

Intestinal handling of iron and calcium in idiopathic haemochromatosis: new data and therapeutic perspectives

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Summary. The fractional intestinal absorption of iron (FAFe), i.e. p. 100 of the total dose (p. 100 TD), was measured in 13 patients with idiopathic haemochromatosis in two situations : in basal conditions (after fasting), and following an oral indigestible fiber load with either pectin (group I, 8 cases) or cellulose (group II, 5 cases). The results obtained were compared to those found in 7 controls investigated in basal conditions. Calcium homeostasis was evaluated in 9 haemochromatotic patients (group III) and in 10 controls using the following parameters : (i) fractional intestinal absorption of calcium (FA Ca, p. 100 TD) ; (ii) bone mineral content (BMC, mg/cm²) ; (iii) plasma 25-OH vitamin D content (25-OH-D, ng/ml). *Results.* The basal FA Fe significantly increased in haemochromatotic patients as compared with the control subjects. In group I, pectin produced a significant decline in FA Fe (25.5 ± 5.0 vs 47.6 ± 9.2 in basal conditions : $P < 0.02$). On the contrary, cellulose has no significant effect on FA Fe. In group III, FA Ca ($P < 0.02$), BMC ($P < 0.05$) and 25-OH-D ($P < 0.01$) significantly dropped as compared with the controls. The present results suggested that fiber-supplemented diets might be useful in the management of haemochromatosis. Furthermore, the osteopenia of haemochromatosis seemed to be due to a deficiency in 25-OH cholecalciferol production. Therefore, a supplement of the latter might be useful in preventing bone mass rarefaction.

Introduction.

Idiopathic haemochromatosis is usually characterized by high rates of intestinal iron absorption. On the other hand, the absorption of such divalent ions as calcium or magnesium is diminished by oral indigestible fiber intake (Heaton and Pomare, 1974 ; Reinhold *et al.*, 1976). In this report, we have studied the effects of pectin and cellulose on iron absorption in haemochromatotic patients. Calcium homeostasis in these patients

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is discussed in the second part of the report in an attempt to clarify the mechanism and treatment of osteoporosis, frequently encountered in the course of idiopathic haemochromatosis (Delbarre, 1960).

Material and methods.

The effects of indigestible fibers on iron absorption were studied in 13 patients suffering from idiopathic haemochromatosis. Iron absorption measured in basal conditions, i. e. after overnight fasting, was compared with absorption after an oral intake (9 g/m^2 of body surface) of either pectin (group I, 8 cases) or microcrystalline cellulose (group II, 5 cases). The results were compared to those of 7 controls who were studied in basal conditions. Intestinal iron absorption was determined by a double radiotracer technique (Cook and Lipschitz, 1977). Each subject was simultaneously given $5 \mu\text{Ci}$ of transferrin-bound radioactive ferric iron (^{55}Fe , Saclay, France) by intravenous route, and $10 \mu\text{Ci}$ of $^{59}\text{FeCl}_2$ (Saclay, France) orally with 1 mg of non-radioactive iron such as ferrous chloride. By applying the mathematical procedure of inverse convolution (Shipley and Clark, 1972) to the appearance/disappearance curves of plasma ^{59}Fe and ^{55}Fe activities, we obtained the time curve of oral iron transit from the gut lumen to the plasma. Four main parameters were computed from this curve : (a) the fraction of oral radioiron absorbed at completion of the absorptive process, i. e. fractional absorption (FAFe) expressed as a percentage of the total oral dose (p. 100 TD), (b) peak absorption rate (p. 100 TD/min), (c) time of peak absorption rate (min), (d) mean transit time across the intestinal barrier.

Calcium homeostasis was evaluated in 9 diabetic patients with idiopathic haemochromatosis using the following criteria : (i) intestinal calcium absorption, measured by a double radiotracer technique (i. v. $^{45}\text{CaCl}_2$ and oral $^{47}\text{CaCl}_2$) similar to that used for iron absorption measurement (Birge *et al.*, 1969 ; Monnier *et al.*, 1978) : the 4 main parameters were obtained for fractional absorption of calcium (FA Ca), expressed as a percentage of the total oral dose (p. 100 TD) ; (ii) bone mineral content (BMC, mg/cm^2), determined on the forearm by Cameron's absorptiometric technique (Cameron and Sorenson, 1963) ; (iii) plasma 25 hydroxyvitamin D level (25-OH-D, ng/ml), measured by a radiocompetitive binding radioassay (Preece *et al.*, 1974). The results were compared to those found in 10 controls and 8 diabetics without haemochromatosis.

Results.

Effects of indigestible fibers on iron absorption.

Group I : Effect of pectin. As indicated on table 1, patients with haemochromatosis had a significantly higher basal FAFE than the controls. Although this basal parameter still remained higher than normal after pectin intake, the pectin induced a significant drop of FAFE in the haemochromatotic patients.

Group II. Effect of cellulose. In the 5 patients of group II investigated for cellulose effects, FAFE and the other parameters of iron absorption remained unchanged after

cellulose intake (table 1). As in group I the haemochromatotic patients were characterized by a significant increase in basal FAFe.

TABLE 1

Comparison of parameters of intestinal iron absorption in different groups of haemochromatotic patients and in control subjects.

	Patients with haemochromatosis (group I)		Control Subjects	Patients with haemochromatosis (group II)	
	before a pectin load	after a pectin load		before a cellulose load	after a cellulose load
No. tested	8	8	7	5	5
Fractional absorption of iron (p. 100 total dose)	47.6 ± 9.2	25.5 ± 5.0	7.0 ± 2.3	32.3 ± 8.6	30.7 ± 6.7
Peak absorption rate (p. 100 total dose/min)	1.22 ± 0.37	0.56 ± 0.10	0.14 ± 0.04	0.59 ± 0.19	0.58 ± 0.14
Time of peak absorption rate (min)	30.0 ± 8.5	28.1 ± 5.6	24.6 ± 4.8	34.5 ± 5.6	34.5 ± 7.3
Mean transit time (min)	40.7 ± 8.3	38.2 ± 5.5	35.3 ± 4.3	54.0 ± 9.6	52.5 ± 8.2

All results are given as mean \pm SEM. Statistical differences are only indicated when significant. (*) $P < 0.05$, (**) $P < 0.02$, (***) $P < 0.01$, (****) $P < 0.001$

Calcium homeostasis. — Intestinal calcium absorption, estimated from fractional absorption and peak absorption rates, decreased in patients with haemochromatosis as compared to diabetic subjects without haemochromatosis and the controls. As shown on table 2, statistical differences were particularly marked when the fractional absorption values and peak absorption rates of patients and controls were compared. *Bone mineral content* was significantly lower in patients with haemochromatosis than in controls, while no difference was found between controls and diabetic patients without haemochromatosis (table 2). *Plasma 25-OH-D levels* significantly diminished in subjects suffering from haemochromatosis as compared with controls and diabetics without haemochromatosis (table 2).

Discussion.

Effects of indigestible pectin and cellulose on iron absorption.

The present results show that pectin produced a significant drop, and thus exerted a beneficial effect on the intestinal absorption of iron. Cellulose, on the other hand, did

TABLE 2

Comparison of intestinal calcium absorption, bone mineral content and plasma 25 hydroxyvitamin D in the various groups of patients and in control subjects.

	Control Subjects	Diabetic patients	
		With haemochromatosis (group I)	Without haemochromatosis (group II)
<i>Parameters of intestinal calcium absorption</i>			
(No. tested)	(10)	(9)	(8)
Fractional absorption of Ca (p. 100 total dose)	64.0	51.9	64.2
	± 2.7	± 3.8	± 6.5
Peak absorption rate (p. 100 total dose/min)	1.2	0.61	0.73
	± 0.14	± 0.06	± 0.12
Time of peak absorption rate (min)	33.0	49.2	28.1
	± 7.2	± 10.8	± 6.3
Mean transit time (min)	59.4	73.8	74.9
	± 12.2	± 8.1	± 12.4
<i>Plasma 25 hydroxyvitamin D</i>			
(ng/ml)	16.4	5.3	14.3
	± 1.3	± 0.6	± 3.5
(No. tested)	(10)	(7)	(5)
<i>Bone mineral content</i>			
(mg/cm ²)	879	784	890
	± 26	± 45	± 26
(No. tested)	(10)	(8)	(6)

All results are given as mean ± SEM. Statistical differences are only indicated when significant. * P < 0.05 ; ** P < 0.02 ; *** P < 0.01.

not appear to have any effect on iron transfer across the intestine. The differences observed between the effects of pectin and those of cellulose might be explained by the mechanism of action of these substances, which cause the formation of unabsorbable complexes with intraluminal ferrous iron (Bjorn-Rasmussen, 1974 ; Reinhold *et al.*, 1975 ; Ismail Beiji, Faradji and Reinhold, 1977). As previously demonstrated, cellulose possesses a smaller binding capacity for divalent ions than pectin (Ismail Beiji, Faradji and Reinhold, 1977). It is therefore reasonable to suppose that pectin, rather than cellulose, would decrease iron absorption by inhibiting iron uptake by the duodenal cells.

Calcium homeostasis.

Intestinal calcium absorption, bone mineral mass and plasma 25-OH-D levels significantly diminished in diabetic patients suffering from haemochromatosis as compared with control subjects and diabetic patients without haemochromatosis. Furthermore, intestinal calcium absorption, bone mass and plasma 25-OH-D levels

were similar in the controls and in diabetics without haemochromatosis. According to the present results, it seemed unlikely that alterations of calcium homeostasis, as observed in haemochromatic patients, were due only to the diabetic state. On the contrary, our data indicate that the impairment of calcium balance is probably explained by metabolic abnormalities directly related to the iron storage disorder. The significant drop in plasma 25-OH-D noted in our haemochromatic patients, seemed to suggest that haemochromatosis is characterized by a reduction of hepatic 25-hydroxycholecalciferol production (Blunt, De Luca and Schnoes, 1968 ; De Luca, 1974). This metabolic abnormality would lead to decreased intestinal calcium absorption (Wills, 1973) and, in turn, to bone mass rarefaction.

Conclusion.

The use of pectin-supplemented diets may be a useful adjunct to repeated phlebotomy which is the standard therapy in haemochromatosis. However, this supplementation may worsen (Heaton and Pomare, 1974) calcium absorption, which is already low in idiopathic haemochromatosis. For this reason, and because our results provide evidence for 25-OH vitamin D deficiency, we recommend 25-hydroxycholecalciferol supplementation in the treatment of haemochromatic patients. Furthermore, plasma 25-OH-D levels should be individually and periodically checked to ensure that the treatment is both effective and has no side effects due to overdosage.

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Résumé. L'absorption fractionnelle du fer (AFFe), p. 100 de dose totale (p. 100 DT), est mesurée chez 13 malades ayant une hémochromatose idiopathique, dans deux conditions : (a) à l'état de base, c'est-à-dire à jeun et (b) après une charge orale en fibres indigestibles sous forme de pectine (groupe I : 8 cas) ou de cellulose (groupe II : 5 cas). Les résultats obtenus sont comparés à ceux trouvés chez 7 témoins explorés à l'état de base. Chez 9 hémochromatosiques (groupe III) et chez 10 témoins, l'homéostasie calcique est évaluée grâce aux paramètres suivant : (a) l'absorption fractionnelle du calcium (AFCa, p. 100 DT) (b) le contenu minéral de l'os (CMO, mg/cm²) ; (c) la 25 OH vitamine D (25-OH-D, ng/ml). *Résultats* : l'AFFe de base est significativement augmentée chez les hémochromatosiques par rapport aux témoins. Dans le groupe I, la pectine provoque une chute significative de l'AFFe : $25,5 \pm 5,0$ contre $47,6 \pm 9,2$ à l'état de base ($P < 0,02$). Au contraire la cellulose n'a aucun effet sur l'AFFe. Dans le groupe III, on note une baisse significative de l'AFCa ($P < 0,02$), du CMO ($P < 0,05$) et de la 25-OH-D ($P < 0,01$) par rapport aux témoins. Nos résultats suggèrent que les régimes enrichis en fibres pourraient être utiles dans le traitement de l'hémochromatose. De plus, l'ostéopénie des hémochromatoses semble due à un défaut de production du 25-OH cholécalférol. De ce fait, une supplémentation en 25-OH cholécalférol peut avoir de l'intérêt pour prévenir la raréfaction osseuse.

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