The potential role of biotin as dietary risk marker for hypertension in black South African children — the THUSA BANA study

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Objective. To determine whether biotin intake might contribute to the aetiology of hypertension in black children.

Design. Cross-sectional study.

Setting. North West province, South Africa.

Subjects. Children between 10 and 15 years of age were recruited from each of 30 schools over a period of 2 years (2000 - 2001). These children comprised 321 boys and 373 girls from communities ranging from rural to urbanised. The hypertensive group included 40 boys and 79 girls with high-normal to hypertensive blood pressure. The normotensive group consisted of 281 boys and 294 girls.

Main outcome measures. Dietary intake, cardiovascular parameters.

Results. Biotin intake in all groups was below the adequate intake level of 20 µg/d. In the stepwise regression analysis biotin was significantly associated ($p \leq 0.05$) with systolic and diastolic blood pressure along with arterial compliance and stroke volume of the hypertensive group. No significant associations were indicated for the normotensive group.

Conclusions. This study is the first to show that biotin might be a possible risk marker for the aetiology of hypertension in black children. Since dietary habits are potentially modifiable, the manipulation of diet could have a significant impact not only on blood pressure levels, but also on rise in blood pressure with age. This means that there is a need for further research concerning the effect of biotin on adults.

Smoking, obesity, hypertension and physical inactivity have been identified as major risk factors for cardiovascular disease. However, recent scientific investigations have examined additional factors contributing to development of this disease.[1] Diet has been implicated as one of many factors influencing blood pressure (BP),[2] and hypertension is an important risk factor for cardiovascular disease and stroke.

Biotin is a water-soluble vitamin and its richest dietary sources include liver, kidneys, heart, pancreas, poultry, egg yolk and milk.[3] Most biotin in meats and cereals appears to be protein-bound. However, the absolute content of even the richest biotin sources is low when compared with the sources of most other water-soluble vitamins.[4] Biotin is also synthesised by the microflora in the colon. Free biotin is absorbed in the proximal small intestine by means of both facilitated and simple diffusion. Biotin can also be absorbed from the colon, which facilitates the utilisation of the vitamin produced by hind gut microflora.[5] Despite increasing interest in biotin nutriture, considerable basic information on biotin bioavailability and nutritional status remains unknown.[6]

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Both marginal and frank biotin deficiencies occur rarely.[1,4,6] The only well-documented cases have occurred in association with total or near-total intravenous feeding without biotin supplementation, chronic egg white feeding, or inborn errors of metabolism that lead to biotin wasting.[7] A single case that does not fit any of the three established associations is that of an infant fed a rice-based formula that was presumably very low in biotin.[8]

According to Mock,[9] however, reduced biotin status may be rare. Apart from the abovementioned cases, biotin deficiency can occur in patients receiving long-term therapy with certain anticonvulsants,[10,11] in children with severe protein energy malnutrition[12] and in a substantial proportion of pregnant women with otherwise normal pregnancies.[9,13]

Speculation that the human biotin requirement can be produced by gut microflora[14] contradicts a report describing an infant who developed biotin deficiency while consuming a biotin-free, elemental formula.[8]

Human biotin requirements in specific populations and at various ages remain uncertain and scientific knowledge is insufficient to provide estimated average requirements (EARs) and recommended dietary allowances (RDAs), in part because indicators of biotin status have not been validated.[4,9] Considerable basic information concerning biotin availability and nutritional status also remains unknown.[6] In cases such as this, adequate intakes (AIs) are provided.[15] Like RDAs, AIs are goals for the nutrient intake of individuals. The AI of biotin

ranges from 20 µg (in 9 - 13-year-olds) to 30 µg (in persons older than 19 years).[16]

In animals biotin functions as a mobile carboxyl carrier in four carboxylases: pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase. These roles link biotin to the metabolic roles of folic acid, pantothenic acid, and vitamin B_{12}.[5]

According to Ho and Cordain[1] there may be a substantial link between cereal grain intakes and cardiovascular diseases stemming from both biotin and essential fatty acid insufficiencies. The urgent need for further research concerning the potential role of biotin insufficiency as a cardiovascular risk factor serves as motivation for this study.

Hypertension is common in the black population of Africa.[17] Studies in South Africa have shown that 25% of adult Zulu speakers in Durban[18] and 20.7 - 22.8% of apparently healthy Tswana-speaking people in the North West were hypertensive.[19]

By using arterial compliance, pulse pressure and total peripheral resistance in addition to cardiovascular parameters such as systolic BP (SBP) and diastolic BP (DBP), a comprehensive study of the cardiovascular effects of biotin can be performed. Vascular compliance is defined as the change in volume of the artery per unit of pressure ($\Delta V/\Delta P$)[20] and can also be estimated easily from the simpler approach to stroke volume divided by pulse pressure.[21]

As arterial compliance decreases there is a rise in SBP and a fall in DBP.[22] This indicates pulse pressure amplifications. An increase in pulse pressure, caused by large artery stiffening, is an independent cardiovascular risk factor.[23]

Dietary factors related to cardiovascular health of black children may be particularly important in this regard because BP levels have been seen to track from childhood to adulthood,[24,25] which means that high BP levels in childhood may lead to hypertension in adulthood. It is also known that micronutrient deficiencies in particular are present in black children in South Africa.[26]

The THUSA BANA study (Transition and Health during Urbanisation in South Africa, Bana = children) was designed to assess the relationship between the level of urbanisation and the health status of children in the North West province of South Africa. The aim of this part of the study was to determine whether biotin might contribute to the aetiology of hypertension in black children.

Methods

Study design

Thirty schools were randomly selected from a list of schools in five regions in North West. These schools were visited during the weeks preceding the collection of data, in order to obtain permission from the relevant school principals as well as from the parents of the children. Children at the various schools were randomly selected from class lists. Data collection took place during normal school hours.

Subjects

Children between 10 and 15 years of age were recruited from each of the 30 schools over a period of 2 years (2000 - 2001). These children comprised 321 boys and 373 girls from communities ranging from rural to urbanised. The hypertensive group consisted of 40 boys and 79 girls with high-normal to hypertensive BP. Hypertension in children is defined as an average SBP or DBP greater than or equal to the 90th percentile for age and sex.[27] Height percentiles were also taken into consideration since body size is the most important determinant of BP in childhood and adolescence.[27] The normotensive group consisted of 281 male and 294 female subjects with BP lower than the 90th percentile for age and sex (Table I).

The Ethics Committee of the University of Potchefstroom approved the study, and all the parents of the subjects gave informed consent.

Data collection and measurements

The subjects were all introduced to the experimental setup, after which each individual was separately subjected to the following procedures.

Cardiovascular parameters

The subjects were connected to a Finapres (finger-arterial pressure) apparatus[28,29] and BP was recorded continuously. After a period of rest of at least 10 minutes, resting BP values were obtained. BP was regarded as resting when the SBP did not change by more than 10 mmHg during the last minute of this period, otherwise the resting period was extended. The resting BP was then recorded continuously for 1 minute. The data were stored on magnetic tape using a Kyowa RTP-50A four-channel data recorder and digitised for further analysis by means of the Fast Modelflo software program.[30] In this way the SBP and DBP, stroke volume (SV), pulse pressure (PP), total peripheral resistance (TPR) and arterial compliance (C) were obtained.

Dietary intake

Dietary intake data were collected by fieldworkers trained by registered dieticians. A 24-hour dietary recall was collected face-to-face and the data collection interview method and nutrient coding were the same for all recalls. Food models and photo books for portion-size estimates were used for the recalls. This type of dietary assessment is widely used in international epidemiological studies.[31-33] Macronutrients

Table I. Characteristics of subjects: age, cardiovascular parameters and dietary intakes

Variable	*N*	Normotensive*	*N*	Hypertensive†
Boys				
Age (years)	281	12.5 ± 1.7	40	12.4 ± 1.5
SBP (mmHg)	281	96 ± 12‡	40	120 ± 11‡
DBP (mmHg)	281	61 ± 8‡	40	81 ± 8‡
C (ml/mmHg)	263	1.09 ± 0.40	33	0.98 ± 0.31
PP (mmHg)	263	34.1 ± 7.5§	33	38.1 ± 11.3§
TPR (mmHg.s/ml)	263	2.1 ± 1.2§	33	2.8 ± 1.4§
SV (ml)	263	34.14 ± 13.3	33	33.2 ± 11.3
Biotin intake (µg/d)	281	16.1 ± 15.8	40	15.4 ± 12.0
Total protein (g/d)	281	62.8 ± 27.8	40	60.9 ± 25.9
Plant protein (g/d)	281	32.0 ± 17.4	40	29.8 ± 15.8
Girls				
Age (years)	294	12.6 ± 1.7	79	12.0 ± 1.9
SBP (mmHg)	294	96 ± 11‡	79	123 ± 9‡
DBP (mmHg)	294	63 ± 8‡	79	78 ± 8‡
C (ml/mmHg)	270	1.04 ± 0.36§	65	0.93 ± 0.38§
PP (mmHg)	270	36.5 ± 7.8‡	65	45.7 ± 9.1‡
TPR (mmHg.s/ml)	270	2.0 ± 0.8	65	2.2 ± 0.8
SV (ml)	270	34.2 ± 13.2	65	36.8 ± 14.5
Biotin intake (µg/d)	294	16.8 ± 16.3	79	15.9 ± 13.4
Total protein (g/d)	294	58.6 ± 23.4	79	59.2 ± 23.0
Plant protein (g/d)	294	29.1 ± 13.1	79	28.9 ± 13.3

*Normotensive defined by blood pressure lower than the 90th percentile. Adjusted for age, sex and height.
†Hypertensive defined by blood pressure in the upper 10th percentile. Adjusted for age, sex and height.
‡ $p \leq 0.05$
§ $p \leq 0.001$.

Values are mean ± standard deviations. *N* = number of subjects; SBP = systolic blood pressure; DBP = diastolic blood pressure; C = arterial compliance; PP = pulse pressure; TPR = total peripheral resistance; SV = stroke volume.

(protein, fat, and carbohydrate), fibre, minerals (such as calcium, magnesium, sodium, potassium, and phosphorus), vitamins (such as A, B_6, B_{12}, C, D, E, and biotin) and cholesterol were calculated in the appropriate units, using the FoodFinder computer program based on the South African food composition tables.[34]

Statistical analysis

All processed data were transferred to Excel and statistically analysed using the STATISTICA software computer package.[35] Owing to skewed distributions all dietary variables were logarithmically transformed. Multivariate analyses and forward stepwise regression analyses were used to assess the association between SBP, DBP, SV, PP and C as dependent variables and the following (log-transformed) independent variables: dietary macronutrients (total protein, plant protein, animal protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, total carbohydrates, added sugar, energy), dietary fibre, dietary cholesterol, dietary minerals (calcium, magnesium, potassium, sodium, zinc, iron, phosphorus, copper) and dietary vitamins (vitamin A, thiamine, riboflavin, nicotinic acid, biotin, pantothenic acid, vitamin B_6, folic acid, vitamin B_{12}, ascorbic acid, and vitamin E). Stepwise regression analyses were done to determine the most significant ($p \leq 0.05$) determinants of SBP, DBP, SV, TPR, PP and C in the four subject groups, namely normotensive boys, hypertensive boys, normotensive girls and hypertensive girls. Independent *t*-tests were used to determine if significant differences existed between the subject groups.

Results

The age, cardiovascular characteristics of participants at baseline and dietary intake values for biotin and total protein for the four subject groups are shown in Table I. As would be expected, the hypertensive and normotensive male groups showed significant differences between SBP ($p \leq 0.001$), DBP ($p \leq 0.001$), PP ($p \leq 0.05$) and TPR ($p \leq 0.5$). The hypertensive and normotensive female groups showed significant differences between SBP ($p \leq 0.001$), DBP ($p \leq 0.001$), C ($p \leq 0.05$) and PP ($p \leq 0.05$). Biotin intake and protein intake showed no significant differences between the groups. The biotin intake for all the groups was well below the AI level of 20 µg/d prescribed for children aged 9 - 13 years.[16] The protein intake,

however, was higher than the RDA values of 45 - 46 g/d for children aged 11 - 15 years.[36]

In the stepwise regression model (Table II), with SBP, DBP, SV, C, PP and TPR as the dependent variables and all the dietary factors used as independent variables, biotin (β = 0.44) together with folic acid (β = –0.35), magnesium (β = 0.43) and added sugar (β = –0.29) accounted for 27.5% of the variance in SBP (R^2 = 0.275) in hypertensive boys. Biotin (β = 0.79) together with pantothenic acid (β = –0.53), added sugar (β = –0.24), zinc (β = 0.40) and energy (β = –0.27) explained 28.9% of the variance in DBP in hypertensive boys. Biotin (β = 0.31) with vitamin E (β = –0.18), nicotinic acid (β = 0.30), carbohydrates (β = –0.46), calcium (β = 0.33) and manganese (β = –0.21) accounted for 34.4% of the variance in C of hypertensive boys and biotin was the only independent variable that showed a significant ($p \leq 0.05$) relationship with C. In hypertensive girls biotin (β = 0.24) together with vitamin A (β = –0.28), energy (β = 0.44), iron (β = –0.58) and folic acid (β = 0.30) accounted for 22.3% of the variance in DBP.

No significant dietary markers were indicated for either of the normotensive groups.

Discussion

The effects of a combination of dietary factors on BP have recently been recognised as important. This subject requires urgent attention.[32] To determine the effects of biotin on the cardiovascular parameters, it was necessary to include all the other dietary factors for the regression analysis to be valid, since the impact of an individual nutrient on BP is modified by the intake of other nutrients.[33]

The dataset on the biotin content of foods in the South African Food Composition Tables is not complete.[34] However, the values of all of the richest sources of biotin are included and the food sources with absent values were those not normally ingested by children in these parts of South Africa, for example goats milk, cheese, roast duck, venison, rye bread and some ready-to-eat breakfast cereals. There were, however, also missing data for some chicken dishes and soup powder. In these cases other food codes were used. A total of 89 children (12.8%) ate chicken dishes, which may have caused an underestimation of the children's biotin intake by 3 µg/100 g intake. Only 4 children (0.005%) ate the soup powder dishes which might have caused an underestimation of their biotin intake of 0.01 µg/100 g.

Because reduced blood concentrations of biotin have been observed in children with severe protein energy malnutrition,[12] it was necessary to determine the protein intake of the subjects. According to the results in Table I none of the groups showed inadequate protein intake, but deficient biotin intakes were observed in all the groups. In our subjects about half the total protein intake was from plant sources (Table I), which may lack essential amino acids.[26]

Biotin showed strong positive associations with SBP, DBP, SV and C, especially in the hypertensive male group, but no significant differences were indicated between the biotin intakes of the normotensive and hypertensive groups. This might be explained by a genetic predisposition in the hypertensive group, but since information on the determinants of biotin remains unknown,[6] the origin for the positive relationships in hypertensives is unclear.

The positive association of biotin with both C and SV is reflected in the equation: C = SV/PP.[21] Biotin was the only dietary factor positively associated with arterial compliance and it seems that biotin intake could possibly play a preventive role in the aetiology of hypertension in black children.

Low biotin intakes were observed in both the normotensive and hypertensive groups, but biotin only showed a strong relationship with cardiovascular parameters in the hypertensive group. A suboptimal biotin status might accelerate or initiate the development of hypertension in a person who is predisposed to be hypertensive. The physiological meaning of the positive relationship between BP and biotin intake may be explained by the following mechanism.

Table II. Stepwise regression of SBP, DBP, SV, C, PP and TPR as dependent variables with all dietary factors as independent variables, but only biotin results are indicated. Regression coefficients beta (β) and level of significance, *p*, are shown

	SBP	DBP	SV	C	PP	TPR
Boys						
Normotensive	NS	NS	NS	NS	NS	NS
Hypertensive	β = 0.44, p = 0.003	β = 0.79, p = 0.001	β = 0.30 p = 0.04	β = 0.31 p = 0.004	NS	NS
Girls						
Normotensive	NS	NS	NS	NS	NS	NS
Hypertensive	NS	β = 0.24, p = 0.02	NS	NS	NS	NS

NS = indicates not significant ($p > 0.05$). Biotin intake is regarded as a significant marker when $p \leq 0.05$.
SBP = systolic blood pressure; DBP = diastolic blood pressure; SV = stroke volume; C = arterial compliance; PP = pulse pressure; TPR = total peripheral resistance.

A specific threshold for biotin intake is proposed and could cause an inversion of the cardiovascular effect of biotin. This means that insufficient intake of biotin could cause an increase in cardiovascular risk for hypertension. Owing to the coenzymatic activity of biotin in the holocarboxylase complexes, insufficient amounts of exogenous biotin could affect elongation and desaturation of essential fatty acids, contributing to endothelial cell dysfunction.[1] A gradual increase in biotin intake could therefore result in a higher risk until a threshold value is reached. From this point, which could also be a sufficient biotin intake, the cardiovascular risk could be lowered.

Conclusion

This study is the first to show that biotin might be regarded as a possible risk marker for the aetiology of hypertension in black children. Despite the inadequate biotin intakes of the children in this study, results indicated a positive association between biotin intake and cardiovascular parameters for hypertensive black children. Diets, however, are made up of multiple nutrients, and one needs to take into account combinations of nutrients to estimate the effects of dietary patterns. Since dietary habits are potentially modifiable, the manipulation of diet could have a significant impact not only on BP levels, but also on the rise in BP with age. This means that there is a need for further research concerning the effect of biotin on adults.

A diet rich in fruits, vegetables, and non-fat dietary foods, and low in saturated fat and total fat is proposed. Such a diet will have a biotin content of about 25 - 30 µg per day. According to the DASH (Dietary Approaches to Stop Hypertension) study such a diet will decrease SBP and it would be effective in the prevention and control of high BP.[37]

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PLEASE ANSWER ALL THE QUESTIONS

(There is only **ONE** correct answer per question)

1. This study is the first to show that _____ might be regarded as a possible risk marker for the development of hypertension in black children.
   [a] biotin
   [b] biotin and proteins
   [c] proteins

2. There may be a substantial link between cereal grain intakes and cardiovascular disease stemming from dietary inadequacies of both biotin and _____ .
   [a] essential amino acid
   [b] essential fatty acid
   [c] carbohydrate

3. The majority of biotin in meats and cereals appears to be:
   [a] carbohydrate bound
   [b] fat bound
   [c] protein bound

4. Biotin is also synthesised by the:
   [a] microflora in the colon
   [b] enzymes in the small intestine
   [c] microflora in the small intestine

5. Dietary factors related to cardiovascular health of black children may be particularly important because blood pressure levels have been seen to track from childhood to adulthood.
   [a] True
   [b] False

6. The subjects of the study consisted of black children between the ages of:
   [a] 5 and 10 years.
   [b] 10 and 15 years.
   [c] 15 and 18 years.

7. _____ is the most important determinant of blood pressure in childhood and adolescence.
   [a] Age
   [b] Diet
   [c] Body size

8. Biotin intake of hypertensive children differed significantly from normotensive children.
   [a] True
   [b] False

9. In the stepwise regression model, biotin, together with folic acid, magnesium and added sugar accounted for 27.5% of the variance in systolic blood pressure of normotensive males.
   [a] True
   [b] False

10. The following dietary markers were significantly associated with cardiovascular parameters for the normotensive groups:
    [a] biotin
    [b] biotin, magnesium, folic acid and added sugar
    [c] biotin, pantothenic acid, added sugar, zinc and energy
    [d] none of the above

11. Neither the male nor female hypertensive groups showed any differences from the male or female normotensive groups regarding biotin intake.
    [a] True
    [b] False

12. Biotin and protein intake were the only dietary factors that were positively associated with arterial compliance.
    [a] True
    [b] False

✂ Cut along the dotted lines and send to: SASPEN Secretariat, SAJCN CPD activity **No 24,** c/o Department of Human Nutrition, PO Box 19063, Tygerberg, 7505 to ***reach the office not later than 5 March 2004***

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(e.g. if the answer to question 1 is a: 1) a ■ b)

1) [a] [b] [c] 2) [a] [b] [c] 3) [a] [b] [c] 4) [a] [b] [c]
5) [a] [b] 6) [a] [b] [c] 7) [a] [b] [c] 8) [a] [b]
9) [a] [b] 10) [a] [b] [c] [d] 11) [a] [b] 12) [a] [b]