Raised serum albumin in hip osteoarthritis: a comparative study in women of some blood chemical parameters in aging and in cases of femoral neck fractures, osteoporotic vertebral crush fractures and hip osteoarthritis

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SUMMARY Twelve blood parameters were studied in five groups of women totalling 126 subjects—group I: 26 blood donors (average age 45.2 years, range 23–66); group II: 18 patients with various cerebral, cardiovascular, or infectious illnesses (average age 79.9 years, range 66–92); group III: 28 patients with femoral neck fractures (average age 79.4 years, range 56–95); group IV: 12 patients with hip osteoarthritis (average age 71.7 years, range 60–87); group V: 36 patients with vertebral crush fractures associated with postmenopausal and involutional osteoporosis (average age 63.0 years, range 51–75). The parameters measured were total proteins, albumin, total, α_1 , α_2 , β , and γ globulins, total calcium, phosphates, alkaline phosphatase, bilirubin, and haemoglobin. Statistical analysis showed that each group differed from the others even with adjustment for age. Among the discriminant parameters, serum albumin had a distinctive position. Significantly high concentrations of serum albumin in the group with osteoarthritis raise the question of the possible existence of a population prone to osteoarthritis in whom the serum albumin level may reflect a special nutritional state associated with the well known bone density in subjects with hip osteoarthritis. Albumin values in patients with femoral neck fractures are lower than normal but non-significantly. The difference between the group with vertebral crush fractures and that with femoral neck fractures seems to be due to age.

Key words: bone aging, osteoporosis.

In previous studies we noted that serum albumin concentration decreased in the course of aging and was low in patients suffering from femoral neck fractures, whereas it was significantly higher in patients with hip osteoarthritis.^{1,2} This change in serum albumin concentration was more predominant than the change in other parameters. The purpose of the present study was to confirm these data in an exclusively female population and to compare them with results obtained in osteoporotic women with vertebral crush fractures.

Patients and methods

One hundred and twenty women (age range 23–98 years) living in or near Geneva, Switzerland were studied. They were divided into five groups as follows: group I: 26 blood donors (age range 23–66 years); group II: 18 patients admitted to hospital for recent acute pulmonary or urinary infection, cardiac insufficiency, cerebral infarction, or dementia (age range 66–92 years); group III: 28 patients with recent femoral neck fractures (16 subcapital and 12 trochanteric) that had occurred one to three days before the blood sampling (age range 56–95 years); group IV: 12 patients with severe hip osteoarthritis.

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Table 1 Age of subjects and blood data for the five groups

	Group I (n=26)			Group II (n=18)			Group III (n=28)			Group IV (n=12)			Group V (n=36)			Statistical significance†	Adjusted for age
																Not adjusted for age	
	$\bar{x}$	SEM		$\bar{x}$	SEM		$\bar{x}$	SEM		$\bar{x}$	SEM		$\bar{x}$	SEM			
Age	45.2	2.2		79.9	1.5		79.4	1.5		71.7	2.8		63.0	1.1		‡	
Total proteins (g/l)	66.6	1.2		64.9	1.1		66.4	1.0		70.8	2.0		66.4	1.1		*I-IV, III-IV, IV-V/**I-IV	*I-IV, II-IV, IV-V
Albumin (g/l)	39.7	0.8		35.6	1.2		34.8	0.7		41.1	0.9		37.7	0.9		**III-V, IV-V/**I-II/**I-III, II-IV, III-IV	*IV-V/**I-IV/**III-IV
Total globulins (g/l)	26.9	0.6		29.4	1.3		31.6	0.7		29.8	1.3		28.1	0.6		*I-II, I-IV/**I-II, III-V	*I-II/V/**III-V
α_1 Globulins (g/l)	2.4	0.1		3.0	0.3		3.5	0.1		2.6	0.2		2.3	0.1		**I-II, II-V, III-IV/**I-III, III-V	*I-II/**I-III, II-V, III-IV/**III-V
α_2 Globulins (g/l)	6.1	0.2		8.5	0.7		8.5	0.3		7.7	0.3		7.5	0.2		*II-V, III-V/**I-IV/**I-II, I-III, I-V	*I-IV, III-V/**I-II, I-III, I-V
β Globulins (g/l)	8.4	0.2		8.5	0.3		8.8	0.2		9.3	0.5		8.5	0.3		*III-V	**III-V
γ Globulins (g/l)	10.1	0.4		10.0	0.6		10.9	0.5		10.2	0.8		9.5	0.4			
Total calcium (mmol/l)	2.34	0.02		2.39	0.03		2.35	0.02		2.49	0.03		2.28	0.02		*I-V, II-IV, III-V/**I-IV, II-V, III-IV, IV-V	*I-IV, I-V, II-IV, II-V/**III-IV, IV-V
Phosphates (mmol/l)	1.16	0.05		1.06	0.04		0.98	0.04		1.10	0.04		1.06	0.03		**I-III	
Alkaline phosphatase (U/l)	32.0	2.9		43.7	4.5		55.6	9.2		46.5	3.7		45.1	3.7		**I-III	
Total bilirubin (μ mol/l)	6.4	0.4		10.2	0.8		13.4	0.9		9.6	0.7		8.0	0.6		*I-IV, II-V/**I-II, III-IV/**I-II, I-III, III-V	*I-II, I-IV, II-V/**I-III, III-IV/ ***I-III, III-V
Haemoglobin (g/l)	141	1.0		131	3.0		129	3.0		135	3.0		129	2.0		**I-II/**I-III, I-V	*I-II/V/**I-V

†p Values associated with the tests of the differences between the group means are indicated for blood data only when ≤ 0.05 and according to the following abbreviations: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.
‡p Values for age differences are NS for II-III, ≤ 0.05 for III-IV, and ≤ 0.001 for the other groups.

requiring total hip replacement (age range 60–87 years); and group V: 36 patients with vertebral crush fractures associated with postmenopausal and involutional osteoporosis (data obtained before fluorine-calcium-vitamin D treatment in a study by Courvoisier *et al*³) (age range 51–75 years).

The five groups were subjected to the same exclusion criteria as those used in preceding studies, i.e., active tuberculosis, malignant tumour, hepatic insufficiency (blood bilirubin $>25 \mu\text{mol/l}$) or renal insufficiency (blood creatinine $>150 \mu\text{mol/l}$), gastrectomy, obvious endocrine disorder, dysproteinæmia, treatment with diphenylhydantoin, calcium, or vitamin D. The blood samples were taken in the morning before breakfast and before surgery for groups III and IV.

The 12 parameters chosen for the study were measured for all subjects: total serum protein concentrations by the biuret method (coefficient of interassay variation (CV)=3.3%), serum albumin and globulins by cellulose acetate electrophoresis (Beckman's microsome system) (CV=6.1%, 18.2%, 11.6%, 11.8%, 8.7% for albumin, α_1 , α_2 , β , and γ globulins respectively), total plasma calcium concentrations by spectrophotometric atomic absorption (CV=2.1%), plasma phosphates and alkaline phosphatase by colorimetry (CV=5.5% and 3.2%—isophosphatases not determined), serum bilirubin by the dichloroaniline method (CV=3.5%), and haemoglobin concentration by spectrophotometry (CV=0.8%). The calcium values given are for total calcium not adjusted for serum albumin.

STATISTICAL ANALYSIS

Statistical evaluation was made by the three following procedures: (a) The differences between the group means were tested pairwise for significance by Student's *t* test (i.e., without adjustment for age) and by covariance analysis (i.e., with adjustment made to exclude the possible effect of age, thus allowing any significant difference to be attributed to a pathological cause). The non-parametric versions of these two procedures were also used (Mann-Whitney test and covariance analysis of ranked data). (b) Canonical analysis (a multivariate procedure) was made on the 12 variables for a global study of the five groups, without and with adjustment for age. It was also used for the subset of variables which jointly had the largest discriminant power, as determined by stepwise discriminant analysis. As canonical analysis showed the effect of age to be negligible, stepwise analysis was not made on data adjusted for age. (c) For each variable the five regression lines (with age as independent variable) were calculated in order to visualise the data.

Results

Table 1 presents the values obtained for the 12 variables studied for each of the five groups. It also indicates the results of the pairwise group mean comparisons with the parametric tests (without and with adjustment for age). The *p* values of the non-parametric tests are not given as they were very

Fig. 1 Regression lines for albumin in groups I to V corresponding respectively to the values 0.35, 0.07, 0.21, 0.57, 0.02 for correlation coefficients; 0.12, 0.05, 0.11, 0.19, 0.01 for regression coefficients; 0.08, 0.78, 0.28, 0.05, 0.93 for slope *p* values. Significant slope *p* values (≤ 0.05) are indicated; they correspond both to an acceptable dispersion of the individual data and to a slope different from zero.

similar to those of the parametric tests. The main significant results obtained with adjustment for age of the data were as follows: Albumin in the group with osteoarthritis (IV) was higher than in the three other groups with pathology (and very significantly higher than in groups II and III). The calcium variations were similar. The concentration of α_2 globulin in groups II to V was greater than that in blood donors. The concentration of bilirubin was significantly lower in blood donors than in all other groups except group V, while in patients with femoral neck fractures (group III) it was higher than in all other groups.

Canonical analysis on the 12 variables showed that, except for groups II and III ($p=0.079$) and groups II and IV ($p=0.064$), the groups were very significantly different from one another ($p<0.001$). The only change observed after adjustment for age was the reduction of the p values when compared with groups II and IV ($p=0.041$). Stepwise discriminant analysis selected, without adjustment for age, the following six variables (in the order of selection): bilirubin, calcium, α_2 globulins, albumin, haemoglobin, and α_1 globulins; with this subset of variables the shortest intergroup distance was still between groups II and III ($p<0.05$).

The various regression lines disclosed different types of patterns. Fig. 1 indicates those for albumin. It is most interesting that for the values of total proteins, albumin, phosphates, and alkaline phosphatases groups I and II could be pooled to give a single regression line.

When the groups I+II composite line was compared with the relevant lines of groups III and IV only group IV proteins ($p=0.0054$) and albumin ($p=0.0062$) were significantly different. An investigation made for albumin showed that it was possible also to pool only the lines II and III, I and V.

Discussion

METHODOLOGY

The selection criteria used for our clinical classification of five groups assured a relative homogeneity, which allowed for a comparison of blood values. As the pairwise comparison of groups II, III, IV, and V showed significant differences in age, except between groups II and III, covariance analysis was required to eliminate the effect of age.

The interassay coefficients of variation showed that reproducibility of results obtained by the methods used was within the range usually reported. It should also be noted that for measurements of albumin and globulins a good correlation of results was obtained by electrophoresis and by immunodiffusion.⁴

PLACE OF ALBUMIN AMONG THE OTHER PARAMETERS

Canonical analysis showed that there were significant global differences between the five groups related to the pathological context as they persisted after adjustment for age. These differences, particularly those for groups II to V, can be explained by recent conjunctural factors (i.e., metabolic and haemodynamic consequences of the femoral neck fracture, bone remodelling and synovial reaction in hip osteoarthritis) as well as by the previous nutritional state. The nutritional state can be correlated with serum albumin, which is known to be 'a good indicator of protein status and regarded as the keystone of body building'⁵ as well as the vector of various substances in blood transport.

As in an unpublished study, that included both men and women, albumin was found to be not only among the most discriminant variables in canonical analysis but also among those that showed many significant differences between the group means and regression lines. The pattern of calcium values was understandably similar to that obtained for albumin as those values were not adjusted.

The possible pooling of the group I regression line (which reflects normal gerontological evolution) and the group II regression line (which corresponds to various old patients without obvious skeletal pathology) is of interest only with albumin for the following reasons: the total proteins correspond to a larger entity; phosphates and alkaline phosphatase are difficult to interpret, particularly as neither a study of the isophosphatases nor an x ray of the entire skeleton were available. Results for the other variables, including those for haemoglobin, were not of basic interest.

The present study confirms, in an exclusively female population, the observations in previous studies of significantly high serum albumin concentrations in patients with hip osteoarthritis. No correlation could be found between albumin concentration and radiological criteria⁶ of either atrophic or hypertrophic hip osteoarthritis. A high albumin concentration was also found in four cases of knee osteoarthritis, but further studies would be needed to determine whether the observations made in hip osteoarthritis studies apply to other types of osteoarthritis.

Serum albumin concentrations also showed a tendency to decrease with age and to be lower in patients with femoral neck fractures than in other old patients and in patients with vertebral crush fractures; however, as with a male and female population, this was non-significant. In addition, a 'heterogeneity of fracture syndrome'⁷ cannot be assumed in the present study as the difference

between the groups with vertebral crush fractures and femoral neck fractures seemed mainly related to the younger patients in the former group.

CONCEPTUAL IMPLICATIONS

These blood chemical data, considered in the light of certain previously reported findings, lead to hypotheses which could be of interest both from a conceptual and a practical point of view.

It is possible that the high serum albumin concentrations in patients with hip osteoarthritis indicate a particular nutritional state already observed in adults (and perhaps earlier) and attenuated in old age. This state may be reflected by the morphotype⁸ and by the rarity of femoral neck fractures in patients with osteoarthritis^{9, 10}; in fact the women of group IV (like those of group I) suffered no fractures of the femoral neck during the five years after blood sampling, while in the same period such fractures occurred in six of group II and five of group III.

This observation, together with reports of high bone density in patients with osteoarthritis,¹⁰⁻¹³ suggests a particularly high bone mineralisation in such patients; this may predispose to fatigue of the overlying cartilage.¹⁴

The results of the present study suggest the possibility of a population prone to osteoarthritis in whom the serum albumin concentration may be correlated with bone quality. It is well known that bone mineralisation is related to non-collagenous proteins of bone matrix and that albumin coming from plasma is one of these proteins.¹⁵⁻²² In addition, albumin reduces the phagocytic recognition of bone mineral by macrophages.²³

By contrast, the low albumin concentration in aged people and lower concentration in patients with femoral neck fractures (even though in both cases the values were non-significant) suggests the possibility of the opposite nutritional condition in such subjects. It seems of interest, therefore, to investigate whether a systematic and controlled improvement of protein intake would have a favourable effect on skeletal mineralisation and thus decrease the incidence of certain fractures, particularly those of the femoral neck.

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