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EFFECT OF MAGNESIUM SUPPLEMENTATION ON BLOOD PRESSURE IN GRADE 1 HYPERTENSIVE ADULTS

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Abstract

Purpose: The primary aim of this study was to assess the change in resting Blood Pressure (BP) following a 6 week magnesium supplementation regimen in grade 1 hypertensive adults. The secondary aim of the study was to assess the change in Resting Heart Rate (RHR) after a 6 week Mg supplementation regimen in grade I hypertensive adults.

Methodology: This study employed an experimental research design. In this study, administration of Magnesium (Mg) was controlled by the researcher and the influences on resting BP and RHR observed. A sample of 18 hypertensive adults was used in the study. The significance level was set at $p < 0.05$. Data was determined to be parametric. A paired t-test was used to compare mean differences from baseline, mid-point and post-test within the group

Results: There was no significant difference observed at baseline for Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) within the MGS group ($p > 0.05$). The Magnesium Supplementation Group (MSG) had a SBP and DBP of 143.2 ± 7.0 mmHg and 86.7 ± 4.6 mmHg at baseline. Following supplementation with magnesium (500 mg/day) SBP reduced by -1.1 ± 4.8 mmHg and DBP increased by $+0.7 \pm 6.0$ mmHg respectively after 3 weeks and reduced further by -3.4 ± 2.7 mmHg for SBP and -1.0 ± 5.2 mmHg for DBP after 6 weeks. These changes were not statistically significant ($p > 0.05$) after 3 weeks for SBP and DBP respectively, however after 6 weeks they were significant for SBP ($p < 0.05$) but not for DBP ($p > 0.05$). In addition, there was no significant difference observed at baseline for Resting Heart Rate within the MGS group ($p > 0.05$). The MGS group has a RHR of 82.4 ± 11.1 bpm. Following supplementation with magnesium (500 mg/day) RHR bpm reduced by -1.7 ± 6.7 bpm after 3 weeks and reduced further by -2.9 ± 6.1 bpm after 6 weeks. These changes in RHR were not significant ($p > 0.05$) after 3 weeks and 6 weeks.

Recommendations for Further Research: For any study dealing with magnesium, intra-erythrocyte magnesium levels need to be taken before and after the study so as to ensure that conclusions drawn from the study are as a direct effect of magnesium

Key Words: *Blood pressure, magnesium supplementation, grade 1 hypertensive adults, heart rate.*

1.0 INTRODUCTION

Background of the study

Although hypertension has a high prevalence rate, it has been acknowledged as one of the modifiable risk factor for cardiovascular disease associated with stroke, heart disease and end-stage kidney disease (Hedayati, Elsayed & Reilly, 2011). Since hypertensive individuals have a higher predisposition for cardiovascular disease, premature death may occur in individuals whose blood pressure is poorly controlled (Varughese & Lip, 2005).

The use of non-pharmacological methods has been shown to have the ability to substantially reduce blood pressure in adults with hypertension (Hedayati, Elsayed & Reilly, 2011). The two most recognized non-pharmacological methods used to manage and control blood pressure (BP) in adults are: Increased participation in physical activity and the adoption of a healthy diet (So, Li, Choi, Sung & Nelson, 2012). In addition an increase in dietary magnesium (Mg) has been shown to lower BP (Kass, Weekes & Carpenter, 2012).

Studies suggest that dietary Mg supplementation (500-1000mg/day) significantly reduce BP (Bain et al., 2015; Choi & Bae, 2015; Kass, Weekes & Carpenter, 2012; Rosanoff, 2010) with values of up to 12 mmHg (Kass & Poeira, 2015), with higher doses eliciting a higher reduction in BP (Dose dependent relationship) (Jee et al., 2002). Possible mechanisms for reduction in BP by Mg acts as a natural calcium channel blocker that induces endothelial-dependent vasodilation. It also reduces circulating Sodium (Na^+) Pottasium (K^+) ATPase inhibitory activity thus decreases vascular tone. In addition, it increases vasodilation through an increase in nitric oxide. It also increases prostaglandin E1 (PGE1) known to cause vasodilation and Induces direct and indirect vasodilation (Houston, 2011).

Statement of the Problem

Since blood pressure treatment and control is expensive, the prevalence of hypertension within lower-middle income countries (such as Kenya) has increased, consequently increasing the cardiovascular disease burden. Hypertensive individuals do not get appropriate care because they cannot afford the medication and treatment which leads to secondary cardiovascular diseases associated with raised blood pressure. The age-adjusted prevalence of raised blood pressure is 21.1% amongst the Kenyan adult population (WHO, 2014) and is on the rise (M'Buyamba-Kabangu *et al.*, 2013). Since hypertension is a major risk factor and driving force for cardiovascular diseases, finding an economical and accessible method of controlling it may reduce the cardiovascular disease burden in Kenya.

Purpose of the Study

The primary aim of this study was to assess the change in resting Blood Pressure (BP) following a 6 week magnesium supplementation regimen in grade 1 hypertensive adults. The secondary aim of the study was to assess the change in Resting Heart Rate (RHR) after a 6 week Mg supplementation regimen in grade I hypertensive adults

Hypothesis

H₀₁- There is no significant difference in the changes observed in resting BP in adults with grade I hypertension following a 6 week magnesium supplementation regimen.

H₀₂ - There is no significant difference in the changes observed in RHR in adults with grade I hypertension following a 6 week magnesium supplementation regimen.

2.0 LITERATURE REVIEW

Magnesium and Blood Pressure

One of the mechanisms by which Mg lowers BP is by functioning as a calcium channel blocker by extracellularly inhibiting trans-membrane calcium transport and calcium entry, or acting intracellularly as a calcium antagonist (Hatzistavri *et al.*, 2009). This controls the vasoconstriction actions caused by increased intracellular calcium. Mg competes with the sodium binding sites of smooth muscles, thus increases circulating levels of Prostaglandin E-1 (PGE-1). This causes co-operative binding to potassium, which prompts vasodilation via decreased intracellular calcium and sodium levels thereby reducing BP (Choi & Bae, 2015; Houston, 2011; Kass, Weekes & Carpenter, 2012). Mg also regulates BP by mediating the action of Na⁺/K⁺ ATPase which regulates trans- membrane sodium and potassium transport. An increase in Mg levels causes suppression of Na⁺/K⁺ ATPase inhibitory activity which in turn reduces vascular tone (Mubagwa, Gwanyanya, Zakharov & Macianskiene, 2007; Touyz, 2004).

Studies have shown that there is an inverse relationship between serum Mg levels and BP (Rosanoff, Weaver & Rude, 2012). Oral Mg supplementation increases intracellular Mg levels and causes a significant reduction in intracellular calcium and sodium concentrations. A study by Hatzistavri *et al.* (2009) showed that this subsequent increase in Mg levels and decrease in sodium and potassium levels following oral Mg supplementation reversed the impaired ionic balance present in hypertensive individuals, thus proposing it as one of the basic mechanisms through which Mg exerts its BP lowering effect.

Mg has also been shown to influence BP through the mediation of nitric oxide (NO) (Barbagallo, Dominguez, Galioto, Pineo & Belvedere, 2016; Lui, 2003) and prostoglandin E₁ (Das, 2006: 2010). NO is a powerful vasodilator, and an increase in Mg levels has been shown to increase NO levels in the body (Barbagallo, Dominguez, Galioto, Pineo, & Belvedere, 2016; Lui, 2003). Increase in Mg has also shown to stimulate the release of PGE₁ which causes an increase in vasodilation in the blood vessels thus reducing BP (Das, 2006: 2010).

Studies have shown that high Mg intake (500 – 1000 mg/day) may reduce BP but these results are inconsistent (Houston, 2011; Choi & Bae, 2015). However these inconsistencies may have been brought about due to variation in the population studies, type and dosage of Mg, pre-treatment BP levels, duration of the trial, dietary nutrients and minerals. (Jee *et al.*, 2002; Touyz, 2004).

In a uniform sub set meta-analysis of seven studies that involved 135 hypertensive individuals on anti-hypertensive medication for at least 6 months and no more than 2 week wash out period demonstrated a mean change of -18.7 mmHg (Rosanoff, 2013). However two other meta-analysis; one conducted by Jee *et al.* (2002) which involved 20 studies (n=1220) and another conducted by Kass, Weekes and Carpenter (2012) which involved 22 studies (n=1173) showed

very minimal but statistically significant changes in BP. Jee et al. (2002) study showed an estimated change of 0.6 (-2.2 to 1.0) mmHg for SBP and -0.8 (1.9 to 0.4) mmHg for DPB while Kass, Weekes and carpenter (2012) showed an overall change of 3-4 mmHg for DPB and 2-3 mmHg for SBP. Another review done by Dickinson et al. 2006 which involved 12 RCTs (n=544) showed a small average reduction of 2.2 mmHg. The uniform sub set of 7 showed a strong effect of Mg treatment in hypertension which was in contrast with the other 3 studies. This suggests that the small effect reported by the other 3 studies may have been due to the fact that the non-uniform sets of studies used acted to seriously underestimate the potential of Mg in some (but not all) subjects.

Mg deficiency may play a pathogenic role in the development of hypertension (Kisters & Grober, 2013). A study by Kisters et al. (2011) showed a reduction of 10.4 mmHg in Borderline Mg deficient hypertensive individuals following Mg supplementation (240-480mg/day) over 12-15 weeks. This suggests that individuals, whose hypertension developed due to Mg deficiency, can control their BP using Mg supplements and have an improved quality of life. Mg has however also been shown to reduce BP in individuals without any disturbances in Mg metabolism (Solati et al., 2014). In a study by Solati *et al.* (2014) on type II diabetic subjects who did not have obvious disturbances in Mg metabolism, showed average reductions of 15.1 and 10.6 mmHg in DPB and SBP respectively following Mg (MgSo₄-) supplementation (300 mg/day) over a 3 month period.

Studies have shown that there is a dose dependent relationship between Mg intake and BP (Choi & Bae, 2015; Jee et al., 2002; Kass, Weekes & Carpenter, 2012; Rosanoff, 2010). A meta-analysis by Jee et al. (2002) showed reductions of -4.3 mmHg SBP and -2.3 mmHg DPB for each 10 mmol/day increase in Mg dosage. Another study by Kass, Weekes and Carpenter (2015) showed that after sub analysis for dosage was conducted (<370mg mg and >370mg mg/day), both DPB and DPB showed higher efficacy of Mg supplementation at higher doses.

Since the present literature suggests that results from previous studies may have been affected by non-homogeneous population, type of Mg supplement and Dosage; this study strived to ensure that the population was as homogenous as possible, by restricting the pretreatment BP levels to grade I hypertension, the age group to 30-60 years, sedentary, drug & supplement naïve without any secondary diseases.

Magnesium and Resting Heart Rate

The studies directly investigating the relationship between magnesium and resting heart rate are very limited. However magnesium is involved in many physiological, biochemical and cellular processes that regulate cardiovascular function (Kolte, Vijayaraghavan, Khera, Sica & Frishman, 2014). Magnesium has been shown to improve endothelial function, vascular smooth muscle tone, myocardial excitability and blood flow in systemic and coronary circulation (Houston, 2011) thus mediating heart rate indirectly by improving cardiovascular function.

Magnesium improves cardiovascular function by reducing vascular tone; Magnesium is a natural calcium blocker, thus inducing endothelial dependent vasodilation. Endothelium plays a crucial role in vascular homeostasis by regulating vascular diameter and tone, coagulation factors, vascular inflammation and cell migration and proliferation. There is also a reduction in arteriolar tension and tone in various arteries and increases the dilatory action of endogenous and

exogenous vasodilators. Magnesium has also been shown to reduce circulating Na^+K^+ ATPase inhibitory activity thus decreases vascular tone and increases vasodilation through an increase in nitric oxide. These factors reduce systemic and pulmonary vascular resistance with an accompanying reduction in BP and slight increase in cardiac index and function. (Houston 2011; Shechter, 2010) This increase in cardiac index may lead to a decrease in the number of beats required to maintain resting cardiac output. In addition Magnesium improves cardiovascular function by improving left ventricular ejection fraction (LVEF) and resting myocardial function. A study by Pokan (2006) on 53 male patients with stable coronary artery disease were either given oral magnesium 15mmol twice daily or placebo for 6 months. After the 6 months investigation there were marked improvements in LVEF. A larger ejection fraction is suggestive of an increased cardiac index and function. This increase in cardiac index may lead to a decrease in the number of beats required to maintain resting cardiac output. Magnesium also resulted in significant decrease in left ventricular diastolic function (LVDD) and left ventricular systolic dysfunction (LVSD), suggestive of a cardio protective trait of magnesium. Since a lower RHR is a good indicator of cardiovascular health (da Silva *et al.*, 2013), improving cardiovascular function through magnesium supplementation may reduce resting heart rate.

3.0 RESEARCH METHODOLOGY

This study employed an experimental research design because specific conditions were controlled and its effects observed. In this study, administration of Magnesium (Mg) was controlled by the researcher and the influences on resting BP and RHR observed. A sample of 18 hypertensive adults was used in the study. Data was analyzed using SPSS version 25 (IBM Limited, UK, 2017) and Microsoft Excel 2013 for Windows. The significance level was set at $p < 0.05$. Data was tested for normal distribution using the Shapiro-Wilk test while the Levenes test was used to test for data normality. Data was determined to be parametric. A paired t-test was used to compare mean differences from baseline, mid-point and post-test within the group.

4.0 FINDINGS

4.1 Blood Pressure Response to Magnesium

Changes in BP (SBP and DBP) after a 6 week magnesium supplementation regimen are presented below in Figure 1.

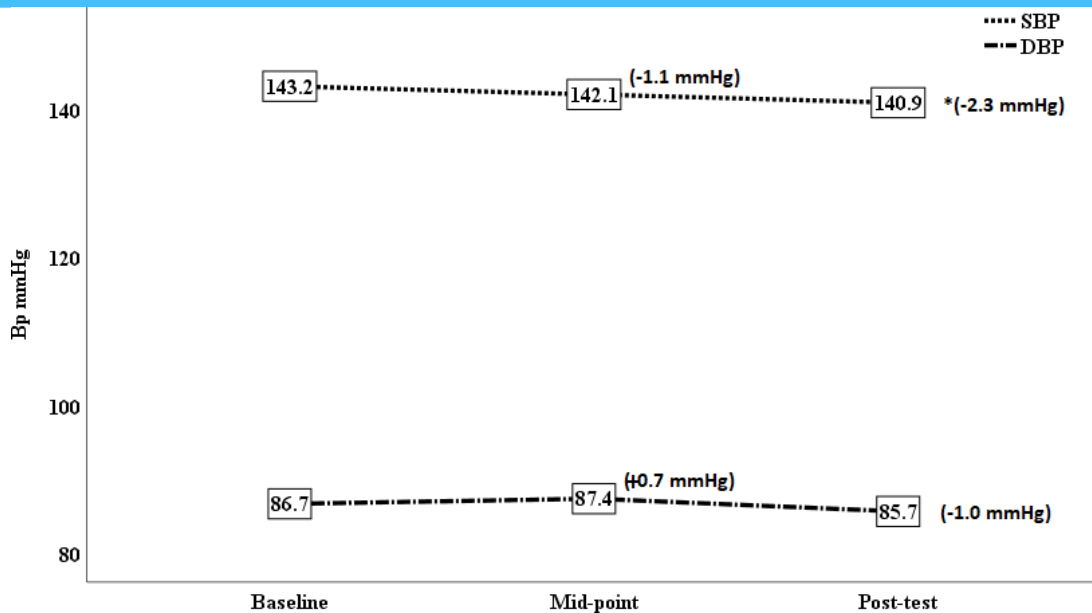


Figure1: BP changes after 6 weeks of magnesium supplementation in adults with grade 1 hypertension.

There was no significant difference observed at baseline for SBP and DBP within the MGS group ($p > 0.05$). The MGS group had a SBP and DBP of 143.2 ± 7.0 mmHg and 86.7 ± 4.6 mmHg at baseline. Following supplementation with magnesium (500 mg/day) SBP reduced by -1.1 ± 4.8 mmHg and DBP increased by $+0.7 \pm 6.0$ mmHg respectively after 3 weeks and reduced further by -3.4 ± 2.7 mmHg for SBP and -1.0 ± 5.2 mmHg for DBP after 6 weeks. These changes were not statistically significant ($p > 0.05$) after 3 weeks for SBP and DBP respectively, however after 6 weeks they were significant for SBP ($p < 0.05$) but not for DBP ($p > 0.05$). Therefore the study rejects the null hypothesis because there was a statistically significant ($p < 0.05$) reduction in resting BP (SBP) following a 6 week magnesium supplementation regimen in adults with grade 1 hypertension.

4.2 Heart Rate Response to Magnesium

Changes in RHR after a 6 week magnesium supplementation regimen are presented below in Figure 2.

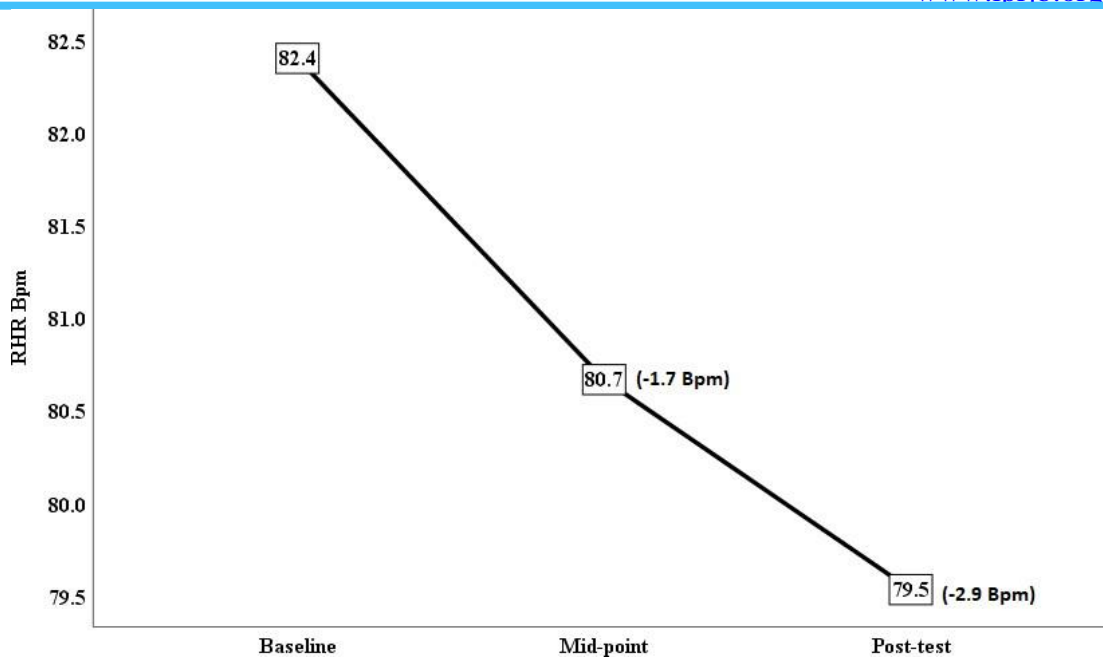


Figure 2: RHR changes after 6 weeks of magnesium supplementation in adults with grade 1 hypertension

There was no significant difference observed at baseline for RHR within the MGS group ($p>0.05$). The MGS group has a RHR of 82.4 ± 11.1 bpm. Following supplementation with magnesium (500 mg/day) RHR bpm reduced by -1.7 ± 6.7 bpm after 3 weeks and reduced further by -2.9 ± 6.1 bpm after 6 weeks. These changes were in RHR were not significant ($p>0.05$) after 3 weeks and 6 weeks. Therefore the study accepts the null hypothesis because there was no statistically significant ($p>0.05$) reduction in resting RHR following a 6 week magnesium supplementation regimen in adults with grade 1 hypertension.

5.0 DISCUSSION OF FINDINGS

Blood Pressure Response to Magnesium Supplementation

The study found a significant ($p<0.05$) reduction in SBP of -2.3 mmHg, but no significant ($p>0.05$) changes in DBP in the MGS group (figure 3). The findings from this study are consistent with a meta-analysis by Zhang et al. (2016) on 34 trials involving 2028 participants (18-84 years), with the total duration varying from 3 weeks to 6 months. The study reported a reduction of -2.0 mmHg in SBP which is similar to the present study. However the study also found a reduction in DBP of -1.78 mmHg which the present study did not find and this may have been due to the fact that the studies within Zhang et al. (2016) meta-analysis may have had a longer duration (>3 months) and larger sample size (>100 participants).

The results from the present are also similar to the systematic reviews and meta-analysis by Jee et al. (2002), Dickinson et al. (2006) who reported reductions in SBP of -2.2 - 1.0 mmHg for SBP in their systematic reviews. The findings from the studies reported small but statistically

significant changes; however there are other studies that have reported larger reductions in BP due to magnesium supplementation.

A meta-analysis by Rosanoff (2013) looked at a group of 7 studies with a uniform sub-set of 135 hypertensive subjects (SBP>155) on anti-hypertensive medication for a minimum of six months found that the mean reduction in BP was -18.7 mmHg. The larger reduction in BP reported in the study by Rosanoff (2013) may have been due to the homogenous nature of the samples, while the smaller reductions in BP reported in the studies by Jee *et al.* (2002), Dickinson *et al.* (2006) and Zhang *et al.* (2016) may be due these inconsistencies brought about due to variation in: The population studies, type and dosage of Mg, pre-treatment BP levels, duration of the trial, dietary nutrients and minerals, this may have acted to seriously underestimate the potential of Mg in some (but not all) subjects. This highlights the importance of homogeneity in the sample population to ensure higher reduction in BP. The present study strived to increase homogeneity by reducing the age bracket (30-60 years), by ensures participants are taking same Mg dosage (500mg/day) over the same duration of time and by restricted the subject within the study to grade I hypertension. The major difference between the present study and the study by Rosanoff (2013) was the study duration. The study by Rosanoff (2013) only included studies conducted over durations longer than 6 months while the present study was conducted over duration of 6 weeks. The study by Zhang *et al.* (2016) also emphasized a time-dependent relationship with durations above 2 months required to cause large reductions in BP.

Since magnesium's effects on BP has a time-dependent relations, studies involving magnesium supplementation should be conducted over a longer duration of time so as to ensure the BP lowering effects of magnesium have taken place. However, a study conducted by Banjanin and Belojevic (2018) on 48 participants (19 men & 29 women) aged 24-65 years with essential hypertension on anti-hypertensive medication reported reductions of -8.9 mmHg and -5.8 mmHg for SBP and DBP respectively after 1 month of magnesium oxide (300 mg/day). The reason the reduction in BP was larger than the present study even though the duration was shorter and the sample size was similar, was due to the fact that the study by Banjanin and Belojevic (2018) was conducted on individuals on antihypertensive medications while the present study excluded any individuals on antihypertensive medications. Magnesium supplements have been shown to enhance the BP lowering effects of anti-hypertensive medications (Rosanoff, 2010).

A limitation of the present study was the lack of accounting for dietary factors. A study by Kass, Skinner and Poeira (2013) on 16 male subjects investigated the effect of magnesium supplementation with high and low dietary magnesium intake over a 2 week period. A significant ($p<0.05$) reduction was found in resting SBP in the low magnesium intake group compared to the high magnesium intake group. This suggests that magnesium supplementation may have a greater effect on individuals that have diets low in magnesium compared to those who have diets rich in magnesium. Since the present study did not account for dietary influences, individual with habitually high magnesium diets may not have benefitted or benefitted less than individuals with low habitual magnesium diets from the magnesium supplement. This means that the conclusions drawn from this study were not due to the direct effect of Mg supplementation but determined by BP reduction.

Heart Rate Response to Magnesium

There was a reduction in RHR (-2.9 bpm) within the MGS group however it was not statistically significant ($p>0.05$). To the author's best knowledge there is no/limited literature on studies done on magnesium supplementation and RHR. The action of magnesium on the cardiovascular system through improved endothelial function, vascular smooth muscle tone, myocardial excitability and blood flow in systemic and coronary circulation (Houston, 2011) would suggest that increased magnesium supplementation may reduce RHR by making the cardiovascular system more efficient. However there was a slight reduction in RHR (-2.9 bpm) even though it was not significant which is suggestive that magnesium may reduce RHR but it needs to be investigated further. The limitation of this study was that the individuals in the MGS group was small ($n=18$) and the study duration was short (6 weeks) thus the power may have not been high enough to produce a statically significant reduction.

6.0 CONCLUSIONS AND RECOMMENDATIONS

Conclusions

The study concluded that magnesium supplements (500 mg/day, Mg Citrate) cause a small but significant reduction in SBP in individuals with grade I hypertension after 6 weeks. Therefore the study rejected the null hypothesis that there is no significant difference in the changes observed in resting BP in adults with grade I hypertension following a 6 week magnesium supplementation regimen, because there was a statistically significant ($p<0.05$) reduction in resting BP (SBP) following a 6 week magnesium supplementation regimen in adults with grade 1 hypertension.

The study also concluded that a magnesium supplement (500 mg/day, Mg Citrate) does not cause a significant reduction in RHR in individuals with hypertension after 6 weeks. Therefore the study accepted the null hypothesis that there is no significant difference in the changes observed in RHR in adults with grade I hypertension following a 6 week magnesium supplementation regimen, because there was no statistically significant ($p>0.05$) reduction in resting RHR following a 6 week magnesium supplementation regimen in adults with grade 1 hypertension.

Recommendations

Since this study was only undertaken over a short period of time (6 weeks) with a small sample size ($n=47$), future studies should focus on having the investigation done over a longer period of time with a larger sample size. This is due to the fact that it does not take the same time for changes in BP to occur when taking a magnesium supplement. Secondly the changes in BP due to magnesium are smaller, thus to increase the power of the study a larger sample size is required so as to get a reliable result. Since it has been suggested that individuals with sufficient magnesium levels may not benefit from a magnesium supplement, research should be focused towards individuals with hypo- magnesium.

Future research should also be done on the effects of magnesium on individuals who have higher levels of hypertension such as grade 2 and Grade 3 to determine whether the effect is larger. This is due to the fact that these individuals are most likely to be sedentary and have hypo-magnesium

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