Digital clubbing: forms, associations and pathophysiology

Among proposed mechanisms to explain digital clubbing, the release of cytokines, specifically vascular endothelial growth factor and platelet-derived growth factor, from aggregated platelets and megakaryocytes has emerged as the most likely explanation. This review describes these and other contributory processes.

Clubbing describes the swelling of the soft tissue of the terminal phalanx of a digit with loss of the normal angle between the nail and the nail bed (*Figures 1* and *2*). This apparently innocent feature is related to many disease states (*Tables 1* and *2*) and remains a source of intrigue to clinicians. As clubbing is frequently indicative of an appalling prognosis, clinicians are often faced with a rigorous search to determine the aetiology.

Clubbing can occur in isolation or in combination with a number of other skeletal and dermatological features which include the conditions hypertrophic (pulmonary) osteoarthropathy and pachydermoperiostostitis, which have several synonyms in addition to the condition thyroid acropachy. Clubbing and its co-features are diagnosed by clinical examination and radiographic imaging (Spicknall et al, 2005; Sarkar et al, 2012; Gibb et al, 2013; Rutherford, 2013). This article discusses these associations with an emphasis on the pathophysiology of the condition.

Hypertrophic pulmonary osteoarthropathy and hypertrophic osteoarthropathy

Hypertrophic pulmonary osteoarthropathy and hypertrophic osteoarthropathy comprise a triad of digital clubbing, arthralgia and ossifying periostitis to the ends of long bones. The condition has ancient origins, being noted in human skeletons over 7000 years old (Masson et

Figure 1. Digital clubbing in a 56-year-old Asian man with no evident precipitatory disease state. Of note, this man's father was suspected as having acromegaly because of his large hands and feet although he had normal growth hormone values. This suggests that both men probably have a form of familial pachydermoperiostitis.

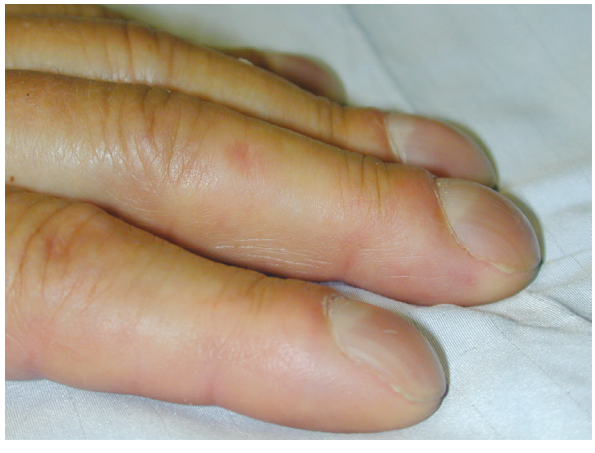
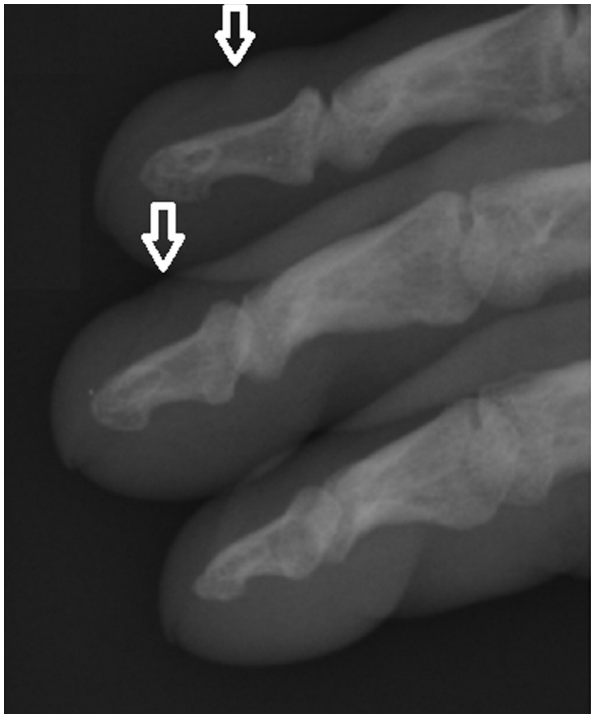


Figure 2. Radiograph of the same patient as *Figure 1* showing expansion of the soft tissue matrix of the digital phalanges. The loss of nail angle (white arrows) can also be appreciated.



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al, 2013) and likely related to tuberculosis. Moreover it is not unique to humans, with hypertrophic osteoarthropathy apparent, albeit without digital clubbing, across numerous domestic animals and most frequently dogs, cats, horses and cattle. Wild animal species, including wolves, foxes, deer, lions, tigers, kangaroos and various lizards, also exhibit hypertrophic osteoarthropathy and as in humans, there is a frequent relationship with thoracic disease and malignancy (Thorsson, 2015).

In humans hypertrophic pulmonary osteoarthropathy is a specific form, usually associated with thoracic malignancies, primarily lung and particularly non-small cell neoplasia (Erkan et al, 2002). Why some patients with lung cancer develop clubbing and others do not remains unexplained. When the underlying disease is not pulmonary, or on occasions is unidentified, then the condition should more correctly be described as hypertrophic osteoarthropathy (Sarkar et al, 2012).

Pachydermoperiostitis

Pachydermoperiostitis is a form of hypertrophic osteoarthropathy, comprising the additional feature of cutaneous thickening (pachyderma), in combination with periostosis, clubbing and frequently arthritis (Carcassi, 1992; Rastogi et al, 2009). Clubbing is seen in around 89% of patients diagnosed with pachydermoperiostitis (Schwartz, 2015). Pachydermoperiostitis represents around 5% of hypertrophic osteoarthropathy cases (Rodríguez et al, 2009). Additional and more variable features include enlargement of the hands and feet, sometimes resembling and confused as being acromegaly (Goette, 1980; Chentli et al, 2014), although growth hormone estimates are usually normal. Patients also describe hyperhidrosis and a feeling of heat in the feet and hands (Rastogi et al, 2009), possibly related to an increase in vasculature. In more extreme forms there is excessive skin thickening of the face and furrowing of the forehead and scalp, termed 'cutis verticis gyrate'. The prevalence of pachydermoperiostitis is frequently quoted as 0.16% (Jajic and Jajic, 1992) although this figure is derived from a small series of five cases from a selected population seen within 1 month. Pachydermoperiostitis usually manifests in adolescence, occurring almost exclusively in males (Castori et al, 2005), with a male:female ratio of between 7 to 9:1 (Nayak et al, 2012; Chentli et al, 2014).

In approximately a third of patients pachydermoperiostitis is hereditary in nature and usually autosomal dominant with incomplete penetrance and variable expression (Castori et al, 2005). This condition has been linked to mutations in the gene on the fourth chromosome (4q33-q34) coding for the enzyme 15-hydroxyprostaglandin dehydrogenase, resulting in increased levels of prostaglandin E_2 (Uppal et al, 2008). Reported cases are frequently of Indian or Pakistani origin with mutations also reported in Turkish and Chinese families (Chentli et al, 2014). Associated with significant morbidity with advancing age, pachydermoperiostitis may represent a paraneoplastic portent. Autosomal recessive states have been identified in some families and are associated with mutations of the prostaglandin transporter SLCO2A1 (Busch et al, 2012).

Table 1. Tumours and malignant causes of clubbing

Organ system	Pathology	
Pulmonary	Bronchial carcinoma (29%)	Non-small cell (35%)
		Small cell (4%)
	Mesothelioma (30%)	
	Pleural fibroma	
	Inflammatory pseudo-tumour*	
	Pulmonary metastases	Sarcomas*
		Uterus* or cervix*
		Renal carcinoma*
		Nasopharynx*
Gastrointestinal	Lymphoma of gastrointestinal tract	
	Oesophageal carcinoma	
	Gastric adenocarcinoma	
Cardiovascular	Atrial myxoma	
Other	Chronic myeloid leukaemia*	
	Hodgkin's lymphoma*	
	Metastatic osteogenic sarcoma	

** Uncommon causes of clubbing. Percentage values within brackets (%) indicate the proportion of patients with that condition exhibiting clubbing (Sarkar et al, 2012; Schwartz, 2015).*

Thyroid acropachy

Clubbing and swelling of the fingers and toes is seen in the condition acropachy which is associated with all forms of autoimmune thyroid disease, but most commonly hyperthyroidism (Fatourechi et al, 2002). Fatourechi et al (2002) demonstrated a higher prevalence of women with acropachy, with a female:male ratio of 3.4:1, although an earlier study suggested an equal gender distribution (Goette, 1980). Thyroid acropachy is almost universally associated with the presence of ophthalmic and dermatological (usually pre-tibial myxoedema) thyroid disease (Gutch et al, 2014). In patients with thyroid dermopathy, the estimates for prevalence of clubbing varies between 7 and 23% (Fatourechi et al, 1994, 2002). In thyroid acropachy, the skin is commonly pigmented and hyperkeratotic, and local warmth over the joints is usually absent (Fatourechi et al, 2002). Involvement of the long bones is much less common than in hypertrophic osteoarthropathy. When long bone periostitis is present, the radiological features show a subperiosteal spiculated, frothy or lacy appearance which is distinct from the laminal proliferation seen in classical hypertrophic osteoarthropathy.

Isolated digital clubbing

Much less commonly, clubbing occurs as an isolated feature without evidence of underlying disease, as an idiopathic or hereditary form (Tariq et al, 2009; Das and Shukla, 2014). In this form the condition is usually bilateral and symmetrical – there can be unexplained sparing of individual digits although the thumbs are almost universally involved. Patients are normally asymptomatic. Reports usually involve sporadic cases and some have determined the involvement of mutations for the enzyme 15-hydroxyprostaglandin dehydrogenase as described in pachydermoperiostitis (Tariq et al, 2009).

The pathophysiology of clubbing

Numerous mechanisms have been described to explain clubbing. These include local humoral effects, neurological, immunological and hypoxic influences. In many cases the pathophysiology appears to overlap (*Figure 3*).

Vascular endothelial growth factor

Perhaps the most convincing humoral mechanism is via the production of cytokines, including vascular endothelial growth factor (VEGF). Circulating VEGF levels are elevated in patients with clubbing (Silveira et al, 2000), the protein itself producing nail bed vascular hyperplasia (angiogenesis), oedema, fibroblast and osteoblast proliferation (Mohle et al, 1997; Atkinson and Fox, 2004; Martinez-Lavin, 2007). Within malignant tumours, over-expression of VEGF promotes the development of tumour vasculature, a role it also accomplishes in embryogenesis helping angiogenesis and haematopoiesis (Mohle et al, 1997).

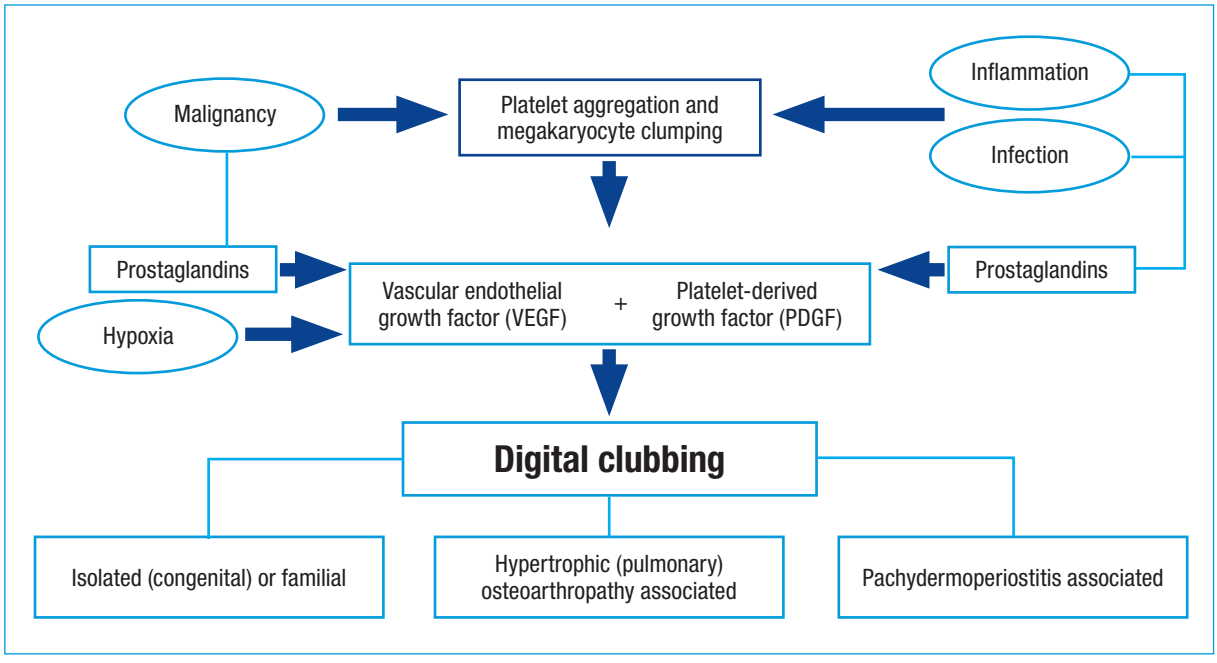
VEGF promotes endothelial fenestration, the extravasation of plasma macromolecules and the migration of monocytes. It is also chemotactic for mast cells and monocytes (Mohle et al, 1997). Synthesis of this factor is stimulated by a number of disease states, including malignancies, hypoxia and conditions affecting the

Table 2. Non-malignant causes of clubbing

Organ system	Pathology		Organ system	Pathology	
Pulmonary	Fibrosing alveolitis (65%)		Gastrointestinal	Hepatopulmonary syndrome	
	Cystic fibrosis		(continued)	Coeliac disease	
	Tuberculosis			Hepatic amyloidosis	
	Asbestosis (14–43%)			Chronic parasitic infections	Schistosomiasis
	Pneumoconiosis				Whipworm
	Chronic suppurative disease	Empyema		Malabsorption syndromes	
		Bronchectasis	Cardiovascular	Congenital cyanotic disease	Tetralogy of Fallot
		Lung abscess			Ductus arteriosus
	Sarcoidosis*			Arteriovenous	Malformations
	Hydatid disease*				Fistulae
	Carbon monoxide and cannabis smoking*			Endocarditis	
	Hypersensitivity: pneumonitis*			Arterial	
Gastrointestinal	Cirrhosis	Biliary	Other	Familial	
		Alcoholic		Isolated congenital clubbing	
	Inflammatory bowel disease	Crohn's disease (38%)		Pachydermoperiostitis (89%)	
		Ulcerative colitis (15%)		Hemiplegia (2–14%)	
		Proctitis (8%)		Human immunodeficiency virus infection	
	Chronic active hepatitis			Thyroid acropachy	
	Biliary atresia			Hyperparathyroidism	
	Polyposis			Thalassaemia	
	Behçet's disease			Myelofibrosis	

** Uncommon causes of clubbing; percentage values within brackets (%) indicate the proportion of patients with that condition exhibiting clubbing (Sarkar et al, 2012; Schwartz, 2015).*

Figure 3. Relationship between causes, signal proteins, prostaglandins and the eventual clinical condition.



circulation. When megakaryocyte fragments gain access to the systemic circulation, 'signal proteins' including VEGF are rapidly released (Mohle et al, 1997). Access of megakaryocytes to peripheral sites is achieved for example through extra-pulmonary arteriovenous malformations, avoiding 'inactivation' of cytokines and 'trapping' of megakaryocytes and platelet clusters in the lungs. In support of VEGF's role, the drug octreotide, a potent inhibitor of VEGF, is beneficial in the management of hypertrophic osteoarthropathy (Angel-Moreno Maroto et al, 2005).

Platelet-derived growth factor

Platelet-derived growth factor (PDGF) is also released from platelets clustering in the vasculature of the fingertips (Fox et al, 1991). PDGF stimulates growth, vascular permeability, monocyte and neutrophil chemotaxis, and leads to proliferation of vascular smooth muscle cells and fibroblasts. Conditions that involve chronic platelet excess (e.g. inflammatory bowel disease) also result in peripheral platelet trapping and release of PDGF. In patients with clubbing in relation to lung tumours, both VEGF and PDGF are released with digitally located platelet clusters at levels higher than in control subjects (Atkinson and Fox, 2004). A number of reports describe the total resolution of clubbing in patients when a bronchogenic adenocarcinoma has been surgically removed, sometimes within only a few weeks (Rutherford, 1999).

Other humoral 'signal proteins'

The list of additional potential signal proteins is long and includes prostaglandins, bradykinin, ferritin, adenosine nucleotides, interleukin-6, von Willebrand factor, serum transforming growth factor-β1 (TGF-β1), tumour necrosis factor-α, growth hormone, epidermal growth factor, hepatocyte growth hormone and 5-hydroxtryptamine (Matucci-Cerinic et al, 1992; Hojo et al, 1997; Silveira et al, 2000; Schwartz, 2015).

Kozak et al (2012) demonstrated that, in patients with lung cancer, digital clubbing was associated with markedly elevated levels (2.3-fold higher) of urinary prostaglandin E_2 metabolites than in those who were not clubbed. Furthermore, debilitating symptoms of hypertrophic osteoarthropathy can be relieved using the COX-2 inhibitor rofecoxib with recurrence on discontinuation (Kozak et al, 2012). In addition, malignancies and inflammatory conditions, such as Crohn's disease, have increased levels of the enzyme cyclo-oxygenase-2 (a prostaglandin-endoperoxide synthase) that is responsible for the formation of various prostanoids, including prostaglandins like E_2 (Kozak et al, 2006). In patients treated with prostaglandins for liver disease, clubbing and hypertrophic osteoarthritic features developed that were reversed when therapy was stopped (Cattral et al, 1994).

The increased expression of VEGF is reported to be stimulated by an effect of prostaglandin E_2 on VEGF messenger ribonucleic acid (mRNA) (Harada et al, 1994), likely as a result of transcriptional regulation. This 'upregulation' of VEGF mRNA expression can be inhibited by dexamethasone. Prostaglandin E_2 stimulates osteoblasts and osteoclasts and is therefore capable of inducing periostosis and acro-osteolysis, in addition to local vasodilatation, all features of hypertrophic osteoarthropathy.

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Harada et al had earlier suggested that the cyclo-oxygenase inhibitor rofecoxib may be of use to suppress over-production of prostaglandin E_2 by certain lung cancers, identified in patients with overt clubbing. Increased levels of prostaglandin E_2 resulting from mutations in genes for both the enzyme 15-hydroxyprostaglandin dehydrogenase and the prostaglandin transporter SLCO2A1 are described in pachydermoperiostitis (Uppal et al, 2008; Busch et al, 2012). Recently, the genes for the solute carrier organic anion transporter family member 2A1 (SLCO2A1) as well as hydroxyprostaglandin dehydrogenase (HPGD) were reported as pathogenic for pachydermoperiostitis. Both genes are involved in prostaglandin E_2 degradation (Lee et al, 2016), with mutations of SLCO2A1 causing increased levels of this prostaglandin because of the failure of extracellular uptake of prostaglandin E_2.

Serum transforming growth factor (TGF-β1), a cytokine found in alpha granules of platelets, is associated with the pathology of a large number of malignancies. Collections of megakaryocytes and platelets could locally release this factor, resulting in an accumulation of extracellular matrix. Whether this is related to clubbing as suggested (Hirakata and Kitamura, 1996) or is simply a reflection of disease extent remains unknown.

There is no consensus on the role, if any, of growth hormone in the development of clubbing, with only one study suggesting a role in patients with lung cancer (Gosney et al, 1990). Toovey and Eisenhauer (2010) have suggested that the chronic activation of macrophages may lead to elevated levels of growth factors; a theory compatible with sarcoidosis, where granulomas are rich in macrophages and in which clubbing is also occasionally described. Although sarcoidosis affects multiple organs commonly associated with clubbing, it remains an unusual feature associated with an advanced fibrotic stage and when present is frequently painful. Differences in the presence or extent of clubbing or the full triad of clubbing, periostosis and arthritis might therefore be explained by variations in an individual's immune system and the degree of macrophage activation (Thorsson, 2015).

In thyroid acropachy, the mechanism is more likely autoimmune related and similar to thyroid ophthalmic and dermatological processes, with an increased proliferation of fibroblasts and deposition of glycosaminoglycans (Parker et al, 1982).

Hypoxia

Many of the conditions associated with clubbing will involve hypoxia as a consequence of the disease process. Patients with large circulatory shunts, typically tetralogy of Fallot, are frequently clubbed and with surgical correction the clubbing can regress. Hypoxia appears responsible in patients with a patent ductus arteriosus shunt, when clubbing of the toes is seen and the fingers are spared.

KEY POINTS

- Discerning a cause remains a priority when clubbing or its associated syndromes are encountered.
- Platelet aggregations and megakaryocyte fragments release vascular endothelial growth factor and platelet-derived growth factor – likely local humoral agents inducing clubbing.
- Conditions involving hypoxia, injury, malignancy and chronic inflammation may all share a pathophysiology involving increased production of prostaglandins, resulting in clubbing and other forms of hypertrophic osteoarthropathy.

In paediatric patients with cystic fibrosis, a tenfold increase in clubbing has been reported in patients with hypoxia compared to patients without hypoxia (Paton et al, 1991). This overlaps with the observation that digital clubbing correlates with disease severity and serum levels of prostaglandins E and F_2 alpha (Lemen et al, 1978). In addition, the release of both VEGF and PDGF is likely triggered by hypoxia when platelets aggregate (Silveira et al, 2000; Atkinson and Fox, 2004). Hypoxia appears to regulate VEGF production in osteoblasts, through stimulation of messenger RNA expression (Steinbrech et al, 2000). These results imply that hypoxia can affect osteogenesis by altering the expression of cytokines, bone-specific extracellular matrix molecules, and their regulators. However, as a universal explanation it fails to explain conditions such as inflammatory bowel disease in which there is no obvious hypoxia (Rhee et al, 2014).

Neurological

Neurological mechanisms also appear implicated in clubbing as it may occur in hemiplegia, a feature not easily explained by the megakaryocyte release of humoral factors. There appears to be no explanation for this aside from alterations in blood flow as a result of autonomic nervous system instability.

The vagus nerve appears to have a particular role in some cases of clubbing. In inflammatory bowel disease, clubbing appears more prevalent when active disease is located in the vagally innervated part of the bowel. Furthermore, in patients with lung tumours, resolution of clubbing is not only described following tumour resection (Rutherford, 2013) but also following vagotomy (Diner, 1962).

Conclusions

The main consideration with digital clubbing remains the identification of any possible underlying serious disease state. The most likely pathophysiology rests with the theory of the local release of 'signal proteins' (VEGF and PDGF). Through their actions, and those of prostaglandin E_2, changes to fibroblasts, osteoclasts (acro-osteolytic) and osteoblasts (periostosis), along with extracellular matrix deposition and angiogenesis, promote the features of clubbing and hypertrophic osteoarthropathy. **BJHM**

Conflict of interest: none.

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