Review

The axial spondyloarthritis clinical phenotype in idiopathic hypoparathyroidism: critical review of concept that muscular hypercontractility can induce enthesopathy lesions

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ABSTRACT

Idiopathic hypoparathyroidism (iHPoPT) is a rare condition infrequently associated with axial spondyloarthritis (SpA) which may mimic ankylosing spondylitis (AS). Axial SpA is a unifying clinical term for chronic inflammatory spinal disorders, although biomechanical factors may play a role. The primary objective of this review is to critically describe the iHPoPT/SpA phenotype defined by established criteria and its differentiation from AS. Five databases were comprehensively searched without time limit to retrieve 14 (11M, 3F) iHPoPT/SpA cases. Their demographic, clinical, laboratory, radiographic, and HLA-B27 status were compared to two national series of AS patients. Mean (SD) onset age of musculoskeletal symptoms [32.5 (9.7)] was significantly older than 943 German AS patients [25.1 (8.5), (p=0.004)] and 842 Spanish AS patients [26.1 (9.7), (p=0.030)]. Radiographic lesions of iHPoPT/SpA differ morphologically from skeletal alterations in hyperparathyroid and hypophosphataemic syndromes which often have inadequate bone mineralisation and decreased bone mineral density (BMD). Clinical musculoskeletal manifestations were greater (p<0.001) in iHPoPT/SpA than AS patients at cervical (62 vs. 10%) and hip (85 vs. 22%) localisations, respectively. Typical AS sacroiliac joint structural lesions of erosions and bony bridging were reported in only 1 iHPoPT/SpA case and HLA-B27 was positive in 2 of 10 tested. The iHPoPT/SpA phenotype may be a natural experiment on the novel concept of how chronic hypocalcaemia of iHPoPT causes axial neuromotor hypercontractility and biomechanically induces the rare SpA association. In iHPoPT/SpA, neuromuscular hypercontractility may predispose to axial radiographic enthesopathy lesions and contribute knowledge on biomechanical contributions and pathways for further research.

Introduction

Parathyroid diseases are associated with rare and well-recognised musculoskeletal disorders, like spondyloarthritis (SpA) and mimics of ankylosing spondylitis (AS) (1-3). Hypoparathyroid syndromes, whether idiopathic, iatrogenic, or familial, are characterised by decreased parathyroid hormone (PTH), *hypo*calcaemia, *hyper*phosphataemia, neuromuscular hyperirritability, subcutaneous calcifications, and normal or increased bone mineral density (BMD) (2). *Pseudo*hypoparathyroidism (PHP) is a genetic form of hypoparathyroidism with *increased* PTH which may have similar SpA manifestations (4) as primary hypoparathyroidism (1, 2).

Primary *hyper*parathyroid syndromes are caused by hypersecretion of PTH resulting in *low* serum phosphate levels, *normo-* or *hyper*-calcaemia, and increased bone resorption at the subperiosteal and bone marrow interface which may result in *reduced* BMD (1, 5). Similarly, secondary hyperparathyroidism from vitamin D deficiency/resistance or chronic renal insufficiency results in *hypo*phosphataemia with comparable increased bone resorption and musculoskeletal manifestations (6). Hyperparathyroidism is the most common cause of increased renal phosphate excretion due to increased PTH (5,6). Hypophosphataemic syndromes, including primary hyperparathyroidism, deficiency or resistance to vitamin D, and inherited X-linked hypophosphataemia (XLH) can result

in impaired bone metabolism and inadequate mineralisation, causing osteomalacia or softening and weakening of bones (6). Hypophosphataemic osteomalacia in adults can result in exuberant enthesopathic calcification of tendon, ligament, and joint capsule insertions in the axial and appendicular skeleton without known pathogenesis (7).

The association of parathyroid diseases and osteomalacia with various musculoskeletal disorders and skeletal abnormalities are not well defined (7). Skeletal abnormalities in XLH, as osteomalacia, enthesopathy, and periosteal hyperostosis, are age related and clinically encountered along sites of muscular attachment (8). Since bone spur formation at entheses (enthesophytes) can occur as an adaptive tissue reaction to mechanical stress (9), bony malformations in osteomalacia may theoretically result from decreased physical resistance to entheseal stresses. Regarding BMD, tibial bone mass in children and adults is increased with greater muscle force, suggesting the pathway of myofascial stress stimulating bone development (10). Younger adult AS patients were reported to have greater resting (passive) lumbar extensor myofascial stiffness than normal volunteers (11).

Idiopathic hypoparathyroidism (iHPoPT) is a rare disease associated with other endocrine dysfunction and musculoskeletal manifestations (1, 2, 12). In 1939, six new cases of iHPoPT were reported with review of eight previous patients (13). This disorder was defined as having neuromuscular manifestations of stiffness, cramps, and rigidity of extremities or whole body (13). The proposed criteria for iHPoPT included: *low* serum calcium; *high* serum inorganic phosphate; chronic tetany, and absence of other explanatory causative conditions for the serum abnormalities (13). In 1952, a new case of iHPoPT and detailed review of the total previous literature yielded 52 patients, none having a possibility of post-operative hypoparathyroidism (14). Rheumatic involvements of iHPoPT are currently recognised to include muscle cramps and myopathies, increased neuromuscular irritability, paraspinal ligamentous and entheseal ossifications, subcutaneous and ectopic calcification, and ankylosing spondylitis-like back disease (1-3, 12, 15).

The primary objective of this critical narrative case review is to describe the clinical-radiographic consistency of reported iHPoPT/SpA cases. The secondary aim is to differentiate its "*neuromuscular hypercontractility*" mechanistic feature (1, 2, 13, 15) from the previously proposed "*innate resting (passive) axial myofascial hypertonicity*" in AS (11,16).

Since 1953, 14 symptomatic cases of iHPoPT were reported to show radiographic syndesmophyte and enthesophyte lesions associated with a clinical axial spondyloarthritis phenotype (iHPoPT/SpA) (17-30). Unlike AS, iHPoPT/SpA cases do not have the typical structural sacroiliac joint (SIJ) plain radiographic lesions of erosions or bony bridging nor its high frequency of HLA-B27 positivity (1-3, 12). No mechanistic pathway has been offered to explain the similarity and differentiation of iHPoPT/SpA and AS. Further study of parathyroid disorders (1, 2, 4, 5) and hypophosphataemic syndromes (6-8) promise to clarify respective structural stresses, strains, microinjury, and repair processes in relation to the axial iHPoPT/SpA phenotype.

Methods

This critical literature review searched PubMed and Embase databases, Medline via Ovid, the Cochrane Database of Systematic Reviews, and the Central Registry of Controlled Trials by a medical reference librarian with input from the principal investigator. The key words searched without time limits were: "hypoparathyroidism"; "spondyloarthropathy" or "spondylarthritis" or "spondylitis", or "ankylosing spondylitis." The search process was initially performed on 03-28-19 and repeated on 04-28-20, yielding an additional report of post-thyroidectomy hypoparathyroidism, not eligible in this review. For greater consistency among reported case subjects, summarised articles included only those describing iHPoPT. Unless titles also included the keywords SpA or AS, the review did not include reports of diffuse idiopathic skeletal hyperostosis (DISH) or ossification of the posterior longitudinal ligament (OPLL). Cited references of retrieved articles were searched for additional case reports (Table I). The lead author determined that accepted cases were documented as primary or idiopathic hypoparathyroidism and not including pseudohypoparathyroidism (2,4, 12). Data were summarised into pre-defined tables by the lead author.

Diagnostic features at presentation of accepted cases (17-30) are summarised (Table I). Cases qualified for serum hypocalcaemia level below 8.0 mg/dl or 2.0–2.12 mmol/L (21 reported 2.2) and serum hyperphosphataemia above 4.5 mg/dl (20 reported 4.3) or 1.46 mmol/L (2, 12). Only the initial accepted case report in 1953 (17) was longitudinal in the sense of a follow-up after a 13-year earlier report in 1940 (31). The majority of iHPoPT/SpA cases had documentation of hypocalcaemia only at presentation (Table I), although a number had earlier neuromotor manifestations of hypoparathyroidism. Each case report was reviewed for authors' diagnoses (Table I). Each of the 14 reported iHPoPT/SpA cases (17-30) was evaluated in terms of quality of a case report (32) and CARE guidelines (33) independently by both co-authors. Individual scores and CARE checklist assessments can be provided on request. Demographic, clinical, and radiographic findings at presentation (Table II) were compared to large series of AS patients from the German and Austrian ankylosing spondylitis societies (34) and the National Registry of Spondyloarthritis of the Spanish Society of Rheumatology (REGISPONSER database) (35, 36). The comparator AS cohorts (34-36) were selected because of their large size, national sampling, and recognition in the literature. Statistical probability of differences in binomial frequencies of attributes in iHPoPT/SpA cases *versus* comparison series was determined by Fisher's exact test calculator <https://www.langsrud.com/fisher.htm> and by t-test of mean (SD) of continuous variables in case subgroups <https://www.medcalc.org/calc/comparison_of_means.php>.

Table I. Diagnostic features at presentation of spondyloarthritis in cases associated with idiopathic hypoparathyroidism, 1953-2016*

Reference no., First author, Year reported	Age and sex	Duration of low Ca^{2+} (years)	Tests at presentation			Authors' diagnoses	Prior cases cited
			Low Ca^{2+}	High P	Low PT		
17, Salvesen, '53	57 M	9	5.4 mg/dL	5.7 mg/dL	ND	Ossification	Earlier adm
18, Gibberd, '65	29 F	present	7.4 mg/dL	5.8 mg/dL	ND	Abn bone	(17)
19, Chaykin, '69	59 M	present	6.6 mg/dL	6.4 mg/dL	ND	SpA	(17,18)
20, Adams, '77	62 M	2	5.9 mg/dL	WNLs	Und	Ossification	(17-19)
21, Korkmaz, '05	45 M	7	2.2 mmol/L	4.6 mmol/L	<1.2pg/mL	AS-mimic	(19, 20)
22, Sivrioglu, '06	48 M	present	4.9 mg/dL	7.1 mg/dL	6.4 mg/dL	SpA	(19, 21)
23, Goswami, '08	48 M	16	Low	High	Low	SpA	(17-22)
24, Fredj, '10	53 M	present	1.1 mmol/L	2.2 mmol/dL	5 pg/mL	AS-mimic	(Cited AS)
25, Gedik, '10	58 M	present	5.4 mg/dL	6 mg/dL	<3 pg/mL	AS-mimic	(Abstract)
26, Ibn Yacoub, '11	48 M	present	5.2 mg/dL	8.5 mg/dL	3 pg/mL	AS-like	(18-21, 23)
27, Kajitani, '11	40 M	present	4.0 mg/dL	5.3 mg/dL	Und	AS-mimic	(21, 23, 26)
28, Jakkani, '11	48 F	26	7.3 mg/dL	6.2 mg/dL	<1.0 pg/mL	SpA	(19, 21, 23)
29, John, '16	30 M	8	2.4 mg/dL	5.7 mg/dL	2.5 pg/mL	X-ray SpA	(23, 28)
30, Memetoglu, '16	58 F	present	5.3 mg/dL	6.3 mg/dL	4.7 pg/mL	AS-mimic	(19-21, 23)

*The case of Salveson (1953) was previously described as Earlier adm (Earlier admission) by Kobro M. Nord med. 1940; 8: 2256; the case of Chakin (1969) was republished by Jiminea CV *et al*. (1971); Memetoglu '16 is Illeez Memetoglu; Duration of low Ca^{2+} (years) is the interval from initial testing and detection or diagnosis of hypoparathyroidism to case present (presentation); SpA (spondyloarthritis or spondyloarthropathy); Goswami (2008) indicated abnormal test values (mg/dL units) for hypoparathyroidism, but did not specify individual patient results and the data extracted from his Table I describes results of his 3rd index case who had SIJ grade 4, plus HLA-B27 (Pos); Yacoub (2011) claimed to report the first case of ankylosing spondylitis (AS) and idiopathic hypoparathyroidism plus Myo (myopathy), although citing Goswami (2008); low parathormone (PTH) is <10 pg/mL or Und (undetected); WNL (within normal limits), Abn (Abnormal) bone (enthesopathic calcification); DX (diagnosis); ossification (increased new bone formation of spine, pelvis, or hips), ND (not done). In column, Cited Prior Cases, (Cited AS) refers to a text statement, but no reference, and Abstract contained no references.

Table II. Main musculoskeletal features at presentation and diagnosis of reported cases of spondyloarthritis in idiopathic hypoparathyroidism*

Ref. no.	Main Musculoskeletal Symptoms at			Radiographic Syndesmophytes & Enthesophytes			
	Presentation and diagnosis	Dur. years	Onset age	Axial	Other	AS-like Posture	ESR (mm/h)
17	Stiffness of back and hips	16	41	T, L, P	hips	NS	29
18	LOM of back and legs	8	21	L, P	hips	Neg	ND
19	Pain, LOM neck, back, hips	9	50	C, T, L, P	Shs, hips	Pos	30
20	Pain neck, low back, hips, elb	22	40	C, L, P	hips	NS	50
21	Pain, LOM neck, back, hips	23	22	C, T, L, P	NS	Pos	38
22	Chronic low back pain	NS	NS	P	Strn, hips	Pos	36
23	Not specified (case in Table)	NS	NS	T, L	hips	Pos	55
24	Spinal pain, LOM neck, hips	14	39	C, L, P	hips	Pos	5
25	LOM spine, AS-like posture	NS	NS	T, L	NS	Pos	ND
26	Lumbar pain, LOM, stiffness	14	34	T, L	hips	Pos	66
27	Pain, stiffness of neck, back	15	25	C, T, L	hips	Pos	31
28	Neck and back stiffness	8	40	C, T, L	hips	NS	ND
29	Pain, spasm, LOM of hips	8	22	T, P	hips	Pos	ND
30	Pain in neck, dorsal, lumbar	35	23	C, T, L, P	Shs, hips	Pos	42

*Dur. Years: duration in years; LOM: limitation of motion; elb: elbows; LBP: low back pain; C: cervical; T: thoracic; L: lumbar or low back; P: pelvis; Shs: shoulders; Strn: sternum; AS-like posture, Pos: positive, Neg: negative, or NS: not specified by authors' description or photo; ESR (mm/h): erythrocyte sedimentation rate by mm/hour.

Results

The typical sacroiliac joint (SIJ) structural lesions in AS of erosions, bony bridging or fusion were reported in only one case (23), and another case (26) had only joint space narrowing and subchondral sclerosis. The latter cases (23,26) were the only HLA-B27 positive patients among the total 10 tested, *i.e*. 20%. The low HLA-B27 positivity is highly (p<0.001) significantly less than 90% positive in 945 German AS patients who knew their HLA-B27 status (34) and 84%in 782 Spanish AS patients who had known testing (35).

The iHPoPT/SpA cases presented mainly in middle ages with range of 29–62 years and mean (SD) of 48.8 (10.3) years (Tables I, III). The male predominance (79%) in the 14 cases (11M, 3F, Table I) did not differ (p=0.163) from 194 iHPoPT subjects in a large reported Japanese cohort with 112 males (58%) and 82 females (42%) (37). The male predominance is also similar to 64% in 943 AS patients of the German and Austrian Societies (34) and 76% in the 842 AS patients from the Spanish National Registry (35). Authors' diagnoses in the titles of case reports revealed: AS-mimic or AS-like (n=6); spondylitis/spondyloarthropathy (n=5), and abnormal bone or ossification (n=3) (Table I). All but 2 reports (24,25) cited one or more previous cases, reflecting a general consistency of the clinical reports.

The main presenting musculoskeletal manifestations are consistent symptoms of pain, stiffness, and limitation of mo-

tion (LOM) affecting the neck, back, and hips in the 13 iHPoPT/SpA cases (excluding 23) with specified data (Table II). The mean (SD) duration of musculoskeletal manifestations at presentation and diagnosis was 15.6 (7.9) years (range 8-35 years) in 11 specified cases (Tables II, III). In the total 14 iHPoPT/SpA cases, 54 radiographic syndesmophyte and enthesophyte lesions were reported involved: 30 syndesmophyte (7 cervical, 10 thoracic, 13 lumbar), 9 pelvic, and 15 other enthesophyte lesions (2 shoulders, 1 sternal, 12 hips) (Table II). Postural abnormalities simulating AS of thoracic kyphosis (n=2), diminished lordosis (n=1), or both (n=7) were described or documented in photos in 10 (91%) of 11 cases having such specification (Table II). Short term hypocalcaemia therapy improved musculoskeletal symptoms in 7 (78%) of 9 cases specified (not 18 or 29), but posture was not improved in any of the 4 cases specified (19, 21, 29, 30). Erythrocyte sedimentation rate (ESR) was reported at presentation in 10 iHPoPT/SpA cases with a range of 5 to 66 mm/h (Table II). The mean (SD) age at diagnosis and presentation of 14 iHPoPT/SpA cases [48.8 (10.3)] is highly (p<0.001) significantly greater than the early reported 52 iHPoPT patients [24.3 (15.1)] (14) (Table III). However, the age at presentation did not differ (p=0.270) from 197 reported iHPoPT subjects in a more recent Japanese national survey [39.3 (20.2)] (37) (Table III). The iHPoPT/SpA mean (SD) age at diagnosis [48.8 (10.3)] is highly (p<0.001) significantly greater than the 943 German AS patients [33.8 (9.5)] (34) and 842 Spanish AS patients [34.0 (11.3)] (35) (Table III). Analogously, the mean (SD) onset age of 11 iHPoPT/SpA cases [32.5 (9.7)] is greater than 943 German AS patients [25.1 (8.5), (p=0.004)] (34) and 842 Spanish AS patients [26.1 (9.7), (p=0.030)] (35) (Table III). Mean (SD) years of delay between onset of musculoskeletal symptoms and presentation/diagnosis of iHPoPT/SpA cases [15.6 (7.9)] is significantly (p<0.001) greater than delay in diagnosis in the early reported 52 hypoparathyroid patients [6.7 (6.5)] (14) and in the German AS [8.7 (7.6), p=0.004] (34) and Spanish AS [8.0 (9.0), (p=0.006] (35) cohorts (Table III). No data on *onset* of iHPoPT or delay in diagnosis was available in the Japanese national survey cohort (37).

Presentation with neck involvement in 8 (62%) of 13 specified iHPoPT/SpA cases is highly (p<0.001) significantly greater than 128 (10%) of the total 1257 Spanish AS patients or even 10 (23%) in the 44 late-onset patients (p=0.015) (36) (Table IV). Hip pain or LOM is highly (p<0.001) significantly greater in iHPoPT/SpA cases (85%) than in the total 1257 Spanish AS patients (22%), the 1213 younger-onset (22%) or 44 older-onset (18%) AS patients (36) (Table IV).

The mean (SD) ESR of 10 specified iHPoPT/SpA cases [38.2 (16.7)] was greater (p<0.010) than clinical series of 42 Spanish AS patients [20.8 (16.7)] (38) and 20 Turkish AS patients [16.3 (20.7)] (39) (Table V). However, the mean (SD) age at ESR testing of 10 iHPoPT/SpA patients [51.8 (7.1)] was greater (p<0.010) than both the total 42 Spanish patients [40.0 (12.0)] (38) and the 20 Turkish patients [40.0 (10.0)] (39) (Table V). The mean (SD) disease duration at ESR testing of the 8 iHPoPT/SpA patients [18.5 (8.0)] was similar (p=0.561) to the total Spanish series [16.0 (11.0)] (38), but greater (p=0.009) than the total Turkish series [8 (range 1–36 years)] (39) (Table V). The mean (SD) ESR of the 10 iHPoPT/SpA cases [38.2 (16.7)] was similar to 21 *active* Spanish AS patients by physician assessment [30.6 (22.1), p=0.344] (38) and the 6 *active* Turkish AS patients [37.7 (26.1), p=0.963] (39) (Table V).

Table III. Ages at diagnosis and onset and years of diagnosis delay of spondyloarthritis cases in idiopathic hypoparathyroidism *vs*. patients with idiopathic hypoparathyroidism and series of ankylosing spondylitis.

Spondyloarthritis in idiopathic hypoparathyroidism (iHPoPT/SpA)				
	Diagnosis age (n=14) Mean (SD)	Onset age (n=11) Mean (SD)	Diagnosis delay (n=11) Mean (SD)	
	48.8 (10.3)	32.5 (9.7)	15.6 (7.9)	
Idiopathic hypoparathyroidism (iHPoPT)				
	Diagnosis age Mean (SD)	Onset age Mean (SD)	Diagnosis delay Mean (SD)	*p* difference (from iHPoPT/SpA)
Steinberg *et al*., (14) (n=52)	24.3 (15.1)	17.4 (15.8)	6.7 (6.5)	Diagnosis: p<0.001 Onset: p=0.004 Delay: p<0.001
Nakamura *et al*., (37) (n=197)	Reported Mean (SD) 39.3 (20.2)			Reported (*vs*. onset iHPoPT/SpA) p=0.270
National series of ankylosing spondylitis				
	Diagnosis age Mean (SD)	Onset age Mean (SD).	Diagnosis delay Mean (SD)	*p* difference (from iHPoPT/SpA)
German, (34) (n=943)	33.8 (9.5)	25.1 (8.5)	8.7 (7.6)	Diagnosis: p<0.001 Onset: p=0.004 Delay: p=0.004
Spanish, (35) (n= 842)	34.0 (11.3)	26.1 (9.7)	8.0 (9.0)	Diagnosis: p<0.001 Onset: p=0.030 Delay: p=0.006

Discussion

Axial SpA is a unifying clinical term for chronic inflammatory spinal disorders (3, 40). It includes AS, or a *radiographic* subgroup diagnosed by plain x-ray with structural lesions of erosions and bony bridging in SIJs.

Table IV. Presenting musculoskeletal manifestations by regional localisations in idiopathic hypoparathyroid spondyloarthritis cases compared to ankylosing spondylitis from the Spanish National Registry by all ages and early- *vs*. late-onset disease.*

Presenting regional manifestations	iHPoPT/SpA manifestations n=13 (%)	Spanish AS patients by onset age		
		All ages n=1257 (%)	<50 yrs n=1213 (%)	50+ yrs n=44 (%)
Neck:				
Pain	5 (38)			
LOM or Stiffness	8 (62)			
Either involvement	8 (62)†	128 (10)	118 (10)	10 (23)
Shoulders:				
Pain	1 (8)			
LOM or Stiffness	1 (8)			
Either involvement	1 (8)	176 (14)	166 (14)	10 (23)
Back or lumbar:				
Pain	8 (62)			
LOM or Stiffness	11 (85)			
Either involvement	12 (92)	896 (71)	870 (72)	26 (59)
Hips:				
Pain	6 (46)			
LOM or Stiffness	10 (77)			
Either involvement	11 (85)‡	275 (22)	267 (22)	8 (18)
Pelvis:				
Pain	**3 (23)**			
LOM or Stiffness	**3 (23)**			
Either involvement	**3 (23)**			

* Ref. no. 36.
†Greater neck involvement of iHPoPT/SpA than in either total or early-onset AS (p<0.001) and also older onset AS (p=0.015).
‡Greater hip involvement of iHPoPT/SpA than total or either early- or late-onset AS (p<0.001).

Table V. Mean (SD) erythrocyte sedimentation rate (ESR) of idiopathic hypoparathyroid spondyloarthritis (iHPoPT/SpA) cases compared to clinical series of ankylosing spondylitis patients.

ESR level, age at testing, and duration of symptomatic iHPoPT/SpA					
	ESR level (n=10) Mean (SD)	Age (n=10) Mean (SD)	Duration (n=8) Mean (SD)		
	38.2 (16.7)	51.8 (7.1)	18.5 (8.0)		
ESR level in ankylosing spondylitis					
	Total AS Mean (SD)	Active AS Mean (SD).	Inactive AS Mean (SD)	***p*** difference (from the total 10 iHPoPT/SpA)	
Muñoz-Villanueva MC, (38)†	20.8 (16.7) (n=42)	30.6 (22.1) (n=21)	11.0 (11.2) (n=21)	Total: Active: Inactive:	p=0.015 p=0.495 p<0.001
Ugur M *et al*., (39)‡	16.3 (20.7) (n= 20)	37.7 (26.1) (n=6)	7.1 (5.2) (n=14)	Total: Active: Inactive:	p=0.017 p=0.495 p<0.001

† Total 42 patients: mean (SD) age 40 (12) years at ESR testing; disease duration 16 (11) years, and 36 (86%) HLA-B27+.
‡ Total 20 patients: mean (SD) age 40 (10) years at ESR testing; disease duration 8 years (range 1-36 years), and 18 (90%) HLA-B27+.

A counterpart *non-radiographic* axial SpA includes patients where sacroiliitis is evident only on magnetic resonance imaging (MRI) (3, 40). Axial SpA is characterised pathologically by new bone formation at entheses of the spine and hip joints to a lesser extent (40, 41). Inflammation is the main suspected key driver of SpA at entheses causing new bone formation in the repair process and occurrence of syndesmophytes and enthesophytes (40, 42, 43). Less is known about the potential role of biomechanical stress contributing to molecular mechanisms of inflammation and new bone formation (16, 41, 44-47).

A classification criteria study of predominantly axial SpA was performed by Assessment of SpondyloArthritis International Society (ASAS) members among patients with chronic back pain for greater than 3 months of unknown origin that began before 45 years of age on first presentation (48). Axial SpA could be classified by satisfying either the "imaging arm" for presence of sacroiliitis [definite plain radiographic or active inflammation on magnetic resonance imaging (MRI)] or the "clinical arm" for presence of HLA-B27. Among 14 iHPoPT/SpA cases, only 1 (23) satisfied imaging and clinical arm criteria for ASAS classification of axial SpA and another (26) was HLA-B27 positive. The remaining 12 iHPoPT/SpA cases do not qualify for ASAS classification of axial SpA (48) and may be considered a separate clinical phenotype of axial SpA. Almost all iHPoPT/SpA cases had negative plain radiographic evidence for sacroiliitis, but only 3 (22, 24, 27) had MRI or scan, all negative for SIJ inflammation.

Ten iHPoPT/SpA cases had higher mean ESR than total or inactive AS patients, but equivalent to those considered clinically active in two cohorts (38, 39) (Table V). A study of 184 AS patients from the Outcome in AS International Study (OASIS) followed for 12 years showed that measures of disease activity, particularly the AS disease activity index (ASDAS), contributed longitudinally to predicting radiographic progression in the spine in AS, more prominently in men and in earlier phases of disease (49). Regard-

ing anti-inflammatory therapy, comparative studies performed for over a decade have not definitely determined that TNF inhibitor (TNFi) therapy over 2 years can inhibit bone proliferation or progression of spinal structural damage in AS patients (50). Such results (50) enhance the present study focusing on biomechanical influences which may precede micro-injury and inflammatory markers not addressed in the preceding TNFi studies (50) and deserve future critical attention.

In a systematic review of SpA which analysed plain radiography or ultrasound (US) techniques (none with MRI), a greater BMI was considered a biomechanical factor which may trigger an inflammatory process and new bone formation in healing at those sites (51). Biomechanical factors may also be a main contributor to entheseal changes of lower extremities in normal adults (52). In a study of 80 healthy adults, the prevalence of ultrasound (US) enthesitis lesions defined by the OMERACT group (53) increased with age, body mass index (BMI), and high physical activity (54). Stratification of subjects <50 years (n=48) *versus* 50+ (n=27) years of age revealed significant correlations of BMI with inflammation (p=0.001), damage (p=0.02) and total (p=0.001) scores in older, but not younger subjects (55). High physical activity correlated with total US scores in younger (p=0.03) and older (p=0.04) subgroups (55).

Idiopathic hypoparathyroidism is a rare disease with estimated period prevalence of 7.2 per million in Japan in 1997 (37) and 22 per million in Olmsted County, MN from 1945–2009 (56). In 544 Korean AS patients screened for cervical radiographs, 19 (3.5%) had ossification of the posterior longitudinal ligament (OPLL) (57). Patients with OPLL had significantly (p=0.007) older mean (SD) age at survey [39.9 (10.7)] than the remaining 525 patients without OPLL [34.1 (9.2)], but similar disease duration [13.3 (7.8) *vs*. 12.4 (7.2), respectively] (57). Diffuse idiopathic skeletal hyperostosis (DISH) is another disorder with ossification of spinal entheses, in which men particularly and older individuals have a higher probability of development (58). Increased BMD, most notable at the lumbar spine, was found in a small cross-sectional study of hypoparathyroid patients with either iHPoPT or post-thyroidectomy and attributed to optimised bone mineralisation (59). The influence of aging and maleness will require further study in iHPoPT/SpA.

The SpA in iHPoPT may be a "natural experiment" (60) which allows probing if chronic axial neuromuscular hyperirritability and hyper-contractility contributes to syndesmophyte and enthesophyte lesions of the spine and pelvis. A 2018 review of axial SpA (61) stressed that the new technique of low dose CT is a major step forward in assessing syndesmophyte score and new bone formation, which may be applied in future to comparison of iHPoPT/SpA and AS. Reports of iHPoPT consistently support hypocalcaemia causing increased neuronal and muscular excitability and stiffness (1, 2, 12, 62-64), which may plausibly contribute to development of associated SpA in susceptible persons. The pattern of syndesmophytes in iHPoPT/SpA are described to originate from the vertebral margin with preserved disc space and can resemble AS (65). A simple chance association of SpA with iHPoPT seems unlikely, because the latter is itself rare (37, 56) and the case reports (17-30) show consistency and homogeneity supporting a distinctive SpA phenotype (Tables I, II).

Since the first accepted case report of SpA and iHPoPT (17, 31), increased neuromuscular hyperirritability was attributed to hypocalcaemia of idiopathic hypoparathyroidism. The 1965 case report of iHPoPT/SpA by Gibberd (18) was the first to attribute enthesopathic calcifications and increased skeletal bone density to hypoparathyroidism. This interpretation was reiterated by almost all subsequent authors of iHPoPT/SpA case reports. The 2008 report of Goswami (23) was the most emphatic in implicating the role of hypoparathyroidism, and even providing data on its duration having contributed significantly to the co-occurrence of SpA. Illeez Memetoglu *et al*. 2016 (30) indicated, "Hypocalcaemia, the ultimate result of IH (idiopathic hypoparathyroidism) may be the causative factor in the skeletal and ligamentous changes resembling AS." However, no iHPoPT/SpA case report inferred a *sequential* causality of hypocalcaemia from iHPoPT causing neuromuscular irritability and hypercontractility, thereby contributing to micro-injury and skeletal enthesopathic lesions, which is the proposed mechanism in this review.

An earlier proposed biomechanical concept of AS (11, 16) was extended to illustrate how hypocalcaemia in iHPoPT increases axial neuromuscular irritability and hypercontractility and differs from AS (Fig. 1). The hypercontractility in iHPoPT is differentiated from innate resting (passive) axial myofascial hypertonicity proposed in AS (11, 16). The SIJs are not entheses, but cartilaginous joints which primarily support the vertical load of the spine and trunk (66). The proposed mechanistic concept (Fig. 1) needs further documentation for its support, *e.g*. a "dose-response" relation of chronic hypocalcaemic axial neuromuscular hypercontractility in iHPoPT leading to development of SpA (23). Longitudinal analysis of separate iHPoPT patients can be critically analysed to determine if the degree and duration of hypocalcaemia was sufficient for the development of associated SpA imaging lesions. Such an example is a 37-year-old male with a 4-year history of intermittent seizures, confirmed hypocalcaemia, and primary hypoparathyroidism reported to clinically mimic AS (67). Over a 4-year interval, he was treated with calcium and vitamin D supplement, but had a significant history of inflammatory lower back pain. After 4 years, no definite syndesmophytes or ossification of spinal ligaments were found on x-ray and SIJs were unremarkable. This 37-year-old iHPoPT patient with calcium and vitamin D treatment over 4 years may be considered an example of *low* dose hypocalcaemia exposure or a *forme fruste* outcome of iHPoPT/SpA (67). Another unusual case report of documented iHPoPT presenting with a clinical picture of AS, but no x-ray evidence for this, is an 81-year-old male reported in 1979 by Schen (68). All clinical manifestations of AS disappeared after first treatment of hypocalcaemia (68). The author (68)

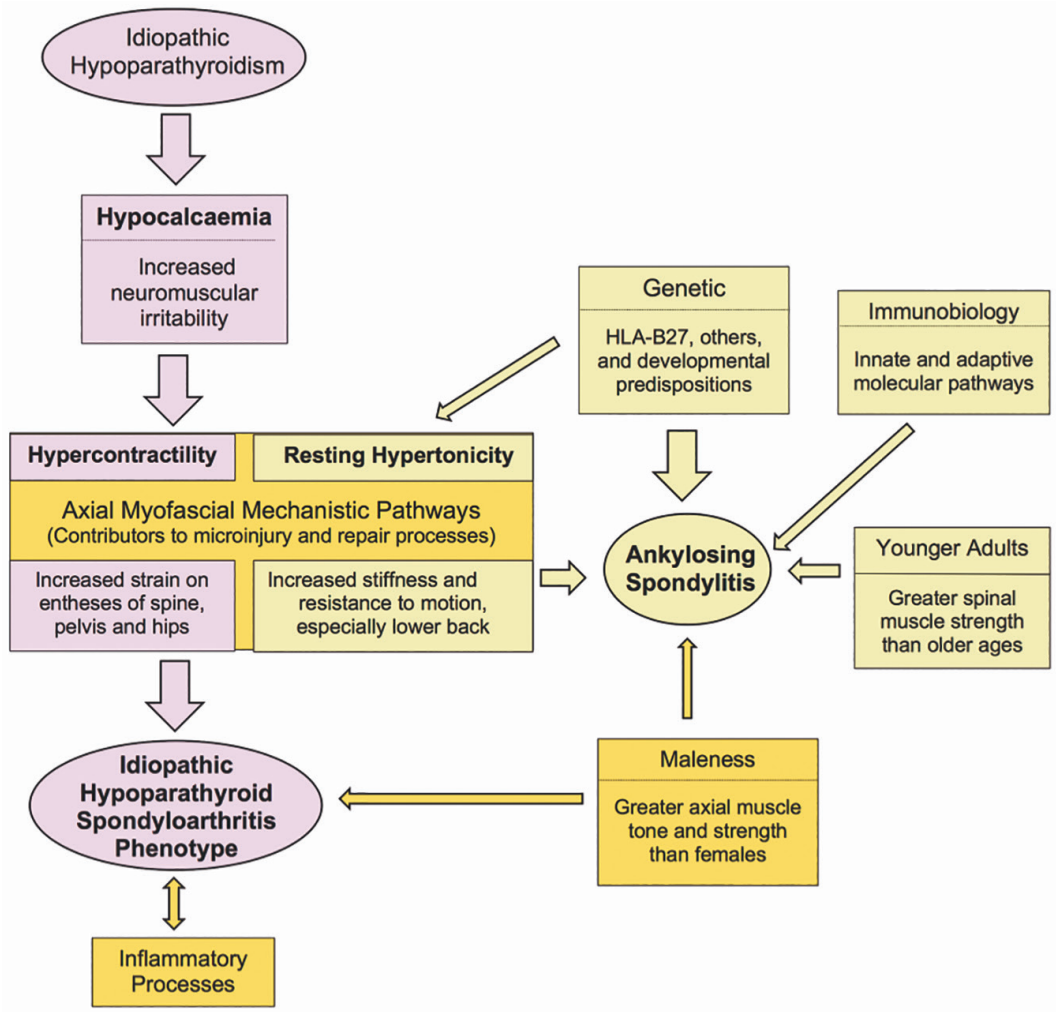

Fig. 1. Proposed pathways of axial spondyloarthritis in idiopathic hypoparathyroidism (active, pink) *vs*. ankylosing spondylitis (resting, yellow) and common demography and mechanobiology factors (orange).

cited 2 previously reported cases in this review (19, 20) as being different from his patient. The duration and degree of hypocalcaemia is an essential determinant for future research in the co-occurrence of iHPoPT and SpA.

A limitation of this review is restriction only to cross-sectional case reports of individual patients with short-term follow-up after iHPoPT/SpA diagnosis and treatment of hypocalcaemia (17-31). Selection bias cannot be excluded in the reporting of age, gender, or duration of SpA manifestations in the analysed cases (Tables I, II). Additional iHPoPT/SpA cases may be available in the literature or textbooks which were not retrieved in our comprehensive search of five databases. Unrecognised potential confounders may not allow generalisability of the findings. Comparison of the iHPoPT/SpA cases was made with two national series of AS patients (34-36) and results may differ with other cohorts or with series of axial spondyloarthritis patients. This literature review is also limited in its ability to determine if a causative sequential relation occurs between iHPoPT and SpA *versus* a coincidental or statistical association.

Randomised clinical trials (RCTs) are often classified as "high quality" evidence regarding efficacy of new treatments for patients with a specific disease, whereas case reports and other observational data are considered as hypothesis generators with *initially* classified lower grade of evidence (69-72). However, an increasing argument is being made in defense of case reports and its restoration as a prominent and useful medical reporting strategy (73). Methods to improve the validity of results from aggregation of single cases are increasingly needed, including estimation of an effect size and generalisability of the data (73). The strength of evidence (SOE) and quality of an observational study may be increased by additional strong evidence of association, consistency and homogeneity of the data, and evidence of a dose response gradient (74, 75).

A strength of this critical analysis includes not detecting bias in case reports regarding descriptions of muscular spasticity or skeletal enthesopathy lesions (Tables I, II). All analysed cases had sufficient data to qualify for a confirmed iHPoPT diagnosis. Only *symptomatic* SpA patients with radiographic documentation of syndesmophytes or axial enthesophytes associated with iHPoPT were included in the review for greater consistency and comparability of the case subjects. Cases had comparable SpA manifestations of pain, stiffness or LOM of the neck, back, or hips (Table II) and all but 2 reports (24, 25) had cited preceding cases of iHPoPT/SpA, reflecting consistency (Table I).

Also, t-test comparison of the continuous variables (Tables I, II) between earlier *versus* later cases was performed to assess consistency. Mean (SD) age at presentation and diagnosis (Table I) was closely similar between the 7 earlier [49.7 (11.2)] and 7 later [47.9 (10.1)] reported cases (p=0.750). Mean (SD) serum Ca (mg/dL) was similar in the earlier [6.3 (1.4)] and later [4.8 (1.6)] cases (p=0.097), as was serum P (mg/dL) of [7.1 (3.3)] and [6.4 (1.0)], respectively (p=0.578) (Table I). Parathyroid hormone (pg/ml) was only reported in 8 cases since 2005, with similar mean (SD) levels in 4 earlier [3.9 (2.3)] and 4 later [2.8 (1.5)] reports (p=0.453). The mean (SD) number of total radiographic lesions per patient was also similar between earlier [3.9 (1.1)] and later [3.7 (1.3)] cases (p=0.822) as was ESR [36.6 (8.4)] *vs*. [39.8 (23.5)], respectively (p=0.782) (Table II). Such agreement suggests that quantitatively combining case reports may improve conclusions in the field of rare diseases (70, 73). A novel hypothesis on causation can derive from a critical review of well-documented case reports describing association of two distinct conditions, especially involving a rare disorder (32, 70).

Alamanos *et al*. (76) recently published a systematic review of incidence studies of SpA subtypes indexed in PubMed electronic database during the last 25 years (1-1-1995 to 12-31-2019). In the latter review (76), the most recent cohort study of SpA incidence (2014-2016) was by Hočevar *et al*. (77) and the only general population comparison of axial and peripheral SpA, based on ASAS criteria (48,78). Of the total 302 SpA cases, 98 (32.5%) were classified as axial *versus* 204 (67%) peripheral SpA. The axial SpA group included 57 (58.2%) AS and 31 (31.6%) undifferentiated SpA (without conventional radiographic SIJ structural changes) for a combined annual incidence rate of 4.6 cases per 100,000 persons per year. As expected, median (IQR) age was significantly (p=0.004) less in axial [39.8 (33.1–55.4)] than peripheral [49.8 (36.0–58.2)] SpA (77) and axial had significantly (p<0.001) higher HLA-B27 positivity [78/95 (82.1%)] than peripheral [82/174 (48.3%)] SpA.

A widely accepted view among axSpA experts is the chronologic transition of chronic back pain clinical manifestations, to SIJ inflammatory changes on MRI, and further radiographic structural lesions on conventional radiography (CR), as mainly preceding syndesmophyte formation (78, Fig. 1). The preceding sequence differs from current findings in the iHPoPT/SpA phenotype which has prominent syndesmophyte formation without SIJ structural lesions. The newly developed scoring method of bone formation on low dose computed tomography (LD-CT) of the whole spine is a more sensitive method for assessing the formation and growth of syndesmophytes than CR (79). Newly detected iHPoPT/SpA cases can be analysed with LD-CT and compared to axSpA patients to compare the respective degrees of syndesmophyte formation in relation to SIJ changes.

The novel translational mechanobiological proposal of innate lumbar human resting myofascial tone (HRMT) contributing to AS physiopathogenesis (Fig. 1) are supported by preceding studies (11, 16, 41, 44-47, 75). Genetic factors contribute essentially all risk to AS development and HLA-B27 strongly (circa 40-100-fold) associates with risk (44). Both HLA-B27 and AS prevalence increase with colder climates, hypothesised to be an evolutionary thermogenesis trait related to increased passive lumbar HRMT (44).

A recent physiologic, proteomic, and genetic muscle study of α-actinin-3 deficient healthy young males (n=8) *versus* normal males (n=11), as well as wild type (n=18) and knockout (n=16) mice for this trait, found that absence of protein α-actinin-3, normally expressed in fast-twitch skeletal muscle, is associated with improved thermogenesis during cold-water emersion (80). The population frequency of this deficiency trait increases with distance from Africa and is inferred to have resulted from modern humans migrating from Africa to colder climates over 50,000 years ago (80), as previously inferred for AS and HLA-B27 (44). The improved thermogenesis in α-actinin-3 deficiency during cold exposure was associated with altered neuronal muscle activation resulting in increased muscle tone rather that overt shivering (80). Whether α-actinin-3 deficient individuals also display an increased passive muscle tone (*i.e*. without neuronal activation) requires further clinical assessment, including myotonometry (11).

The concept in this review could be tested independently in a follow-up determination of SpA occurrence in the large HypoparaNet iHPoPT cohort (81) compared to a population and disease control. This large-scale national database of chronic hypoparathyroidism is derived from expert medical-surgical centres in Italy and includes 61 adult iHPoPT, 352 post-surgical and 37 genetic and other forms (81). Association and development of SpA could be a future research objective of this project (81). Such further SpA outcome studies can incorporate newly standardised myotonometry (11) or shear wave elastography (82) techniques to measure axial myofascial stiffness. Future longitudinal study of adult iHPoPT and other parathyroid disorders is needed to determine an objective dose-response effect of degree and duration of hypocalcaemia interacting with age and sex in the development of SpA. As important new quality evidence becomes available (83), the proposed hypothesis can be reconsidered and appropriately revised.

Conclusions

The rare iHPoPT/SpA phenotype presents mainly in middle-aged males as widespread axial pain and LOM, particularly in cervical, lumbar, and hip regions. Its radiographic syndesmophyte and enthesophyte lesions simulate AS. The mean ESR was similar to 2 cohorts of active AS patients by physician assessment. The iHPoPT/SpA cases differ from AS by a paucity of structural SIJ lesions of erosions and bony bridging and infrequent HLA-B27 positivity. Its hypocalcaemic axial neuromuscular hyperirritability and hypercontractility are differentiated from a previously proposed resting (passive) innate axial muscular hypertonicity and increased stiffness in AS. The iHPoPT/SpA cases suggest that biomechanical factors are the predominant mechanism in its physiopathogenesis.

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