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THE PLASMA CONCENTRATION OF ALKALINE PHOSPHATASE, PHOSPHORUS AND CALCIUM FOLLOWING FEMORAL NECK FRACTURE

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The presence of alkaline phosphatase in healing bone has been experimentally demonstrated by Bourne (1948), Pritchard & Ruzicka (1950), Mäjno & Rouiler (1951) and Raekallio & Mäkinen (1969). Buring & Semb (1970) and Firschein & Urist (1971) found that alkaline phosphatase was also induced in extra-skeletal bone implants.

Struck et al. (1969) found that the serum alkaline phosphatase activity after fracture initially decreased, but later on significantly increased over the base level. In experimental fractures in rats Semb et al. (1971) demonstrated a significantly increased serum alkaline phosphatase within four hours after fracture.

In man, even minor fractures may cause the serum alkaline phosphatase level to increase for months (Hunsberger & Ferguson 1932, Klein 1966).

Except for fractures, conditions such as Paget's disease, osteomalacia and cancer metastasis may raise the serum alkaline phosphatase level.

The object of the present study was to describe the changes in the alkaline phosphatase level in relation to time after fracture. As a model was chosen the cervical fracture of the upper end of the femur, which is a fairly uniform injury with regard to the amount of bone tissue involved.

MATERIAL AND METHODS

Altogether 63 individuals, 19 men and 44 women, with cervical fracture of the upper end of the femur were included in the study. The age ranged from 24 to 91 years (62 ± 11 *).

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* Standard deviation.

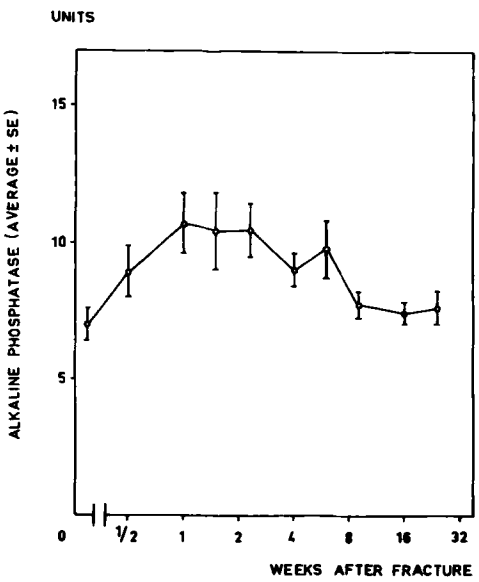

Figure 1. The relationship of plasma alkaline phosphatase activity and time elapsed after femoral neck fracture.

Alkaline phosphatase was estimated by a modified Busch & Busch method, using 2-amino-2-methyl-1-propanol buffer, para-nitrophenyl-pnosphate as substrate and magnesium as activator with an optimal pH of 10.8. With this method the normal variation in adults is 2–8 units**.

The plasma phosphorus was measured by the method of Hurst (1964) and expressed in mg/100 cc. The normal variation in the laboratory is 2.4–4.7 mg/100 cc**.

The plasma calcium level was measured by flame photometry (Eppendorf) and expressed in m. equivalents/l with a normal variation of 4.5–5.5 m. equivalents/l**.

All patients had their hip fracture pinned within the first few days after admission and were mobilized and started on walking within a day or two after the operation. None of the patients included in the study had Paget's disease or cancer metastasis of the skeleton.

In 10 of the patients the data were obtained at regular intervals as a prospective study. In the remainder the data were collected at more irregular intervals. At the time of discharge the data collection was usually discontinued and, later on, occasional values were obtained in conjunction with visits to the out-patient department. As the prospective and the cross-sectional data did not disagree, they have been pooled and presented together in the following.

RESULTS

The alkaline phosphatase increased significantly, reached a plateau level after one week, and returned after two months to the initial mean value (Figure 1). Values of 12 units or more were observed in 14

** 95 per cent confidence limits.

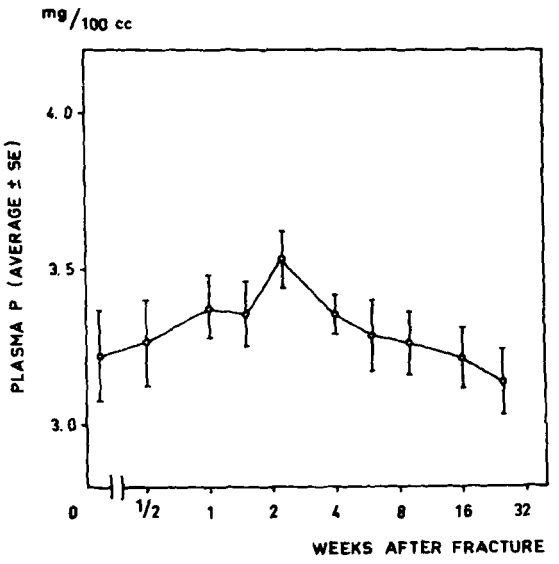

Figure 2. The relationship of plasma phosphorus activity and time elapsed after femoral neck fracture.

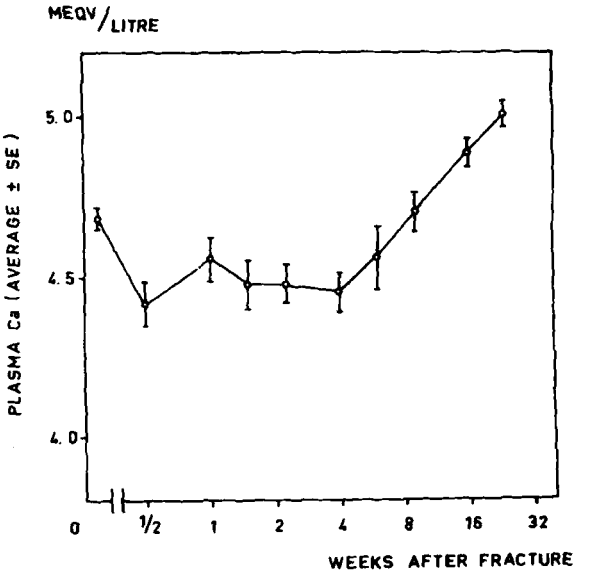

Figure 3. The relationship of plasma calcium activity and time elapsed after femoral neck fracture.

patients. The highest value, 30 units, was observed in a 47-year-old man.

The plasma phosphorus increased slowly, reached a peak level after 2–3 weeks, and then slowly returned to initial value (Figure 2).

The plasma calcium decreased significantly and remained low for a month and then increased to normal level or over at the end of the observation period (Figure 3).

DISCUSSION

Alkaline Phosphatase

Semb et al. (1971) demonstrated how the alkaline phosphatase activity in healing fractures in rats increased during the first two weeks of the healing process. The serum level of alkaline phosphatase started to increase already within 2 hours after the fracture. The same authors demonstrated that this phosphatase did not originate from liver or intestine and claimed that the increase of the serum level probably reflected an early cell proliferation in the healing fracture. In dogs as well, experimental fractures have been demonstrated to increase the serum content of alkaline phosphatase, but not until after one week (Struck et al. 1969).

Hunsberger & Ferguson (1932) found, in seven patients with fractures of various types, an increase in the phosphatase activity, which occurred within the first week and remained for months. Klein (1966) studied 15 patients with one or more fractures of varying types. The average serum alkaline phosphatase activity increased three to four times with a maximum value between two and four weeks after the injury. Howard et al. (1945), on the other hand, found in fracture patients an unaltered phosphatase concentration during the course of the fracture healing; only in occasional patients were the values increased.

In the present study, which only includes femoral neck fractures, the findings largely agreed with the above investigations. However, the values were on average only doubled as compared to the base level. Only individual cases deviated from that pattern. The base values, obtained at the time of admission and after eight weeks, are close to the upper limit of the normal range (2–8 units). However, most of these patients belong to an age group were the alkaline phosphatase level is usually somewhat elevated above that of a non-selected population (Hobson & Jordan 1959).

In clinical work it should be kept in mind that cervical fracture of the upper end of the femur *per se* will cause a rapid and lasting increase of the alkaline phosphatase activity to a level about the double of normal.

Plasma Phosphorus and Calcium

With regard to the changes in plasma phosphorus, the findings in the present study are in good agreement with earlier studies. Tisdall & Harris (1922) pointed out that the plasma phosphorus decreased in man after the cessation of growth, but that after fracture the value increased for some weeks and approached the level of a growing individual. Eddy & Heft (1923) also found increased phosphorus levels after surgery other than bone surgery. Speed (1931) described increased blood phosphorus as a constant finding in fracture patients. The same has been found after experimental fractures in dogs (Struck et al. 1969).

With regard to plasma calcium, the literature is less unanimous. Petersen (1924) thought that the plasma calcium level might decrease after fracture and prevent healing. Speed (1931) found no changes in plasma calcium in fracture patients. Howard et al. (1945) found that the plasma calcium frequently increased somewhat after fracture. In experimental fractures in dogs, however, Struck et al. (1969) found a significant decrease in the blood calcium after fracture.

Table 1. Plasma calcium and protein in 50 fracture cases as compared to 50 controls (Average ± SD).

	Fracture	Control
Plasma Ca meqv/litre	4.50 ± 0.10	4.82 ± 0.23
Plasma Prot g/100 cc	6.53 ± 0.57	6.99 ± 0.57

In the present study a significantly decreased serum calcium was demonstrated for a considerable time after the fracture. In fact, the serum calcium was somewhat below the normal average already at the time of admission and did not approach normal before 4 months. In this group of patients a low plasma protein may be expected to result from the trauma (Table 1). In order to study the interaction between plasma protein, plasma calcium and fracture, 50 values of plasma calcium were drawn from the data obtained between one-half and four weeks after admission and correlated to the plasma protein values obtained on the same occasion. There was a highly significant positive correlation. Similarily, there was a significant positive correlation in 50 orthopedic patients with an age distribution matched to that of the fracture patients who had been admitted for reasons other

than fracture. In an analysis of covariance, the decrease of plasma calcium was found to be greater than could be accounted for by the drop in serum protein alone. The disagreement between the present and previous studies may be due to the selection of cases, for the elderly patients are more likely to respond to even moderate trauma with a negative protein balance. In addition, there is an unexplained small change in plasma calcium which may be related to the changes in bone mineral metabolism responsible for this type of fracture.

SUMMARY AND CONCLUSIONS

In a mixed prospective and cross-sectional study the plasma alkaline phosphatase activity, plasma phosphorus, and plasma calcium were measured in 63 patients with cervical fractures of the upper end of the femur. The alkaline phosphatase activity was rapidly doubled and remained high for about two months before it returned to the initial level. The plasma phosphorus increased after fracture and later returned to normal. The plasma calcium level dropped and remained significantly decreased for about two months. The decrease was greater than could be accounted for by the changes in plasma protein.

REFERENCES

Bourne, G. H. (1948) Alkaline phosphatase and vitamin C deficiency in regeneration of skull bones. *J. Anat. (Lond.)* **82**, 81–87.

Buring, K. Semb, H. (1970) Enzyme patterns during bone induction. *Calcif. Tiss. Res.* **4** (Suppl), 102–104.

Eddy, W. H. & Heft, H. L. (1923) The relation of fracture healing to the inorganic phosphorus of the blood serum. *J. biol. Chem.* **55**, 12–13.

Firschein, H. E. & Urist, M. R. (1971) The induction of alkaline phosphatase by extraskeletal implants of bone matrix. *Calcif. Tiss. Res.* **7**, 108–113.

Hobson, W. & Jordan, A. (1959) A study of serum alkaline phosphatase levels in old people living at home. *J. Geront.* **14**, 292–293.

Howard, J. E., Parson, W. & Bigham, Jr., R. S. (1945) Studies on patients convalescent from fracture. III. The urinary excretion of calcium and phosphorus. *Johns Hopk. Hosp. Bull.* **77**, 291–313.

Hunsberger, A. Jr. & Ferguson, L. K. (1932) Variations in phosphatase and inorganic phosphorus in serum during fracture repair. *Arch. Surg.* **24**, 1052–1060.

Hurst, R. A. (1964) The determination of nucleoitide phosphorous with stannous cloridehydrazine sulfat reagent. *Canad. J. Biochem.* **42**, 287–292.

Klein, L. (1966) The relationship between urinary hydroxyproline, calcium and serum alkaline phosphatase during fracture healing and acute disuse osteoporosis. *Exerpta Med.*, International Congress, Series No 120.

Mäjno, G. & Rouiller, C. (1951) Die alkalische Phosphatase in der Biologic des knochengewebes. *Virchows Arch. path. Anat.* **321**, 1–61.

Petersen, H. A. (1924) Study of ununited fractures. *J. Bone Jt Surg.* **22**, 885–899.

Pritchard, J. J. & Ruzicka, A. J. (1950) Comparison of fracture repair in the frog, lizard and rat. *J. Anat. (Lond.)* **84**, 236–261.

Raekallio, J. & Mäkinen, P.-L. (1969) Alkaline and acid phosphatase activity in the initial phase of fracture healing. *Acta path. microbiol. scand.* **75**, 415–422.

Semb, T. H., Gudmundson, C. R., Westlin, N. E. & Hallander, L. B. (1971) Alkaline phosphatase activity and isoenzymes in experimental fractures. *Clin. chim. Acta* **31**, 375–380.

Speed, K. (1931) Blood serum calcium in relation to the healing of fractures. *J. Bone Jt Surg.* **13**, 58–67.

Struck, H., Dabew, D., Hernandez-Richter, H. J. & Benfer, J. (1969) Klinischchemische Befunde im Serum bei experimenteller Fraktursetzung und verschiedener Behandlung. *Enzym. biol. clin.* **10**, 463.

Tisdall, F. F. & Harris, R. I. (1922) Calcium and phosphorus metabolism in patients with fractures. *J. Amer. med. Ass.* **79**, 84–87.

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