073 | r=0.156                   | p=0.45  | r=-0.066                       | p=0.75  | r=-0.072                          | p=0.73  |
| Nighttime SBP (00:00-04:00), mmHg             | r=0.446                 | p=0.022 | r=0.505                        | p=0.008 | r=0.507                           | p=0.008 | r=0.039                   | p=0.86  | r=0.204                        | p=0.34  | r=0.202                           | p=0.34  |
| Nighttime DBP (00:00-04:00), mmHg             | r=0.414                 | p=0.035 | r=0.349                        | p=0.081 | r=0.353                           | p=0.077 | r=-0.018                  | p=0.93  | r=-0.131                       | p=0.54  | r=-0.136                          | p=0.53  |
| CIMT, mm                                      | r=0.112                 | p=0.54  | r=0.285                        | p=0.11  | r=0.302                           | p=0.087 | r=0.206                   | p=0.31  | r=0.146                        | p=0.48  | r=0.128                           | p=0.53  |

SBP, Systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima-media thickness.



**Figure 2:** Carotid intima-media thickness (CIMT) as a function of nighttime (00:00-04:00) systolic (SBP) and diastolic (DBP) blood pressure in non-dipper African and Caucasian men in single regression analysis. Solid and dashed lines represent the regression line and the 95% CI boundaries.

After full adjustment (age, BMI, smoking, alcohol intake, physical activity, C-reactive protein and baroreceptor sensitivity) (Table 4), nighttime (00:00-04:00) SBP was the only measure of blood pressure that correlated positively with HbA1c ( $p=0.069$ ) and eAG ( $p<0.001$ ) in the African men. Furthermore, CIMT correlated positively with HbA1C and eAG in the African men. No significant relationships were found for Caucasian men.

**Table 4:** Independent associations of various glucose measurements with several blood pressures and carotid intima-media thickness.

| Serum glucose, log mmol/L                    | African men          |                          |          | Caucasian men        |                          |          |
|--|----------------------|--------------------------|----------|----------------------|--------------------------|----------|
|  | R <sup>2</sup>       | β (95% CI)               | P        | R <sup>2</sup>       | β (95% CI)               | P        |
| Daytime SBP, mmHg                            | 0.564                | 0.200 (-0.085 to 0.488)  | 0.16     | 0.637                | -0.013 (-0.380 to 0.353) | 0.94     |
| Daytime DBP, mmHg                            | 0.548                | 0.210 (-0.081 to 0.508)  | 0.15     | 0.479                | 0.101 (-0.256 to 0.459)  | 0.57     |
| Nighttime SBP (22:00-06:00), mmHg            | 0.517                | 0.203 (-0.098 to 0.509)  | 0.18     | 0.480                | -0.060 (-0.481 to 0.362) | 0.77     |
| Nighttime DBP (22:00-06:00), mmHg            | 0.560                | 0.140 (-0.156 to 0.438)  | 0.34     | 0.466                | -0.019 (-0.446 to 0.408) | 0.93     |
| Nighttime SBP (00:00-04:00), mmHg            | 0.388                | 0.254 (-0.123 to 0.598)  | 0.19     | 0.457                | 0.088 (-0.290 to +0.460) | 0.64     |
| Nighttime DBP (00:00-04:00), mmHg            | 0.616                | 0.198 (-0.166 to 0.484)  | 0.22     | 0.463                | -0.190 (-0.622 to 0.254) | 0.39     |
| CIMT, mm*                                    | 0.594                | 0.092 (-0.185 to 0.350)  | 0.53     | 0.456                | 0.254 (-0.071 to 0.579)  | 0.12     |
| <b>Glycosylated hemoglobin A1c, log %</b>    | <b>R<sup>2</sup></b> | <b>β (95% CI)</b>        | <b>P</b> | <b>R<sup>2</sup></b> | <b>β (95% CI)</b>        | <b>P</b> |
| Daytime SBP, mmHg                            | 0.555                | 0.206 (-0.105 to 0.528)  | 0.18     | 0.632                | 0.221 (-0.054 to 0.497)  | 0.11     |
| Daytime DBP, mmHg                            | 0.568                | 0.088 (-0.227 to 0.406)  | 0.57     | 0.483                | 0.114 (-0.213 to 0.441)  | 0.48     |
| Nighttime SBP (22:00-06:00), mmHg            | 0.577                | 0.230 (-0.080 to 0.559)  | 0.14     | 0.463                | 0.215 (-0.111 to 0.540)  | 0.19     |
| Nighttime DBP (22:00-06:00), mmHg            | 0.573                | 0.019 (-0.294 to 0.333)  | 0.90     | 0.515                | -0.277 (0.643 to 0.088)  | 0.13     |
| Nighttime SBP (00:00-04:00), mmHg            | 0.512                | 0.363 (-0.029 to 0.723)  | 0.069    | 0.424                | 0.172 (-0.187 to 0.539)  | 0.32     |
| Nighttime DBP (00:00-04:00), mmHg            | 0.646                | 0.074 (-0.264 to 0.401)  | 0.67     | 0.487                | -0.247 (-0.645 to 0.135) | 0.19     |
| CIMT, mm*                                    | 0.494                | 0.319 (0.050 to 0.539)   | 0.020    | 0.431                | 0.178 (-0.136 to 0.492)  | 0.25     |
| <b>Estimated average glucose, log mmol/L</b> | <b>R<sup>2</sup></b> | <b>β (95% CI)</b>        | <b>P</b> | <b>R<sup>2</sup></b> | <b>β (95% CI)</b>        | <b>P</b> |
| Daytime SBP, mmHg                            | 0.550                | 0.188 (-0.138 to 0.525)  | 0.24     | 0.632                | 0.222 (-0.053 to 0.497)  | 0.11     |
| Daytime DBP, mmHg                            | 0.574                | 0.055 (-0.271 to 0.383)  | 0.73     | 0.484                | 0.119 (-0.207 to 0.445)  | 0.46     |
| Nighttime SBP (22:00-06:00), mmHg            | 0.576                | 0.221 (-0.102 to 0.568)  | 0.17     | 0.462                | 0.211 (-0.114 to 0.536)  | 0.19     |
| Nighttime DBP (22:00-06:00), mmHg            | 0.576                | 0.0041 (-0.327 to 0.328) | 0.99     | 0.516                | -0.275 (-0.637 to 0.087) | 0.13     |
| Nighttime SBP (00:00-04:00), mmHg            | 0.511                | 0.583 (0.270 to 0.858)   | 0.001    | 0.423                | 0.169 (-0.189 to 0.540)  | 0.33     |
| Nighttime DBP (00:00-04:00), mmHg            | 0.651                | 0.112 (-0.256 to 0.466)  | 0.55     | 0.487                | -0.244 (-0.642 to 0.135) | 0.19     |
| CIMT, mm*                                    | 0.451                | 0.331 (0.043 to 0.520)   | 0.022    | 0.427                | 0.164(-0.151 to 0.480)   | 0.29     |

Adjusted for age, body mass index, smoking, alcohol intake, physical activity, C-reactive protein and baroreceptor sensitivity. \*carotid intima-media thickness (CIMT) was additionally adjusted for 24 hour mean arterial pressure. SBP, Systolic blood pressure; DBP, diastolic blood pressure.

### Sensitivity analysis

To determine if the associations between nighttime (00:00-04:00) SBP and eAG were independent of CIMT, we additionally adjusted for CIMT. By doing so the positive association between SBP and eAG remained significant in non-dipper African men ( $R^2=0.617$ ;  $\beta=0.438$ ;  $p=0.008$ ) and non-significant in the non-dipper Caucasian men ( $R^2=0.423$ ;  $\beta=0.169$ ;  $p=0.33$ ). In addition, to determine if the association between CIMT and eAG was independent of nighttime (00:00-04:00) SBP, we additionally adjusted for this variable. Consequently, the association between CIMT and eAG disappeared in African men ( $R^2=0.628$ ;  $\beta=0.064$ ;  $p=0.69$ ) and remained non-significant in Caucasian men ( $R^2=0.435$ ;  $\beta=0.163$ ;  $p=0.32$ ).

## Discussion

This study investigated the relationship between various blood glucose measurements and non-dipping nocturnal blood pressure in African and Caucasian men. We found a significant association between nighttime SBP and chronically elevated blood glucose only in the African men. In addition, associations between CIMT and blood glucose were dependent on blood pressure, suggesting that the blood pressure-blood glucose relationship drives intima-media thickening. Lastly, this result was only applicable to the stable early morning blood pressures (00:00-04:00), and not to the nighttime period that is normally used.

Previous studies found that a blunted nocturnal decline in blood pressure is a predictor of increased cardiovascular complications, and that especially SBP is closely associated with cardiovascular events.<sup>4,25,26</sup> Our study showed that Africans had higher nighttime blood pressures and a higher prevalence of non-dipping individuals than Caucasians. In addition, early morning SBP showed an association with chronically elevated glucose. Although sympathetic activity could drive both blood glucose and blood pressure, we showed that this relationship was independent of baroreceptor sensitivity, a marker of sympathetic activity.

It has been reported that an association between glucose below the diabetic threshold and cardiovascular risk exists. This suggests that a moderate increase in the HbA1c level can increase the risk for cardiovascular disease.<sup>14,27</sup> In addition, mild hyperglycemia has previously been shown as a risk factor for atherosclerosis.<sup>28</sup> However, in the Africans of the present study, the association found between CIMT and blood glucose was dependent on blood pressure, suggesting that the increase in blood pressure due to elevated glucose is the main contributor to the thickening of the carotid intima-media. Therefore, the SBP of the Africans driven by elevated blood glucose can be seen as the more prominent contributor in the development of early atherosclerotic alterations in this population. Previous investigators found that CIMT is more closely associated with nighttime blood pressure, than any other ambulatory blood pressure measurement taken.<sup>29</sup> Our findings confirm this, but also add to these findings by obtaining these associations with the lowest, stable nighttime blood pressure.

The precise mechanism causing the non-dipping pattern is still unknown.<sup>7,30</sup> However, blood glucose, at least in part, seems to have an influence on the non-dipping pattern in Caucasians and people from African descent. The kidneys are essential organs in the control of blood pressure and it seems impossible to have a non-dipping blood pressure pattern without a disturbance in renal function.<sup>31,32</sup> Therefore, the well-known salt sensitivity observed in the African population might be a significant contributor to the increased nocturnal blood pressure seen in this group.<sup>33</sup> Previous investigators reported that elevated blood glucose levels may also contribute to a salt sensitive state.<sup>12</sup> Elevated blood glucose levels cause an increase in renal sodium absorption that leads to an elevated glomerular capillary pressure, resulting in a salt sensitive state.<sup>12</sup> This causes an increase in the nocturnal blood pressure that leads to a non-dipping blood pressure pattern. This may explain the relationship found between blood pressure and glucose in the Africans from the present study. Furthermore, this sustained elevated nocturnal blood pressure in these non-dipping individuals may contribute to vascular remodeling and structural changes in the arteries, which causes an increase in CIMT.<sup>34</sup>

A possible explanation why no relationship between blood pressure and blood glucose was found in the Caucasian population could be because of lower blood pressures and blood glucose concentrations of these individuals. This could perhaps also explain why there were less non-dipping subjects in this group.

There are some important clinical aspects of our study that deserve to be mentioned. HbA1c and eAG are more reliable glucose measurements when determining the influence of elevated blood glucose in seemingly healthy individuals. This is confirmed by other investigators who found controversial results with serum glucose and its prediction of cardiovascular disease in non-diabetic patients.<sup>14,35</sup> The stable early morning (00:00-04:00) period during which a relationship between SBP and eAG was found in the present study seems to be a better period when investigating early relationships between glucose and nocturnal blood pressure since this is the period during which the blood pressure was the lowest and most stable.

The present study should be interpreted within the context of its limitations and strengths. Although the results were consistent after multiple adjustments, we cannot exclude residual confounding. Also, due to the cross-sectional nature of this study, causality cannot be inferred. We did not measure urine sodium excretion to support the influence of chronically elevated blood glucose on sodium sensitivity in these participants. The participants of this study were still young and it is possible that the results are limited to this age group. The subject group was small and cannot be seen as a representation of the entire South African population, since this group was only recruited from the Potchefstroom district of the North West province. This was a well-designed study under controlled conditions in two ethnic and socio-economic homogeneous groups. The inclusion of Africans in this study was of value since they are known to have higher incidences of cardiovascular disease and limited information exists about this ethnic group. To our knowledge, our study is the first to investigate associations between chronically elevated glucose levels and nocturnal blood pressure in Africans.

In conclusion, in African men a blunted nocturnal decline in systolic blood pressure during the early morning hours was associated with chronically elevated blood glucose, independent of a marker of sympathetic activity. This suggests that the early morning blood pressures (00:00-04:00) might be a reliable period to use when investigating the blood glucose-nocturnal blood pressure relationship. This study also emphasizes the importance of glycemic control and may pave the way for more studies investigating the coexistence of hypertension and type 2 diabetes mellitus in Africans.

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# **CHAPTER 4**

## **SUMMARY**

## **Introduction**

This chapter is a summary of the main findings from the study. The results will be interpreted, explained and compared to the relevant literature, after which conclusions will be drawn and recommendations will be made to future researchers investigating the relationship between blood glucose and nocturnal blood pressure in African and Caucasian men.

## **Summary of the main findings**

This study aimed to investigate the relationship between a blunted nocturnal decline in blood pressure and blood glucose in African and Caucasian men. The results showed that the prevalence of non-dippers tended to be higher, while nocturnal blood pressure and blood glucose were significantly higher in non-dipping African men. Therefore, the first hypothesis may be accepted. Secondly, an association between early morning (00:00-04:00) systolic blood pressure (SBP) and chronically elevated blood glucose measurements were found in the non-dipping African men only, therefore, the second hypothesis may be partially accepted.

An additional finding of our study was that an association between carotid intima-media thickness (CIMT) and blood glucose in the African men were found to be dependent on blood pressure, suggesting that intima-media thickening in the African non-dippers may be driven by a blood pressure-blood glucose relationship.

## **Comparison to relevant literature**

The results of the present study are similar to the results found in previous studies that investigated the blood pressure serum glucose relationship.<sup>1,2</sup> The Africans from the present study also had higher nocturnal blood pressures, non-dipping blood pressure patterns and elevated blood glucose levels compared to Caucasians.

According to the American Diabetes Association, the development of vascular complications can already exist in individuals with glycosylated hemoglobin A1c (HbA1c) levels between 5.7-6.4 percent.<sup>3</sup> This was indeed the case in our study with the HbA1c levels of the African men being within this range (6.09 %). Furthermore, HbA1c and estimated average glucose (eAG) seems to be more reliable markers than fasting serum glucose in identifying early

cardiovascular complications associated with blood glucose such as, thickening of the carotid intima-media as observed in the African population. This was confirmed by previous investigators who reported that glycemic markers are better predictors of cardiovascular complications than serum glucose in non-diabetic subjects.<sup>4,5</sup>

Furthermore, it is reported that nighttime blood pressure, especially a blunted decline in SBP is closely associated with CIMT.<sup>6</sup> This was also observed in the present study with SBP (00:00-04:00) correlating positively with CIMT. In addition, the association between blood glucose and CIMT disappeared when adjusting for nighttime SBP (00:00-04:00), emphasizing the prominent relationship between CIMT and SBP.

### **Chance and confounding**

It is crucial to reflect on some important factors that might have affected the results of this study, such as some methodological issues that could have weakened the outcomes of this study.

The number of subjects in this study could be questioned. Although the sample size consisted of 101 African and 101 Caucasian men, only 41 African men and 28 Caucasian men were non-dippers. This group cannot be seen as a representation of the entire South African population, since this group consisted of school teachers in the Potchefstroom district in the North West Province of South Africa. However, this was a well designed study conducted under controlled conditions. In addition, all participants were selected from the same socio-economic class.

In relation to the results, the possibility of chance ought to be taken into account. By using partial and forward stepwise regression analyses, statistics indicate that one out of twenty significant correlations might be due to chance.

Confounding factors such as age, body mass index, smoking, alcohol intake, physical activity, C-reactive protein and baroreceptor sensitivity could have influenced the results by causing over or underestimation of the associations between the different blood pressure and blood glucose variables investigated in this study. It was necessary to investigate all the statistical results from a physiological perspective, which entail that all statistical significance does not necessarily indicate physiological significance.

## **Discussion of main findings**

Both hypertension and type 2 diabetes can cause a non-dipping blood pressure pattern.<sup>7-9</sup> These risk factors are known to be more prevalent in Africans than Caucasians. Therefore, the focus of the study was to investigate if blood glucose is associated with a non-dipping blood pressure pattern in Africans and Caucasians. Associations between early morning SBP (00:00-04:00) and chronically elevated blood glucose in the African men indicate that a prediabetic state may already exist in this subject group that could contribute to cardiovascular complications. The relationship between CIMT and blood glucose was dependent of blood pressure and, therefore, indicating that the thickening of the carotid artery is driven through the blood pressure-blood glucose relationship. Furthermore, these results were only applicable to the stable early morning SBP (00:00-04:00). This is unique to this study and can be seen as a more reliable time period to use when investigating the influence of blood glucose on the nocturnal dipping pattern of blood pressure since, this was the period during which blood pressure was most stable. Although these findings cannot be generalized to the whole male population of South Africa, it confirms the importance of blood glucose control and could provide a reference for future studies.

## **Conclusion**

In African men a blunted nocturnal decline in systolic blood pressure during the early morning hours was associated with chronically elevated blood glucose, independent of a marker of sympathetic activity. This suggests that the early morning blood pressure (00:00-04:00) might be a more reliable period to use when investigating nocturnal blood pressure. This study also emphasizes the importance of glycemic control and may pave the way for more studies investigating the coexistence of hypertension and type 2 diabetes mellitus in Africans.

## **Recommendations**

It is recommended for future studies:

- That a larger population sample should be used to investigate the relationship between nocturnal blood pressure and blood glucose. These future studies should also have a prospective design.
- Due to the strong relationship found between blood glucose and systolic blood pressure during the early morning hours (00:00-04:00), it is recommended that future researchers must also investigate this period when they determine the influence of various factors on blood pressure regulation during the night.
- When investigating the role of blood glucose on nocturnal blood pressure, it is recommended to measure the individual's insulin levels and sodium excretion to determine more accurately the mechanism by which blood glucose influences the nocturnal blood pressures in these non-dipping individuals.

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