CIRCULATING VITAMIN K LEVELS IN PATIENTS WITH FRACTURES

LUCILLE BITENSKY, J. P. HART, A. CATTERALL, S. J. HODGES, M. J. PILKINGTON, J. CHAYEN

From the Mathilda and Terence Kennedy Institute of Rheumatology and Charing Cross Hospital, London

It is now clear that vitamin K₁ is part of a biochemical cycle that is essential for the conversion of specific bone peptides into a form that can bind calcium. We have used a recently described procedure for assaying vitamin K₁ in plasma to test the involvement of this vitamin in fracture healing. Markedly depressed circulating levels were found in patients with fractures and the time taken for this level to return to normal appeared to be influenced by the severity of the fracture.

Metabolic effects governing the healing of fractures have not been readily definable, but a possible line of enquiry came from the relatively recent discovery (Hauschka, Lian and Gallop 1978) that vitamin K₁, formerly regarded as playing a role solely in blood clotting, also had a major role in bone formation. The biochemical mechanism in both functions was similar: glutamic acid residues (Glu) are converted to γ-carboxyglutamic acid (Gla). The double carboxy-group can then chelate calcium; vitamin K₁ acts as a hydrogen-donor in this mechanism. It is therefore relevant to assess the vitamin K₁ levels in patients with fractures.

However, until recently, this has not been readily possible. Interest therefore concentrated on circulating levels of a small peptide, called either osteocalcin (Hauschka et al. 1978) or bone Gla-protein (Price 1985), which is synthesised in bone and which has a cluster of three Glu residues, fairly close together; these can be converted into the active Gla form. This peptide could be assayed by radioimmunoassay. However, such assays do not distinguish between fully, partially or non-carboxylated osteocalcin (Triffitt 1987). Moreover it is known that osteocalcin is not the only bone peptide that can contain Gla (Price and Williamson 1985); it is only the most readily extractable. It therefore seemed preferable to study the circulating levels of vitamin K₁ directly, by means of recently developed chromatographic procedures with electrochemical detection (Hart et al. 1985).

MATERIALS AND METHODS

Plasma samples were obtained from 16 patients admitted for treatment of traumatic fractures. There were 14 males and two females with an age range of 15 to 72 years. Thirteen were sampled within 10 days, and the others within 20 days of sustaining the fracture. The site of fracture was the ankle in six cases, metatarsals in two, with one case each involving bilateral tibia and fibula, humerus, humerus and pelvis, midshaft femur, femur and forearm, pelvis and hip dislocation, lumbar spine and calcaneum.

Sequential samples were taken up to 80 days after the fracture in 10 of these patients. Samples were also taken from 15 normal subjects (11 males, 4 females; age range 23 to 59 years). In two of these normal subjects, six sequential samples were taken over a period of 50 days. The plasma was extracted, separated by high performance liquid chromatography and the vitamin K₁ measured by means of an electrochemical detector (Hart, Shearer and McCarthy 1985).

RESULTS

Vitamin K₁ levels
Variation in normal individuals. Six samples were taken from two normal men aged 40 and 21 years at near weekly intervals. In the older subject, the mean value was 214 pg/ml, with a range of 145 to 295 pg/ml; in the younger, the mean value was 359 pg/ml, with a range of 245 to 620 pg/ml.

Normal subjects. The mean level in a single sample from 12 of the 15 normal subjects was 385 pg/ml (range 80 to 680 pg/ml); in the other three the values were 1 110, 1 240 and 1 360 pg/ml.
Patients after fracture. In all the samples taken shortly after fracture, including those taken up to 20 days after injury, the mean circulating level was 113 pg/ml (range 16 to 305 pg/ml). This value was significantly different from that found in the normal subjects (Mann Whitney U test: p<0.01; Fig. 1).

Samples of blood were obtained from some of the fracture patients during the course of healing. Those with relatively small fractures (three ankle fractures and one of the humerus) showed a fairly quick return to normal circulating levels of vitamin K₁ (Fig. 2a). In two patients with relatively major fractures, the circulating level of this vitamin did not return to normal levels until about 300 days after injury (Fig. 2b).

In two others, one with a fracture of the femur and the other with a fractured lumbar spine, the K₁ levels did not return to normal values over the period at which sampling was possible (30 and 40 days). In one patient with a fractured calcaneum, the vitamin K₁ level remained remarkably stable at around 150 pg/ml for over 300 days.

DISCUSSION

Our results indicate that the circulating level of vitamin K₁ is depressed shortly after a fracture. This is in keeping with the concept that this vitamin, and the vitamin K₁ cycle generally, is required for the Glu to Gla transformation of special bone-peptides, so that this vitamin becomes sequestered from the circulation for use at the fracture site. This view gains some support from the finding that the rate at which normal circulating levels are restored may be related to the severity of the fracture or the size of the callus and thus to the amount of new bone that has to be formed.

It is recognised that other factors must be involved, including those that ensure the supply of reducing equivalents that this vitamin would carry in the process of bone formation, as shown by Dodds et al. (1986) in an experimental system. However, it may be worthwhile assessing the circulating level of vitamin K₁ in patients with delayed union of fractures.

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REFERENCES


