Estimation of Different forms of Serum Calcium and Mg in Iraqi Patients with Primary Hypertension

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الخلاصة:

يعتبر ارتفاع ضغط الدم من المشاكل الصحية الرئيسية عند البالغين ويساهم في التسبب بأمراض القلب والشرايين. إن سوء التغذية ونقص بعض المواد الغذائية قد تكون من مسببات هذا المرض. لا توجد علاقة واضحة بين مستوى الكالسيوم والمغنسيوم في الدم ومرض ارتفاع ضغط الدم. في هذا البحث تم قياس تراكيز الكالسيوم الكلي و المتأين والمصحح بالألبومين بالإضافة إلى المغنسيوم الكلي و المتأين عند مرضى ضغط الدم ومقارنته بمستوياتهما عند الناس الأصحاء.

اشترك في هذه الدراسة ٧٣ شخصا (ذكور فقط) مصابا بمرض ضغط الدم فقط وليس لديهم أمراض أخرى أعمارهم بين (٢٦-٥٥ سنة). كان مستوى ضغط الدم لدى المرضى أعلى من 95/140 ملليمتر زئبق مقاسا بوضعية الجلوس. و اخذ 30 شخصا سليما من المرض لغرض المقارنة أعمارهم بين (٢٢- ٤٦ سنة). كل المرضى لم تتم معالجتهم بأي دواء. تم قياس تركيزي الكالسيوم و المغنسيوم بالطرق اللونية باستعمال العدد القياسية الجاهزة.

أظهرت النتائج انخفاضا معنويا ($p<0.05$) في تراكيز الكالسيوم الكلي و المتأين والمصحح بالألبومين في أمصال مرضى ضغط الدم مقارنة بمجموعة السيطرة بينما لا يوجد اختلاف معنويا ($p>0.05$) في تركيز المغنسيوم بين المجموعتين. لاتوجد اختلافات معنوية بين نسب الكالسيوم الى المغنسيوم وغيرها من النسب بين مجموعتي المرضى والسيطرة.

مرضى ضغط الدم لديهم تركيز اقل من الكالسيوم في المصل مقارنة بمجموعة السيطرة. يوصى بإضافة الكالسيوم كمساند الى برنامج علاج المرضى وتقليل تناول ملح الطعام لتقليل طرح الكالسيوم في الإدرار ودراسة مواد كيموحيوية أخرى لدى مرضى ارتفاع الضغط وبحجم عينات اكبر

Abstract:

Background: Hypertension is a major health problem in adults, and contributes to cardiovascular disease. Malnutrition or deficiency in different nutrients found to be a risk factor for pathogenesis of essential hypertension. No clear association between calcium or magnesium with blood pressure level could be identified. In this work serum total, ionized, albumin corrected calcium and total and ionized Mg in primary hypertension patients were measured and compared with healthy control.

Patients and Methods: Seventy-three uncomplicated, untreated, hypertensive, but otherwise have no other systemic diseases males, ranging in age from (26–55) years old, were entered into the study. Their blood pressure values were more than 95/140 mm Hg (seated posture). Control group consists of thirty healthy males with

normal blood pressure and their age range is between (22-46) years old. Serum calcium and serum albumin were measured colorimetrically using ready for use kits.

Results: There is a significant decrease ($p<0.05$) in S.Total Ca, S.Ionized Ca, and albumin-corrected Ca in hypertensive group in comparing with control group. No significant change noticed in serum total and ionized magnesium, and in different ratios between the groups.

Conclusion: Hypertensive patients have significantly lower serum total calcium and Mg than control group. Calcium supplements may be required as adjuvant treatment in addition to decrease NaCl in the diet to reduce excretion of calcium in urine. In this work a new ratio (S.albumin/ S.calcium) is introduced as a useful marker for calcium state. Further studies are required for other biochemical parameters in larger patients sample size.

Introduction

High blood pressure (BP) results from either an increased output of blood by the heart or, most often, increased resistance to blood flow in the arteries. In those with high blood pressure, the heart must work harder than normal to force blood through the arteries [(1)]. Hypertension is a major health problem in adults, and contributes to cardiovascular diseases [(2)]. Prevalence of hypertension is showing alarmingly steep rise due to rapid changes in diet and lifestyle [(3)]. There are two types of hypertension; primary (essential hypertension) which accounts for 90% of cases and secondary hypertension which account for 10% of cases is secondary from other identifiable disorders [(4)].

Investigational efforts to detect an independent effect of a dietary cation on BP level are complicated by the intercorrelation of multiple nutrients in the diet [(5)]. In observational studies, significant inverse associations of blood pressure with intake of Mg, potassium, Ca, fiber, and protein have also been reported [(6, 7)]. However, in trials that tested these nutrients, often as dietary supplements, the reduction in blood pressure has typically been small and inconsistent [(8, 9)]. There are many reports about alteration in the metals level in hypertensives. Altered plasma status of Ca, Cu, Mg, and Zn in hypertension has been reported [(10, 11, 12)]. Dietary intake of Mg [(13)] has been reported to have favorable effects on blood pressure. Additionally, intake of these elements and calcium was cited to reduce blood pressure [(4)]. A relationship of Ca [(14)] and Mg intake [(5)] with BP levels in the young has been studied, with variable results. In one study, no clear association of Ca with BP level could be identified [(15)].

Measured total Ca in serum consists of ~15% bound to organic and inorganic anions, about 40% bound to albumin, and the remaining as biologically active ionized Ca. A variety of formulae have been proposed to permit calculation of the albumin-corrected total Ca or ionized Ca from the total Ca and protein concentration [(16, 17)]. Some reports recommend the use of albumin-corrected total Ca for routine clinical interpretation of Ca [(17)], and the use of ionized Ca is recommended when more exact

values are required. The sample collection and handling are crucial for an accurate measurement of ionized Ca [18].

Serum content of total Mg is found to be significantly reduced in hypertensive animals [19]. Experimental studies on Mg and blood pressure have showed that *in vivo* chronic marginal Mg deficiency either did not affect blood pressure or initially decreased and subsequently increased it [20]. While an inverse correlation between serum Mg and blood pressure is sometimes observed [21] but it is not the rule [21, 22]. Mg can ameliorate atherosclerosis and hypertension, and promote coronary vasodilation and unloading of the heart and increases its efficiency [19, 23]. It is becoming clear that a large body of epidemiologic data supports the idea that lower than normal dietary intake of Mg can be a strong risk factor for hypertension and different heart diseases. Deficits in serum Mg appear often to be associated with arrhythmias, coronary vasospasm and high blood pressure [24].

In the present study, an attempt is carried out to define which form of the metals, Ca and Mg, is correlated with hypertension by estimating different forms of serum calcium (total, ionized, and albumin-corrected calcium) and magnesium (total and ionized Mg) in addition to serum total protein and albumin in hypertensive patients and compare them with healthy control. The aim is obtaining a recommendation about the benefit of using Ca or Mg supplements as an adjuvant for the treatment of hypertensive patients by altering serum Ca (if present).

Subjects and Methods

Seventy-three uncomplicated, untreated, hypertensive, but otherwise have no other systemic diseases males, ranging in age from (26–55) years old, were entered into the study. Smokers were excluded from the study. Each hypertensive subject had a blood pressure measurement by conventional sphygmomanometry in excess of 95/140 mmHg (seated posture), with the arm in the horizontal position after five minutes of quiet sitting, and had never received any antihypertensive treatment. The study was performed under out-patient conditions. Control group consists of thirty healthy males with normal blood pressure and their age range is between (22-46) years old.

Five milliliters of venous blood samples were collected from cases without tourniquet. Sera were separated and measured immediately or, if necessary, stored at (-20° C) until analysis. Serum Ca and Mg were measured spectrophotometrically using ready for use kits purchased from Spinreact®-Spain and Human®-Germany, respectively. Serum albumin was estimated by ready for use Randox® kit according to bromocresolgreen method and serum total protein was estimated according to Biuret method using the procedures described by Randox® kits leaflets.

Serum ionized Ca levels were estimated with the following equation: [16, 25]:

Ionized Ca= ((6.25 * (total Ca) - ((total protein)* 3/8)) / ((total protein) + 6.5)

Albumin-corrected calcium was estimated with the following equation [26]:

Albumin-corrected calcium = total Ca + [0.02 * (41.3–albumin g/l)]

Serum Mg levels were calculated according to the following formula [27]:

Ionized Mg in mmol/L= (0.66 * (total Mg in mmol/L)) + 0.039

Results:

The results of all measured parameters in both groups expressed as mean±standard deviation are shown in Table (1). There is a significant decrease ($p<0.05$) in S.Total Ca, S.Ionized Ca, and albumin-corrected Ca in hypertensive group in comparing with control group. No significant change noticed in serum total and ionized magnesium, and in different ratios between the groups.

Discussion:

The decrease in serum Ca noticed in the present work is in accordance with other researches. Several experimental and clinical studies suggested that Ca depletion elevates blood pressure [28]. In one study, Hypertensive subjects had lower mean serum levels of ionized calcium [29]. The Ca metabolism altereation: high urine Ca excretion, low serum ionic Ca [30] may explain the indifference in serum albumin and decrease in serum Ca in hypertensive patients noticed in our research.

Also the results support the studies related to the treatment of hypertension by mineral supplements including Ca [31]. The reduction in sodium intake reduces Ca excretion [32] and vice versa [33], and hence decrease in B.P. The maintained natriuretic ability found in patients with higher salt sensitivity could be mediated not only by the degree of underlying volume expansion but also by a well known natriuretic effect of Ca (Ca^{+2}) through an increase in the renal tubular Ca^{2+} concentration [34].

The research observations may elucidate the mechanism(s) by which oral Ca supplementation decreases blood pressure in patients with salt-sensitive hypertension [35]. Significant inverse correlation of blood pressure with the increase intake of some metals including Ca and different other nutrients have been frequently recorded [36]. There is also some evidence that other diet nutrients, including potassium, Ca, and Mg are inversely related to BP levels [37], the BP level is higher in those with diets lower in potassium, Ca, Mg, and vitamins. Indeed, several studies suggest that the effect of Na intake on blood pressure is determined by the adequacy of other minerals, such as Ca [38], and Mg [39]. The pressor effect of NaCl seems to be expressed in subjects with the lowest intake of these minerals [38]. The natriuretic effect of Ca may be mediated either through increases in serum and/or renal tubular Ca concentration. The kidney plays a key role in the maintenance of mineral ion homeostasis, particularly that of Ca [40].

Urinary Ca (UCa) excretion depends on the filtered load of Ca and on several other factors, including PTH levels, sodium (Na) excretion, serum concentrations of Ca and Mg (Mg), Ca intake and absorption, and acid-base status [41]. Untreated hypertensive patients had a higher prevalence of hypercalciuria in patients with essential hypertension. It was concluded that hypercalciuria is a frequent finding of untreated essential hypertension[42]. The results of this research revealed additional evidence to the fact that the retention in Ca excretion and subsequent maintenance in serum Ca is good for hypertension.

The insignificant change in serum Mg in hypertensive patients is in accordance with some researches [21, 22]. However it is encountered by findings of some old papers which have noticed an inverse correlation between serum Mg and blood pressure [21]. Mg can ameliorate atherosclerosis and hypertension, and promote coronary vasodilation and unloading of the heart and increases its efficiency [19, 23]. When the perfusate Mg ion concentration is elevated to hypermagnesemic levels (2.4-4.8 m*M*), coronary flow, stroke volume, cardiac output and aortic pressure are seen to rise rather significantly, suggesting that Mg ions can exhibit inotropic-like effects. At the same time, the heart rate and rate-pressure product are decreased,

Elevated Mg resulted in spectral shifts, which suggest that alterations in myocardial intracellular, free Mg ions and intracellular pH must have occurred. Elevation in ionized Mg (i.e. 2.4-4.8 m*M*) clearly resulted in elevation of intracellular, free Mg ions and alkalinization of the cytosol. Elevation of the intracellular pH in the presence of elevation of intracellular, free Mg ions would increase the creatine kinase reaction, resulting in more phosphocreatine, contractile force and stroke volume, exactly as we have observed. It was clear from our data that elevation in extracellular Mg ions to 4.8 m*M* resulted in a 40% rise in phosphocreatine [23]. Ascherio and colleagues [6] found that blood pressure tended to be lower in people whose fruit and vegetable intake—and therefore Mg intake—was high. In the Honolulu Heart Study, the factor most strongly associated with blood pressure control, was high Mg intake.

In the Atherosclerosis Risk in Communities Study, involving more than 15,000 participants, dietary Mg intake was inversely associated with systolic and diastolic blood pressures [43].

A weak *positive* association was found between free Mg and mean blood pressure. This relationship was lost in a multivariate regression analysis[25]. Higher ionized Ca:Mg ratio in cells, in comparison with that in normal individuals, has been reported in atherosclerosis and essential hypertension [44] Usually, ionized Ca is increased or normal as ionized Mg is decreased.

Conclusion:

Hypertensive patients have significantly low level of all forms of serum Ca than control group. There is no significant difference between the two groups in serum albumin and total and ionized Mg. Ca supplements may be required as adjuvant treatment in addition to decrease NaCl in the diet to reduce excretion of Ca in urine.

Further studies required for other biochemical parameters in larger patients sample size.

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Table (1): Different Serum parameters in patients and control groups expressed as (Mean ± Standard deviation) in addition to the p-values of t-test of the comparison between the groups.

Parameter	Patients	Controls	P-Value
S.Total Ca (mmol/L)	2.01±0.20	2.21±0.23	0.0004*
S.Ionized Ca (mmol/L)	0.87±0.11	0.95±0.11	0.0019*
Albumine-Corrected Ca (mmol/L)	2.01±0.21	2.19±0.23	0.0317*
S.Total Mg (mmol/L)	0.88±0.21	0.91±0.20	0.4879
S.Ionized Mg (mmol/L)	0.57±0.12	0.58±0.12	0.5360
Ca/Mg	2.51±0.61	2.51±0.61	1.0234
Ionized Ca/Mg	1.63±0.54	1.70±0.46	0.5545
S.Albumine (g/L)	41.36±5.54	44.22±5.65	0.1782
T.S.Protein (g/L)	72.18±6.03	74.20±5.44	0.1014

(*): The difference is significant when p-value is less than 0.05.