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BRIEF REPORT

Hypertrophic osteoarthropathy: estrogens, prostaglandin E_2, prostaglandin A_2, and the inflammatory reflex

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Abstract

It has been claimed that hyperestrogenism occurs in hypertrophic osteoarthropathy (HOA), but not in simple clubbing. However, one of our patients had simple clubbing and hyperestrogenism. We therefore measured estrogens, androgens, sex hormone-binding globulin (SHBG), and gonadotropins in five patients with HOA and in 18 patients with simple clubbing. Of the patients with HOA, 80% had a high urinary estriol concentration. In their serum, 80% had high estrone, 0% high estradiol, and 40% high SHBG. Of the patients with simple clubbing, 89% had a high urinary estriol concentration. In their serum, 76% had high estrone, 6% high estradiol, and 31% high SHBG. In all patients, urinary estriol concentration correlated positively with the degree of clubbing. Serum concentration of androstenedione, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) was mostly normal, but androstenedione concentration correlated positively with the degree of clubbing. Spider angiomas were present in 74%, palmar erythema in 39%, and gynecomastia in 9%. Urinary creatinine concentration was low in 48% and correlated positively with the degree of clubbing. We reject the claim that hyperestrogenism occurs in HOA, but not in simple clubbing. Hyperestrogenism occurs both in HOA and in simple clubbing. Our results also support earlier reports that clubbing and HOA are associated with spider angiomas, palmar erythema, gynecomastia, adrenal cortical hyperfunction, muscle atrophy, and water retention. These results led to a new hypothesis on the pathogenesis of HOA, involving estrogens, prostaglandin E_2, prostaglandin A_2, and the inflammatory reflex.

Keywords Estrogen · Hypertrophic osteoarthropathy · Inflammatory reflex · Palmar erythema · Postaglandin · Spider angiomas

Introduction

Hypertrophic osteoarthropathy (HOA) is a relatively rare syndrome, characterized by digital clubbing, subperiosteal new bone formation, and polyarthritis, the latter resembling rheumatoid arthritis. The affected periosteum and joints may be tender but also very painful. Other symptoms of HOA include a less severe clinical presentation in women; thickening of the facial skin with deep nasolabial folds, furrowing of the forehead, and seborrhea; excessive sweating of hands and feet; delayed closure of cranial sutures; patent ductus arteriosus; hypertrophic gastropathy; myelofibrosis; spider angiomas; palmar erythema; muscle atrophy; water retention; adrenal cortical hyperfunction; signs of endothelial activation or damage; acro-osteolysis and hyperestrogenism; female distribution of pubic hair; gynecomastia; and elevated excretion of estrogens in the urine. In the majority of patients, HOA is caused by a malignant disease (e.g., lung cancer) or a nonmalignant one (e.g., cyanotic heart disease or cirrhosis). In the minority of patients, HOA is familial or primary. The latter form of HOA is also known as pachydermoperiostosis.

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Almost since the first description of the syndrome, it was noted that digital clubbing and subperiosteal new bone formation do not always develop simultaneously. In fact, digital clubbing often occurs without any physical sign of subperiosteal new bone formation, a condition called "simple clubbing." Conversely, subperiosteal new bone formation rarely occurs without clubbing. In some conditions, such as congenital heart disease, subacute bacterial endocarditis, interstitial pulmonary fibrosis, and chronic hypoxia clubbing is common, but subperiosteal new bone formation is rare. Another remarkable observation is that ipsilateral vagotomy causes complete disappearance of all symptoms of HOA in patients with lung cancer, but without influencing the degree of clubbing [1]. It was therefore suggested that digital clubbing and subperiosteal new bone formation are two different diseases, each with a different pathogenesis [1]. This hypothesis was strongly supported by the observation that urinary estrogens were raised in patients with subperiosteal new bone formation, but not in patients with simple clubbing [2].

However, one of our patients had simple clubbing and gynecomastia. He excreted an elevated amount of estriol in the urine (patient 7, see below). In addition, elevated concentration of serum estradiol was found in patients with digital clubbing [3]. These contradictory observations prompted us to re-evaluate the relationship between digital clubbing and hyperestrogenism.

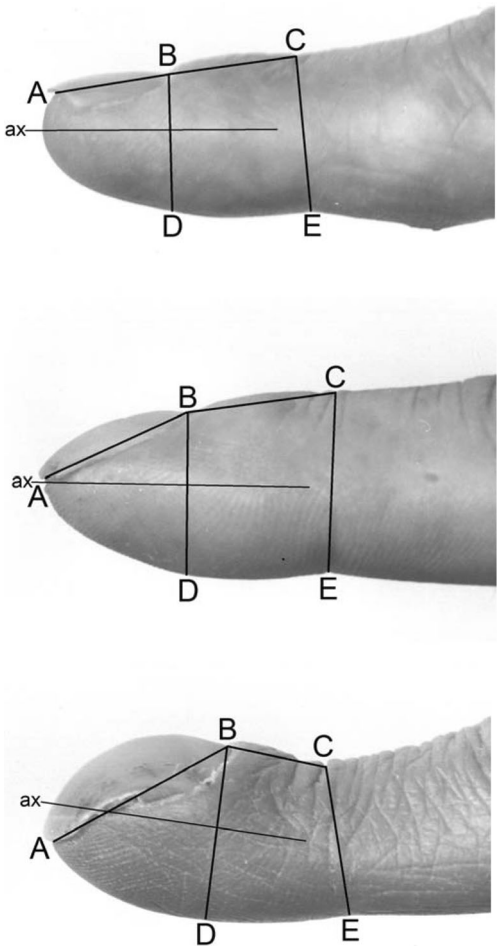

Fig. 1 Normal finger (top, HNA and PDR normal), watch glass nail (middle, HNA increased but PDR normal), clubbed finger (bottom, HNA and PDR increased). A, hyponychium; B, cuticle; C, distal digital crease; ABC, hyponychial angle (HNA). D, point located by dropping a line from B perpendicular to the long axis (ax) of the distal segment of the finger; E, interphalangeal skin fold; BD, distal phalangeal finger depth; CE, interphalangeal finger depth; BD/CE, phalangeal depth ratio (PDR) [4, 5]. Waring et al. located point C by erecting a line from E perpendicular to the long axis of the middle segment of the finger [5]. For simplicity, we used the distal digital crease as point C

Materials and methods

Measurement of finger clubbing

Presence and degree of clubbing were determined by measuring hyponychial angle (HNA) and phalangeal depth ratio (PDR) on a photograph of the lateral side of the right index finger (Fig. 1) [4, 5]. Based on the results of Kitis et al. we considered a finger as clubbed if the HNA was greater than 186° [4]. Patients with a PDR greater than 1.00 are also considered to have finger clubbing [5].

Clinical chemistry

Estriol in urine, as well as estrone, androstenedione, and sex hormone-binding globulin (SHBG) in serum were determined by an external laboratory, BCO Medical Services (Breda, the Netherlands). Estradiol, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were determined in the Gelderse Vallei Hospital (Ede, the Netherlands). Urine samples were collected from 8:00 a.m. until next day 8:00 a.m. and transported to the laboratory in plastic containers containing 1 g/50 ml boric acid. Blood and urine samples were transported and stored at 4 °C and analyzed within 7 days. Urinary estriol was determined by fluorescent polarization immunoassay using the Abbott TDx instrument (Abbott Diagnostic Division, Hoofddorp, the Netherlands) after separation of estrogens from urinary chromogens using octadecyl columns [6]. Intra- and inter-assay coefficients of variation were 2 and 3.1%, respectively. Serum estrone was determined manually by radioimmunoassay (Bühlmann Laboratories AG, Schönenbuch, Switzerland). Serum estradiol, androstenedione, and testosterone were determined manually using the Siemens "Coat-A-Count" direct radioimmunoassay (Siemens Health Care, den Haag, the Netherlands). Serum SHBG was determined manually using the Spectria Immuno Radiometric Assay (Orion Diagnostica Oy, Espoo, Finland). Intra- and inter-assay coefficients of variation for estrone, estradiol, androstenedione, and SHBG were 11% or lower and 15% or lower, respectively. For

testosterone, intra- and inter-assay coefficients of variation were 4.5 and 7.7%, respectively. Serum LH and FSH were determined manually using the Amerlite luminescence-enhanced enzyme immunoassay (GE Healthcare, Eindhoven, the Netherlands). Intra- and inter-assay coefficients of variation were 6.9 and 9.0% for LH, and 6.0 and 7.5% for FSH, respectively. Interpretation of results was based on reference values provided by the laboratory that performed the testing.

Statistical analysis

Spearman's rank two-tailed correlation test (IBM SPSS Statistics, release 19.0.0 (Armonk, New York, USA)) was used. Spearman's rank correlation coefficient was denoted as ρ, and its significance (2-tailed) as p. A significance level of 0.05 was considered significant, a significance level of 0.01 very significant.

Results

Definition of finger clubbing

All patients had finger clubbing based on the HNA. However, five patients had a normal PDR (Table 1). We classified these patients as having an early form of clubbing. The HNA may be a more sensitive criterion, but the PDR may be a more specific criterion for the presence and degree of finger clubbing.

Estrogens

Twenty-three male patients with finger clubbing were studied (Tables 1 and 2). Of the five patients with HOA, urinary estriol concentration and urinary estriol/creatinine ratio were high in four; serum estrone concentration was high in four and SHBG was high in two patients. Of the 18 patients with simple clubbing, urinary estriol concentration was high in 16 and urinary estriol/creatinine ratio was high in 17 patients; serum estrone concentration was high in 13 (one missing value), estradiol was high in one, and SHBG was high in five patients (two missing values). Of all patients, each had at least one sign of hyperestrogenism, with the exception of patient 1. It made no difference whether clubbing was primary, familial, or secondary. Urinary estriol concentration of all patients correlated positively with HNA ($\rho = 0.527$, $p = 0.010$) and with PDR ($\rho = 0.419$, $p = 0.047$), but estriol/creatinine ratio did not (HNA $\rho = 0.358$, $p = 0.094$; PDR $\rho = 0.192$, $p = 0.381$). The latter may have been due to the fact that the urinary creatinine concentration of all patients also correlated positively with HNA ($\rho = 0.503$, $p = 0.014$) and PDR ($\rho = 0.593$, $p = 0.003$). Although serum estradiol concentration was mostly normal in most of our patients, serum estradiol concentration correlated positively with PDR ($\rho = 0.461$, $p = 0.027$), but not with HNA ($\rho = 0.259$, $p = 0.233$).

Androgens

Of all patients, serum androstenedione concentration was normal in 20 and low in two. Testosterone was normal in 21 and low in two patients. LH was normal in 20 and high in one patient; FSH was normal in 18, high in two, and low in one patient. Only androstenedione concentration correlated positively with HNA ($\rho = 0.487$, $p = 0.022$) and PDR ($\rho = 0.618$, $p = 0.002$).

HOA versus simple clubbing

Patients with HOA did not always have more marked clubbing and did not always excrete more estriol in the urine than patients with simple clubbing (Table 2). Note that the patient with the highest degree of clubbing, patient 23, had no signs of periostitis, neither physically nor radiologically (Table 1).

Spider angiomas, palmar erythema, and gynecomastia

Of the five patients with HOA, three had spider angiomas, two had palmar erythema and one had gynecomastia. Of the 18 patients with simple clubbing, 14 had spider angiomas, seven had palmar erythema and one had gynecomastia (Table 2). In total, 74% of our patients had spider angiomas, 39% had palmar erythema, and two patients had gynecomastia.

Creatinine in the urine

Of all 23 patients, 11 had a low urinary creatinine concentration. All these 11 patients had simple clubbing, whereas all patients with HOA had a normal concentration of creatinine in the urine.

Incidental observations

Patient 3 had primary hypogonadism (LH high, testosterone normal). Patients 9 and 12 both had primary and secondary hypogonadism (testosterone low, LH inappropriately normal). Patients 3 and 14 may have had damaged seminiferous tubules (FSH high) (Table 2).

Discussion

Clubbing and hyperestrogenism

Our main finding is that hyperestrogenism not only occurs in patients with the full syndrome of HOA, but also in patients with simple clubbing. We therefore reject the claim that

Table 1 Patient characteristics

Patient number	Age (years)	HNA (degree)	PDR	Ossifying periostitis	Types of clubbing	Pain medication (mg/day)	Clinical diagnosis
1	44	**188**	0.91	–	SC	0	Dubious primary clubbing
2	73	**189**	0.89	–	SC	0	Dubious primary clubbing
3	79	**194**	0.94	–	SC	0	Esophageal cancer
4	63	**194**	0.96	–	SC	0	Primary clubbing
5	23	**196**	**1.04**	–	SC	0	Cyanotic heart disease
6	49	**197**	**1.03**	–	SC	0	Primary clubbing
7	49	**197**	**1.06**	–	SC	0	Cyanotic heart disease
8	64	**198**	**1.02**	–	SC	0	Chronic bronchitis
9	65	**198**	**1.07**	1	HOA	Naproxen 1000 Morphine 40	Bronchial carcinoma
10	41	**199**	**1.07**	1	HOA	Naproxen 500	Familial HOA
11	70	**202**	0.95	–	SC	0	Chronic bronchitis
12	78	**202**	**1.06**	–	SC	0	Bronchiectases
13	48	**203**	**1.13**	–	SC	0	Familial clubbing
14	59	**205**	**1.05**	–	SC	0	Primary clubbing
15	38	**205**	**1.10**	0	SC	0	Familial clubbing
16	60	**205**	**1.14**	1	HOA	Ibuprofen 800	Bronchial carcinoma
17	72	**206**	**1.10**	1	HOA	Diclofenac 100	Bronchial carcinoma
18	33	**206**	**1.13**	–	SC	0	Primary clubbing
19	32	**207**	**1.11**	–	SC	0	Familial clubbing
20	35	**211**	**1.09**	1	HOA	Acetaminophen 500	Alcoholic liver disease
21	55	**212**	**1.03**	–	SC	0	Familial clubbing
22	62	**212**	**1.07**	–	SC	0	Primary clubbing
23	37	**216**	**1.18**	0	SC	0	Primary clubbing
Normal range		<187	<1.01				

Values are in ascending order according to HNA. Numbers in column 5 refer to the presence, 1, or absence, 0, of periostitis on bone scan or radiographs. Bold values represent increase. Bars represent missing values. All patients are male

HNA, hyponychial angle; *PDR*, phalangeal depth ratio; *SC*, simple clubbing; *HOA*, hypertrophic osteoarthropathy

hyperestrogenism occurs in hypertrophic osteoarthropathy (HOA), but not in simple clubbing [2]. Most of our patients, whether they had the full syndrome of HOA or simple clubbing, had a raised urinary estriol concentration and a raised urinary estriol/creatinine ratio. Urine estriol concentration even correlated positively with degree of clubbing. However, this might also be caused by increased concentration of the urine proportional to degree of clubbing, because urinary creatinine concentration also correlated positively with degree of clubbing (see below). In the serum, most of our patients had a raised serum estrone concentration, and one third of them had a raised serum SHBG concentration, all signs of estrogen excess. In contrast with an earlier report [3], serum estradiol concentration was normal in most of our patients. However, serum estradiol concentration correlated positively with PDR, not with HNA. Of the two patients with gynecomastia, one had simple clubbing (patient 7), and the other had HOA (patient 10). The hyperestrogenism of HOA appears to be caused by increased production of estrogens, because conjugation and inactivation of estrogens were not impaired in HOA [2]. Why our results differ from those of an earlier study [2] is not clear. It is possible that relatively small elevations in urinary estrogen concentration were more difficult to detect in 1961, when that study was carried out, than they are now. Our observation that digital clubbing is associated with hyperestrogenism lead to a new hypothesis, which may explain the pathogenesis of clubbing and other symptoms of HOA, and which may provide new opportunities for the treatment of the syndrome.

HOA and PGE_2

It is now generally accepted that digital clubbing and the other symptoms of HOA can be caused by prostaglandin E_2 (PGE_2)

Table 2 Results

Patient characteristics					Urine					
Patient number	Group	HNA	PDR	Gynecomastia	Spider angiomas	Palmar erythema	Estriol (nmol/day)	Creatinine (mmol/day)	Estriol (nmol/mmol creatinine)	Estrone (nmol/l)
1	SC	**188**	0.91	0	0	0	41	*12*	3	*0.00*
2	SC	**189**	0.89	0	0	0	**74**	*9*	**8**	–
3	SC	**194**	0.94	0	1	1	**102**	*9*	**12**	0.18
4	SC	**194**	0.96	0	1	1	**91**	14	**6**	**0.32**
5	SC	**196**	**1.04**	0	0	1	**72**	*8*	**9**	*0.00*
6	SC	**197**	**1.03**	0	1	0	**101**	*10*	**11**	**0.37**
7	SC	**197**	**1.06**	1	1	1	43	*9*	**5**	**0.62**
8	SC	**198**	**1.02**	0	1	0	**168**	13	**13**	**0.35**
9	HOA	**198**	**1.07**	0	1	1	29	14	2	**0.47**
10	HOA	**199**	**1.07**	1	1	0	**221**	15	**15**	**0.38**
11	SC	**202**	0.95	0	1	0	**180**	*10*	**18**	**0.39**
12	SC	**202**	**1.06**	0	1	1	**96**	*8*	**13**	**0.29**
13	SC	**203**	**1.13**	0	1	0	**315**	16	**20**	**0.29**
14	SC	**205**	**1.05**	0	1	0	**179**	*9*	**20**	**0.35**
15	SC	**205**	**1.10**	0	1	1	**79**	15	**5**	**0.24**
16	HOA	**205**	**1.14**	0	0	1	**189**	15	**13**	**0.32**
17	HOA	**206**	**1.10**	0	1	0	**133**	14	**10**	0.21
18	SC	**206**	**1.13**	0	0	0	**126**	15	**8**	**0.32**
19	SC	**207**	**1.11**	0	1	0	**279**	16	**18**	**0.49**
20	HOA	**211**	**1.09**	0	0	0	**159**	16	**10**	**0.43**
21	SC	**212**	**1.03**	0	1	1	**176**	*10*	**17**	**0.27**
22	SC	**212**	**1.07**	0	1	0	**132**	19	**7**	**0.33**
23	SC	**216**	**1.18**	0	1	0	**157**	*11*	**14**	0.19
Normal range		<187	<1.01				10–50	13–20	0.5–4	0.07–0.22

Serum					
Estradiol (nmol/l)	SHBG (nmol/l)	Androstenedione (nmol/l)	Testosterone (nmol/l)	LH (U/l)	FSH (U/l)
0.00	–	*1.6*	12	–	–
0.00	–	–	13	–	–
0.00	**81**	2.2	17	**12.6**	**8.1**
0.06	**51**	2.6	19	5.2	5.9
0.03	25	3.2	10	1.9	*1.5*
0.08	23	3.4	12	3.8	5.3
1.00	**76**	3.5	13	5.3	1.6
0.03	35	2.6	14	2.8	2.7
0.22	37	2.1	*2*	2.4	1.6
0.10	**55**	5.6	22	5.0	7.0
0.18	39	2.8	26	3.1	5.3
0.06	19	3.6	*3*	3.2	3.5
0.12	36	5.7	19	3.3	4.4
0.00	23	3.8	19	7.5	**8.9**
0.08	**56**	4.3	22	4.0	2.2

Table 2 (continued)

Serum					
0.03	33	5.7	13	4.0	2.7
0.09	29	*1.8*	11	6.4	6.8
0.09	35	3.7	12	3.6	3.5
0.06	21	8.0	16	6.5	7.2
0.15	**41**	7.2	24	5.4	3.5
0.00	33	3.7	11	5.9	2.3
0.06	**44**	2.0	16	6.3	4.5
0.12	37	5.6	17	7.0	5.5
0.05–0.22	10–40	2.0–9.0	10–35	1.9–8.0	1.6–7.7

All patients were male. 0 represents absent; 1 represents present. Bold items represent above normal range; italic items represent below normal range. Bars represent missing values

SHBG, sex hormone-binding globulin; *LH*, luteinizing hormone; *FSH*, follicle-stimulating hormone

excess [7]. Prostaglandins are local hormones that are generated de novo from phospholipids in response to a wide range of stimuli. Their presence can be detected in virtually every tissue of the body. Prostaglandins signal diverse biological events, depending upon cell type and receptor subtype. By analogy with neurotransmitters, signal termination is achieved by re-uptake and oxidation of the prostaglandin in the cell. The main re-uptake transporter for most prostaglandins is the prostaglandin transporter (PGT). The oxidative enzyme is 15-hydroxyprostaglandin dehydrogenase (HPGD). A major breakthrough in HOA research was the discovery that mutations in the *SLCO2A1* gene, which encodes the PGT, or mutations in the *HPGD* gene, which encodes HPGD, cause familial or primary HOA. Thus, the cause of familial or primary HOA is prostaglandin excess because of insufficient breakdown of prostaglandins. Secondary HOA may have the same cause. In patients with lung cancer, levels of the major urinary metabolite of PGE_2 (PGE-M) were greatly increased; downregulation of HPGD occurs in various tumor types; and patients with digital clubbing due to cystic fibrosis had elevated prostaglandin levels in their circulation [8]. Of all prostaglandins, PGE_2 appears to be the cause of all symptoms of HOA. First, because PGE_2 is the most common prostaglandin in man. In normal subjects, the concentration of PGE-M in urine is up to 100-fold greater than that of the major urinary metabolite of all other prostaglandins [9]. Second, because chronic administration of prostaglandins of the E series to patients with liver disease caused all symptoms of HOA: arthralgias after 1 week, acute arthritis after 2 weeks, and clubbing with subperiosteal new bone formation after 4 weeks. All these effects were dose-related and resolved with reduction or cessation of therapy [10]. Chronic administration of PGE_2 to dogs also caused all symptoms of HOA [11, 12], except for clubbing, because digital clubbing is unique to humans. However, it was not clear how exactly PGE_2 causes each individual symptom of HOA, and why clubbing and other symptoms of HOA do not always develop simultaneously. This may be explained by the following hypothesis.

Digital clubbing, hyperestrogenism, and PGE_2

Clubbing of the fingers and the toes may be caused by hyperstimulation of a mechanism that protects the tips of the fingers and toes against ischemia (Fig. 2). This mechanism is angiogenesis, the process by which blood vessels are formed from pre-existing vessels [13]. With the use of immunochemistry, clubbed digits showed an increase in hypoxia inducible factor (HIF)-1α, HIF-2α, vascular endothelial growth factor (VEGF), the major VEGF receptor, and platelet-derived growth factor (PDGF), as compared with control fingers. Microvessel density was increased as well [14]. These findings suggest activation of the HIF-1 pathway, resulting in angiogenesis, in which VEGF and PDGF play a role [13]. It

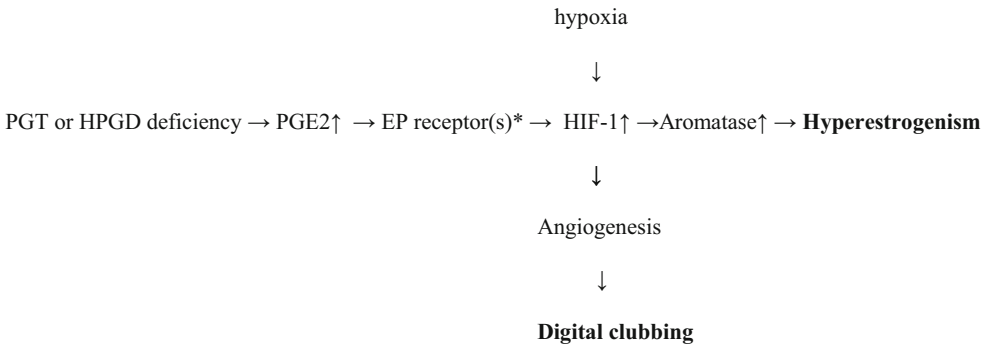

Fig. 2 Hypothetical mechanism causing digital clubbing and hyperestrogenism
*Subtype dependent on cell type [15].

was suggested that VEGF synergizes with PDGF in inducing the stromal and vascular changes that cause digital clubbing [14]. The archetypal stimulus of the HIF-1 pathway is hypoxia [13]. This explains why chronic hypoxia causes clubbing (Fig. 2). However, PGE_2 also activates the HIF-1 pathway by activation of one or more EP receptors [15]. This explains why clubbing occurs in situations in which PGE_2 levels are elevated, such as in PGT or HPGD deficiency (Fig. 2). Interestingly, PGE_2 may not only cause clubbing by activating the HIF-1 pathway. Activation of the HIF-pathway also increases the expression of aromatase (Fig. 1) [15]. Aromatase converts androgens into estrogens. This explains the association between digital clubbing and hyperestrogenism. Thus, contrary to earlier impressions [2], hyperestrogenism appears to be associated with digital clubbing, and not with subperiosteal new bone formation (see below).

Subperiosteal new bone formation, PGA_2, and the inflammatory reflex

Subperiosteal new bone formation may be caused by hyperstimulation of a mechanism that transforms mechanical load to new bone formation (Fig. 3). Dynamic mechanical loading of the tibia releases PGE_2 from its proximal metaphysis [16]. It may be assumed that this also occurs in other parts of the bone and in other bones. If PGE_2 is not immediately removed, such as in PGT or HPGD deficiency, it may accumulate, not only locally, but also systemically. In human blood, in the presence of albumin, PGE_2 is rapidly converted to PGA_2 [17]. PGA_2 is a cyclopentenone prostaglandin. Cyclopentenone prostaglandins do not appear to activate conventional prostaglandin receptors but interact with other cellular target proteins. Conventional prostaglandins activate their receptor(s) in physiological concentrations, but cyclopentenone prostaglandins need higher (pharmacological) concentrations to have an effect [18]. We suggest that high PGA_2 concentrations are achieved in HOA by activation of the "inflammatory reflex" [19]. This is a recently discovered reflex, the afferent arm of which is formed by afferent fibers in the vagus nerve. The efferent arm of the reflex is termed "cholinergic anti-inflammatory pathway." This reflex appears to inhibit cytokine synthesis, and thus protect against cytokine-mediated diseases. It may do so via the release of PGE_2 from monocytes of the reticuloendothelial system [20]. According to our hypothesis, PGE_2 stimulates the EP3 subtype of its receptors on the afferent fibers of the vagus nerve [21]. This results in activation of the inflammatory reflex, which may release PGE_2 from the monocytes of the reticuloendothelial system [20]. If this PGE_2 is not immediately removed, as in PGT or HPGD deficiency, it may accumulate and cause more stimulation of afferent vagus fibers, causing a fast-forward mechanism, resulting in even higher systemic PGE_2 levels. These high PGE_2 levels are rapidly converted to high PGA_2 levels, which may now be high enough to activate peroxisome proliferator-activated receptors α/δ (PPARα/δ) on osteoblasts, which cause subperiosteal new bone formation [17]. This explains the dramatic relief of the symptoms of HOA after ipsilateral vagotomy (or local anesthesia of the vagus nerve [22]) in patients with lung cancer [23]. One patient was reported in whom vagotomy relieved all pains in bones and joints within 24 h, with regression of swelling and edema of the hands and feet and improvement of the movements of hands and fingers. In 3 days, the edema had completely disappeared, the dyspnea was considerably improved, and the patient got up. At the end of 10 days, he was walking round the ward pain-free. On the 25th postoperative day, all symptoms of HOA had disappeared, gynecomastia included. Only digital clubbing remained [23]. This dramatic effect of vagotomy also explains why atropine is beneficial in HOA [24]. Interestingly, splenectomy, or selective interruption of the abdominal vagus nerve at the common celiac branch, also inactivates the inflammatory reflex [25]. This observation provides a number of potentially therapeutic options for patients with HOA which needs further exploration.

Prostaglandins tend to occur in pairs with opposing action, such as prostacycline and thromboxane on hemostasis, and PGE_2 (vasodilator) and $PGF_{2\alpha}$ (vasoconstrictor) on some vascular beds [26]. It is therefore not surprising that the cyclopentenone prostaglandin 15d-PGJ2 inhibits angiogenesis by inhibiting the HIF-1 pathway [27]. PGA_2 also is a cyclopentenone prostaglandin, and PGA_2 may therefore inhibit the HIF-1 pathway as well. This explains why our patients with the full syndrome of HOA did not always have the highest degree of clubbing, and why they did not always excrete the highest amount of estriol in their urine, as compared to the patients with simple clubbing. However, if our

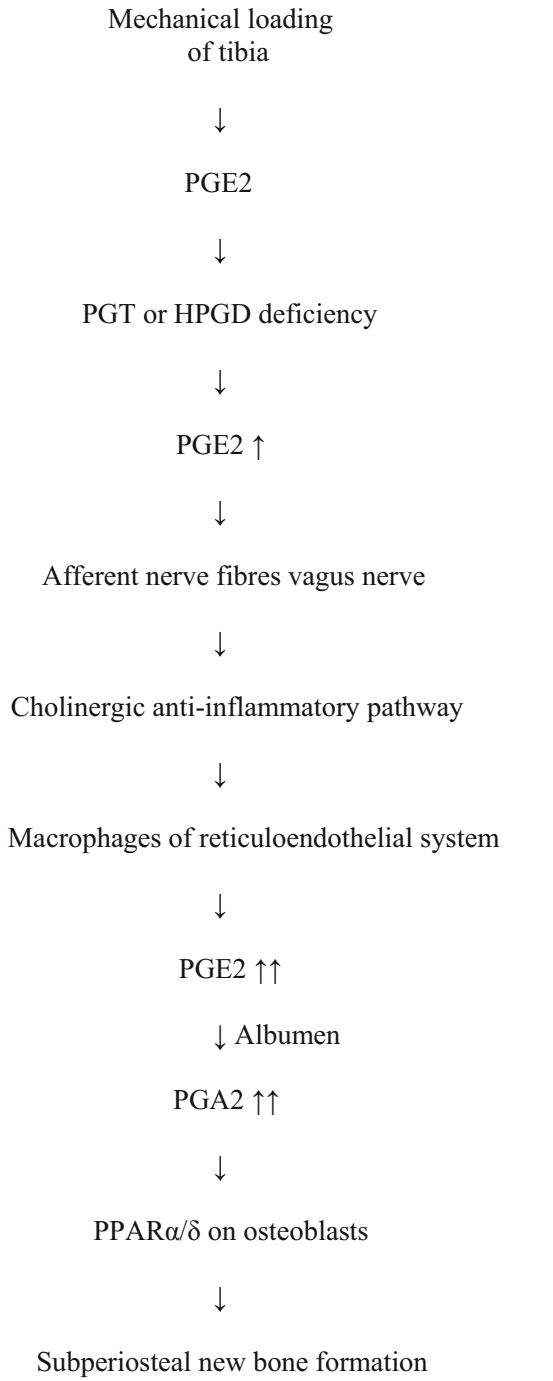

Fig. 3 Hypothetical mechanism causing subperiosteal new bone formation on the tibia in HOA

hypothesis is true, then the stimulatory effect of PGE_2 on clubbing and hyperestrogenism is much stronger than the inhibitory effect of PGA_2 on these symptoms.

Polyarthritis

PGA_2 may cause the polyarthropathy of HOA by inducing apoptosis of chondrocytes [28].

HOA and women

HOA is less severe in women, maybe because they appear to produce less PGE_2 than men. This is suggested by the observation that men excrete about twice as much PGE-M in the urine as women [9].

Water retention

Urinary creatinine concentration correlated positively with degree of clubbing in our patients. This suggests water retention, proportional to degree of clubbing. Indeed, HOA is associated with water retention [1, 29, 30]. There are three possible causes for this, or a combination of these causes. PGE_2 stimulates the secretion of antidiuretic hormone (ADH) via its EP1 receptor subtype [31]; PGE_2 has a direct effect on the kidneys [31]; and PGE_2 increases vascular permeability, probably indirectly by mast cell activation via EP3 receptors [32]. In our patients, urinary estriol concentration correlated positively with degree of clubbing. This is in agreement with our hypothesis, but this correlation might also be due to concentration of the urine proportional to degree of clubbing, caused by water retention.

Muscle atrophy

About half of our patients with digital clubbing had a low urinary creatinine concentration. This might be due to incomplete urine collection, but all but one of them still had a high urinary estriol concentration, and all of them had a high urinary estriol/creatinine ratio. These patients may have had muscle atrophy, because urinary creatinine concentration reflects muscle mass. Indeed, HOA is associated with muscle atrophy [33, 34], but all our patients with low urinary creatinine concentration had simple clubbing. This suggests involvement of PGE_2, not PGA_2. Indeed, PGE_2 causes muscle atrophy by activating the lysosomal apparatus [35], possibly by extrusion of lysosomes from myo-fibrocytes, as has been observed in the connective tissue of the cervix before delivery [36]. Enzymes released by these lysosomes might cause the proteolytic muscle degradation. Our patients with the full syndrome of HOA had a normal urinary creatinine concentration in the urine. This might suggest an opposing effect of PGA_2 on the effect of PGE_2 on muscle. However, the effect of PGA_2 on muscle is disputed. Nonetheless, PGA_2 activates the peroxisome proliferator-activated receptor γ (PPARγ), which is required for skeletal muscle cell differentiation [37]. More studies on the effect of cyclopentenone prostaglandins on muscle are needed, because it is likely that katabolic and anabolic mechanisms in muscles, tendons, and bones are similar.

Spider angiomas

Spider angiomas are vascular skin lesions which originate from normal cutaneous arteries and thus conform to the definition of angiogenesis. They strikingly resemble uterine spiral arteries, which temporarily supply blood to the endometrium of the uterus during the luteal phase of the menstrual cycle [38]. Uterine spiral arteries have already been associated with activation of the HIF-1 pathway by PGE_2 [26]. The association between spider angiomas and HOA has been noted before [39]. Spider angiomas occurred in 74% in our patients, about as much as in cirrhosis of the liver (75%) [40].

Palmar erythema

Palmar erythema is a sharply delineated, intense redness over the hypothenar and thenar eminence of the palms of the hand with relatively central palmar pallor. Spider angiomas and palmar erythema are considered to have the same or a very similar cause. Palmar erythema may be caused by PGE_2 as well, because PGE_2 is a vasodilator.

Adrenal cortical hyperfunction

Serum androstenedione concentration correlated positively with the degree of clubbing in our patients. This suggests adrenal cortical hyperfunction, proportional to degree of clubbing. The presence of adrenal cortical hyperfunction has been suggested in patients with digital clubbing before [3]. Indeed, both prostaglandins of the E and of the A series stimulate the release of corticotropin-releasing hormone (CRH) in the hypothalamus, which might eventually lead to adrenal cortical hyperfunction [41]. However, this hyperfunction appears to be rather slight, because, although serum androstenedione concentration correlated positively with degree of clubbing, individual serum androstenedione concentrations did not exceed normal reference values in our patients.

Patent ductus arteriosus

PGE_2 causes patent ductus arteriosus via the EP4 receptor [42].

Delayed closure of cranial sutures

Long-term PGE_2 administration to two newborn infants caused widening of cranial sutures [43]. This suggests that the delayed closure of cranial sutures in HOA is caused by PGE_2 and/or PGA_2.

Seborrhea

What causes the thickening of the skin in HOA is not clear, but cyclopentenone prostaglandin 15d-PGJ2 causes seborrhea [44]. PGA_2 is also a cyclopentenone prostaglandin. It may therefore cause seborrhea as well.

Hypertrophic gastropathy

PGE_2 may cause hypertrophic gastropathy [12, 45], but whether it may do so directly or via PGA_2 is not known.

Myelofibrosis

In a patient with severe myelofibrosis due to familial HOA, bone marrow fibroblasts proliferated almost twice as fast as normal, and their number of PDGF receptors was increased. In myeloproliferative syndromes, the proliferation of fibroblasts is normal [46]. The question is whether this increased proliferation is also due to activation of the HIF-1 pathway by PGE_2, as in clubbed digits. PGA_2 may be involved as well, because the osteoblasts involved in subperiosteal new bone formation derive from mesenchymal precursor cells in the bone marrow [17].

Endothelial activation or damage

PGA_2 may activate or damage endothelium cells by inducing apoptosis, as it does in chondrocytes [47] .

Acroosteolysis

Acroosteolysis is resorption of the distal bony phalanges. It is likely caused by vascular occlusion [48]. In HOA, it may be due to the endothelial damage caused by PGA_2, causing vascular occlusion, despite the protective presence of vasodilator PGE_2.

Hyperhidrosis

Hyperhidrosis may be another effect of activation of the inflammatory reflex.

Pain

PGE_2 potentiates other pain-producing mediators such as histamine and bradykinine, but causes no pain. In contrast, PGA_2 does cause pain by stimulation of nociceptors via the irritant transient receptor potential A1 (TRPA1) channel [49]. Acetaminophen (paracetamol) desensitizes TRPA1 channels [50] and is indeed effective against the pain of HOA, although not completely. Contrary to expectation, the effect of many non-steroidal anti-inflammatory drugs (NSAIDs) is

disappointing. In our patients, celecoxib or meloxicam was the most effective in men, and carbasalatecalcium was the most effective in women.

Conclusion

Our main finding is that hyperestrogenism not only occurs in the full syndrome of HOA, but also occurs in simple clubbing. We therefore reject the claim that hyperestrogenism occurs in hypertrophic osteoarthropathy (HOA), but not in simple clubbing [2]. The observation that hyperestrogenism occurs in clubbing enables us to present a new and comprehensive hypothesis on the pathogenesis of clubbing and of the other symptoms of HOA.

According to this hypothesis, digital clubbing and hyperestrogenism are caused by PGE_2 excess. PGE_2 excess is due to decreased degradation of PGE_2 because of PGT or PGDH deficiency. According to our hypothesis, PGE_2 stimulates the HIF-1 pathway, resulting in angiogenesis and increased expression of aromatase. Angiogenesis may cause clubbing. Increased expression of aromatase causes hyperestrogenism.

Subperiosteal new bone formation, in contrast, may be caused by PGA_2 excess. In the presence of albumen, PGE_2 is rapidly converted to PGA_2. Thus, PGT or PGDH deficiency causes PGE_2 excess, which is rapidly converted into PGA_2 excess. However, PGA_2 needs to be present in a much higher concentrations than PGE_2 to have an effect. According to our hypothesis, this is achieved by activation of the inflammatory reflex. PGE_2 may activate the afferent leg of the inflammatory reflex, resulting in increased PGE_2 production by the effector cells of the efferent leg, i.e., the monocytes of the reticuloendothelial system. If this PGE_2 is not immediately removed, as in PGT or PGDH deficiency, total PGE_2 concentration will rise, further stimulating the inflammatory reflex, resulting in high PGE_2 levels. These high PGE_2 levels will be rapidly converted into high PGA_2 levels, now high enough to activate the PPARα/δ receptors on osteoblasts which cause subperiosteal new bone formation. Interruption of the afferent leg will abolish the inflammatory reflex. This explains the dramatic relief of symptoms by vagotomy in patients with lung cancer, and the favorable effect of atropine on secondary HOA. Interestingly, interruption of the efferent leg of the reflex by denervation of the spleen or by splenectomy also interrupts the inflammatory reflex [25]. The latter procedure might also reduce the concentration of both PGE_2 and PGA_2. At best, it might reduce the full syndrome of HOA to simple clubbing. This can be tested in animals, because HOA can be induced with relative ease in dogs [11, 12]. However, possible benefits of interruption of the inflammatory reflex should be carefully weighed against the risks. For instance, it is possible that some chronic inflammatory conditions which are associated with HOA, such as inflammatory bowel disease, may benefit from the inflammatory reflex, and might worsen after interruption of the reflex. Nonetheless, interruption of the inflammatory reflex may provide a number of options for the treatment of HOA, i.e., pharmacological (atropine), anesthesiological (local anesthesia of vagus nerve or splenic plexus), or surgical (vagotomy, interruption of the splenic plexus, splenectomy).

The other symptoms of HOA may be caused by PGE_2, PGA_2, both prostaglandins, or by the inflammatory reflex.

HOA is an experiment of nature which provides important information on the role of prostaglandins in the katabolism and anabolism of muscles, tendons, and bones, on the development of arthritis and pain, and on the development of endothelial damage. HOA also provides important information on the role of prostaglandins in diverse conditions, including pediatric, gastroenterologic, cardiologic, pulmonologic, endocrinologic, immunologic, dermatologic, hematologic, gynecologic, and nephrologic conditions. Finally, HOA may provide more information on the role of prostaglandins in the inflammatory reflex. All this information may hopefully contribute to better treatment of all diseases and symptoms caused by prostaglandins.

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Compliance with ethical standards

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments at the time of data collection. All persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study have been omitted.

Conflict of interest PL has received honorarium from Friesland Campina dairy industry for advice. The other authors have no potential conflict of interests to declare.

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