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Review

Mechanism of non-specific-fistula-in-ano: Hormonal aspects—Review

A.M. El-Tawil *

Department of Surgery, University Hospital Birmingham, East Corridor, Ground Floor, Edgbaston B15 2TH, United Kingdom

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Abstract

Abscesses could occur anywhere, but quite few that could proceed forward and develop fistulae. Crypto glandular abscess formation concept has been forming the basis for almost all designed strategies for management of cases of idiopathic fistula-in-ano for ages. Yet, this hypothesis failed to explain the reason(s) for the recorded lower incidences of idiopathic anal fistula in females than in males.

Gram negative bacteria are largely the causative agents for these anal glands' abscesses that processed further and developed fistulae. Lipopolysaccharide component (LPS) of the bacterial cell wall could significantly attenuate the expression of mRNA of the oestrogen receptors and accordingly reduces the down signalling pathway. Yet, this kind of action could be inhibited in the presence of oestrogen.

In addition, tumour necrosis factor-alpha (TNFα) is a key proinflammatory cytokine that induces the secretion of other cytokines and enzymes in various cells and tissues. And LPS could activate pro-inflammatory cytokine by activating plasma membrane proteins (e.g. the toll like receptor 4 [TLR4] and CD14 that leads to the production of TNFα and other pro-inflammatory cytokines). This activation could be enhanced by testosterone but inhibited by oestrogen. These are likely the reasons for the higher prevalence of idiopathic fistula-in-ano in males than in females.

Keywords: Anal fistula; Perianal fistula; Surgery; Estradiol; Oestrogen receptors; *E. coli*; Bacteroids; Lipopolysaccharides; Pro-inflammatory mediators; Cytokines

Contents

1. Introduction

Ninety percent of abscesses result from non-specific crypto glandular suppuration. This theory was first described by Chiari in 1878, but more expressively studied by Parks [1], suggesting that abscesses result from obstruction of the anal glands and ducts. Persistence of anal gland epithelium in part of the tract between the crypt and the blocked part of the duct leads to formation of a fistula. But the recorded complete healing after medical therapy in published reports is contradicting this assumption and suggests other hidden

* Tel.: +44 121 6978231; fax: +44 121 4466220.
E-mail address: atawil20052003@yahoo.co.uk

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factors that may lead to the development of idiopathic fistula-in-ano.

In addition, the lower incidence of non-specific anal fistulae in females than in males suggests a possible hormonal role. This review is thus aimed at discussing this probability.

2. Infecting agents and fistulae development

Acute infection of anal glands often result in the formation of a chronic intrasphincteric collection that may drain down to the perineum, up into the supra alveolar compartment or across the sphincter into the ischiorectal fossa [1–3]. Abscess complicating an infection in an anal gland are caused by intestinal organisms and are variably associated with an internal opening at the outset. Drainage consequently often results in the creation of a track or fistula between the skin and anal mucosa at the dentate line.

The conducted prospective study by Eykyn and Grace in 1986 [4] evidently provides the most informative data on the causative agents in these cases. The participant patients had an initial examination under anaesthesia and a further examination, one week later, by an experienced surgeon to inspect the presence of a fistula. This clinical assessment was harmonized by an enormously inclusive microbiological survey. The significant microbiological findings are summarized in Table 1.

Table 1 provides an objective evidence to support the idea that gram negative bacteria are mainly responsible for the development of fistulae in those with anal abscess.

3. Steroid hormones and development of non-specific fistula-in-ano

In 1998, Oettling and Franz [45] investigated the expression of androgen, oestrogen and progesterone receptors (ARs, ERs, PRs) in the tissues of the anal continence organ in 23 patients (seven men, seven premenopausal women and nine postmenopausal women) using immunohistochemical techniques. In their report, they concluded that specific immunostaining for ARs, ERs and PRs was found over cell nuclei. ARs were found in the smooth muscle cells of the anal sphincter in all but one of the females (10/11) and all males (7/7), ERs were found in 12/12 females and 4/7 males, and PRs were found in 4/10 females and 1/7 males. The squamous epithelium exhibited a similar pattern of immunostaining. The nuclei of the striated muscle fibers expressed none of the sex steroid receptors investigated. These data suggest possible role of feminizing hormones in the development of different anal problems.

4. Sex hormones and idiopathic fistula-in-ano

The discrepancy in the incidence of non-specific fistula-in-ano between the adult males and females is well acknowledged. Sainio [5] in his population study over ten years period reported an incidence of 5.6:100 000 for females and 12.3:100 000 for males, with a male: female ratio of 1.8:1. Others quote an even higher ratio, reaching 9:1 in some series [6]. This discrepancy suggests some protective role of female sex hormones against the development of idiopathic peri-anal fistula in women.

In 1995, Lunniss et al. [7] reported their results on the levels of steroid hormones in patients with non-specific fistula-in-ano and then compared their concentrations with those in matched healthy controls. The main reported data in female patients and controls are recorded in Table 2. It is likely that there is some abnormality that affected the structure, function or both or the presence of autoantibodies that directed against cell-surface receptors or alterations in the signalling pathway in female patients with idiopathic anal fistula, which led to the reported increased

Table 1
Type of organisms isolated from anorectal abscesses with and without fistulae.

Type of organism	Fistula present ($n=53$)	No fistula ($n=27$)	
Number of abscesses yielding anaerobes	49 (92.5%)	8 (29.6%)	$P<0.0001$
Escherichia coli	45 (84.9%)	5 (18.5%)	$P<0.0001$
Staphylococcus aureus	1[a] (1.9%)	8 (29.6%)	$P=0.0012$
Anaerobes 'gut-specific bacteroids'	47 (88.7%)	5 (18.5%)	$P<0.0001$
Anaerobes not 'gut-specific' (only)	2 (3.8%)	17 (63%)	$P<0.0001$
Gut aerobes + 'gut-specific anaerobes'	45 (85%)	4 (14.8%)	$P<0.0001$

Includes *E. coli*, *Klebsiella* spp., *Proteus* spp., *Citrobacter* spp., *Salmonella* sp., *Streptococcus faecalis*.
[a] Only 2 colonies isolated.

Table 2
Concentrations of circulating hormones (median values and interquartil ranges) in female patients with idiopathic fistula-in-ano compared with age-matched healthy controls.

Hormone	Controls	Patients	*P*
Estradiol (pmol/l)	163 (117–207)	253 (169–292)	0.03
Progesterone (nmol/l)	3.0 (1.2–6.5)	1.05 (1.0–2.48)	0.039
DHEAS (μmol/l)	4.5 (1.1–9.4)	3.3 (1.9–5.3)	Not significant