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Gorham Stout Disease- A Rare Disorder with Ambiguous Recommendations: A Systematic Review of literature

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Abstract

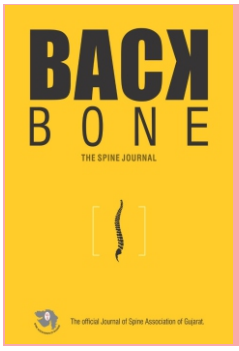
Background: Vanishing bone disease/Gorham-Stout disease (GSD) is a condition that produces deformity and instability of bone. The fibro lympho-vascular tissue replaces the bone leading to massive osteolysis and its sequelae, but the exact cause is yet unknown. The disease involves the spine infrequently, but due to the proximity of the spinal cord it can seriously affect the patient. The aim of this study is to report as a review to contribute to the diagnosis, and treatment modalities in GSD affection of spine with the reported literature available from 1983 till March 2022.

Materials & Method: This metanalysis study is focused on GSD involving the spine. The search was done in two databases PubMed and Google scholar from 1983 up to March 2022. The Study selection was done to study the demographic pattern of GSD in spine and its outcome with conservative and surgical treatment and to determine the best suitable medical treatment for stopping disease progression and achieving remission.

Results: We retrieved 72 articles from Google scholar and PubMed out of which 5 articles were excluded (90 reported cases). Heffez criteria was followed for diagnosis in all these cases (n= 86, 95.5%). 57 patients (64%) were operated and 33 patients (36%) were managed conservatively. Per-operative failure to achieve a fixation/reconstruction were reported in 2(2.53%) cases. Number of surgeries till follow-up were average 170±1.23 (1-5) surgeries. The average follow-up of cases reported was 47.1±48.9 (3-240 months). Union was documented in 10 cases (3.4%). 9 of these cases needed additional bone graft/substitute. Bisphosphonates(n= 40), sirolimus (n= 5), interferon (n= 17), radiotherapy (n= 31) and beta-blockers (n= 4) were given in medications. 23 patients had remission. Death occurred in 17 patients (18.88%).

Conclusion: Surgery is needed frequently. Failure of fixations, achieving union and remission are daunting and "offlabel" therapies are the dictum. Radiotherapy has been used more frequently with or without bisphosphonates. Though promising medical treatment are evolving and focus of treatment is directed towards anti-angiogenic, anti-osteolytic and anabolic therapy, but no standard treatment recommendations can be made out from existing literature.

Keywords: Vanishing bone disease, Gorham stout, Osteolysis, Spine, Deformity, Sirolimus, TNF



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Introduction

Vanishing bone disease is a condition that produces deformity and instability of bone, the fibro vascular tissue replaces the bone, but the exact cause behind resorption and destruction of the bone is yet unknown [1]. In the first ever case it was reported as "boneless arm". The first person to report this rare condition was Jackson in 1838. However, in 1955 Gorham and Stout published a report which correlated the massive osteolysis with hemangiomatosis, paving the way for the terminology of vanishing bone disease as Gorham-Stout

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disease (GSD) [2,3]. GSD is known by many other names such as "Phantom bone disease" and "Disappearing bone disease" [4]. Osteolysis can affect both axial & appendicular skeleton [5]. Since then, more than 300 cases of GSD has been reported worldwide[6]. There is no evidence of genetic, metabolic, malignant, neuropathic, and infectious cause [7]. This disease occurs at any age without gender or race predilection [8–10]. GSD can occur in any part of the skeleton, but more commonly in the bones of pelvic and shoulder girdles [11]. The disease also involves the spine, and due to the close proximity of the spinal cord it can seriously affect patient's final outcome [12]. Surgical treatment of GSD is difficult, especially in the spine [13]. Regeneration of the bone does not occur even after the osteolysis has stopped [14, 15]. Multiple treatment modalities for GSD are reported, such as chemotherapy, radiation therapy, bisphosphonates, calcium supplements, interferon, vitamins, calcitonin, hormones, antibiotics, antivirals, antifungals, embolization, and surgical resection, but none of them gives scientifically proven better outcomes [15–18]. The treatment strategy of GSD in spine is still not delineated and is usually complicated by failure, failed reconstruction, recurrence, re-surgery and/or death [4]. This article is a systematic review to arrive at standard recommendations for GSD, to reaffirm the importance of considering GSD as a diagnosis and guiding the proper treatment of GSD in the spine in view of the rarity of the disorder and non-standardized recommendations.

Materials & Methods

The literature was searched for all available articles of GSD involving the spine. We begin our search with two databases Google Scholar, and PubMed. The article language was set to be in English and translation wasn't done for any other language to be included. The search year was set from 1984 to March 2022. Studies that had GSD without spine involvement and non-specified conservative or surgical treatment were excluded. The data was searched to find demographic variables with management of the patients of GSD and its outcomes to define recommendations. The Demographic variables in the form of age, sex, affection of region of spine (Cervical, Thoracic, Lumbar, Sacral or/and Cervico-Thoracic Junction, Thoraco- Lumbar Junction, Lumbo-Sacral Junction), number of vertebrae involved, visceral affection and other musculoskeletal involvement were assessed. The confirmation of diagnosis was made by following Heflez criteria; 1. A positive biopsy for angiomatous tissue, 2. Absence of cellular atypia, 3. Minimal or no osteoblastic response and absence of dystrophic calcification, 4. Evidence of local progressive osseous resorption, 5. No expansile, non-ulcerative lesion, 6. Absence of visceral involvement. 7. Osteolytic radiographic pattern, 8. Negative hereditary, metabolic, neoplastic, immunologic, or infectious etiology [19]. Typical Biopsy and radiological criteria were analyzed and described to arrive at diagnosis. The surgery if performed Anterior, Posterior/Combined approach, Decompression with or without fixation (DF), number of surgeries and bone-graft substitute if used were noted. The number of surgeries was considered one if the reconstruction was done in same stage or multiple stage around same admission. The therapeutic method used for suppression and achieving remission, outcome assessment by union, stable reconstruction, progression, remission, death (and its cause if mentioned) and number of years of follow-up were analyzed. Remission was considered if the follow-up was more than 2 years and there was no progression of disease. If there was remission reported, then it was categorized as objectified (tested with MRI or Blood reports) or inferred without objective criteria followed. We also identified the article's corresponding author/institution, and he/she was contacted by email for getting current follow-up and status of all patients. The authors were not contacted if the patient died related or unrelated to the disease. The email reply was analyzed for any add-on value over the published report.

Statistics

Patient demographics and characteristic categorical variables were analyzed and the mean ± standard deviation (minimum-maximum) for all applicable variables were calculated. Non classified (NC) entries were also included in calculations. Each category was compared by using appropriate statistical tools such as IBM SPSS software ver. 20.0 (IBM Corp., Armonk, NY, USA)

Results

We retrieved 72 articles from Google scholar and PubMed out of which 5 articles were excluded. Our review achieved finally full detailed 67 articles (90 reported cases) with involvement of spine (Figure 1) (Table 1). Year wise articles published were analyzed and the average value was 3±1.86 (1-7) publication per year in our review. The average number of patients was 1 ±1.39 (1-11) in each article. The average age was 24.42±18.47 (2-77 years). The age wise affection was noted as <5 years (n= 10, 11.1 %), 5-10 years (n= 15, 16.66 %), 10-15 years (n= 18, 20%), >15years (n= 45, 50%), NC (n= 2, 2.22%). The male and female affection were 67.44% and 32.56% respectively. The vertebral affection noted in spinal regions is graphically represented individually, in combination or junctional (Figure 2). The average vertebral number affection was 5.04± 3.57 (1-17). Biopsy was done in (n= 86, 95.5%). Heffez criteria was followed for diagnosis in all these cases. 57(64%) of patients were operated and 33(36%) were managed conservatively. In the surgical group, only posterior approach was executed in 32

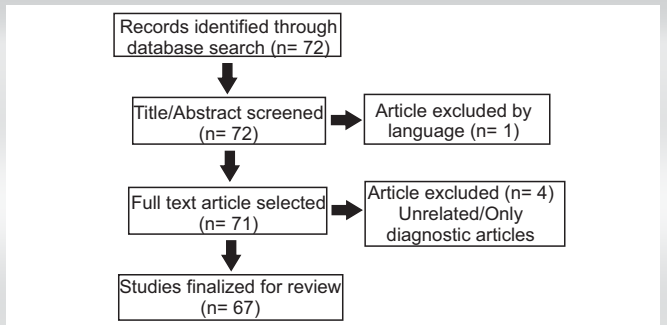

Figure 1: Flowchart of the literature search

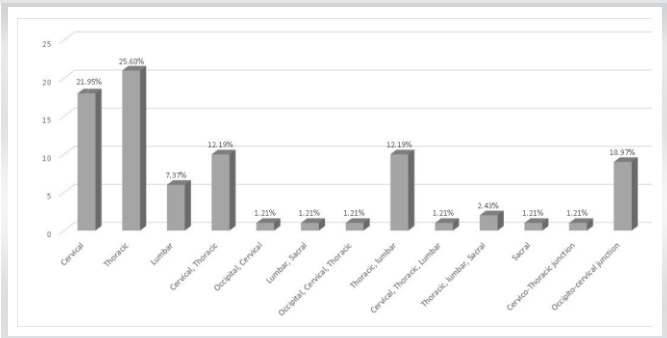

Figure 2: Bar diagram showing affection of different regions of spine alone or in combinations.

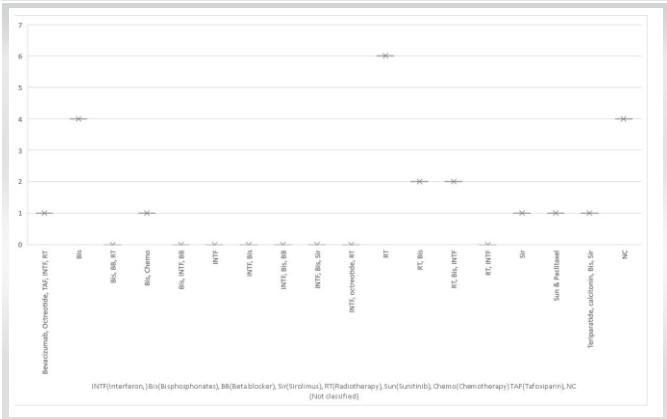

Figure 3: Histogram showing different modalities of treatment given in the 23 patients in whom remission was achieved. Medications in 4 patients were not classified.

(68.08%), anterior approach in 4 (4.4%), and combined approach was executed in 11 patients (12.22%). Decompression only was done in 4(4.4%%) Dural fistula repair has been additionally done in 1(2.2%) patient. Vertebroplasty have been solely done in n= 2 (2.53%) patients. Per-operative failure to achieve a fixation/reconstruction were reported in 2(2.53%) cases. Number of surgeries till follow-up were average 1.70±1.23 (1-5) surgeries. The average follow-up of cases reported was 47.1±48.9 (3-240 months). In follow-up stability was maintained in 35 cases. Of these patients in which stability was maintained, 8(34.78%) cases were in conservatively treated group (n= 33) and 27(47.36%) were in surgical group (n= 57).

In our review, a total of 8 patients with visceral involvement were noted. Only 1(12.5%) had remission in cases of visceral involvement in GSD (n= 8, 8.8%) in our review. Morselized local autograft was used in all the cases. Union was documented in 10 cases (9%) of total cases. 23 cases were put with other bone graft/substitute. External auto graft (n= 9), BMP (bone morphogenic protein) (n= 7), Allograft (n= 5), External Auto graft + Allograft (n= 1) and Calcium phosphate (n= 1) were used for additional facilitation of union. Of these 23 cases 8 (34.78%) documented union.

Medications were given in 67 patients out of which out of which 33 patients were treated conservatively and 34 patients were given medications before/after surgery. Bisphosphonates (n= 40), sirolimus (n= 5), interferon (n= 17), radiotherapy (n= 31) and beta-blockers (n= 4) alone or in combinations. Histogram showing different modalities of treatment given in the 23 patients who had remission with medications. In 4 patients, the given medical treatment was not classified patients. (Figure 3). Out of remitted 23 patients 15 patients were treated surgically, and 8 patients were treated conservatively. 21 patients had inferred remission and only 2 patients had objectified remission. 15 patients with non-spinal involvement had remission(16.67 %) and only 1 with visceral involvement had remission (1.11%).

Death in 17 patients (18.88%) were noted. In deaths, age wise affection was noted as ≤ 5 years (n=2, 2.22%), ≥ 5-10 years (n=6, 6.66%), ≥10-15 years (n=1, 1.11%), >15years (n=7, 7.77%), NC (n=1, 1.11%). In 3 patients' death were related with non-spinal disease. Death rate was higher in cervical regional affection (n=8/18, 44.44%), Thoracic regional affection (n= 2/21, 9.52%), lumbar (n= 0), sacral (n= 0), cervico-thoracic junction (n=1, 100%), occipito-cervical junction (n=2/9, 22.22%).

We sent email to all the correspondent authors (only for the patients whose death were not reported) to know if any of the patient required any additional surgical or conservative treatment, for the authors whose email were not found we sent a mail to the hospital and out of 67 authors we got reply from only 5 authors and status of 3 patients were updated.

Discussion

The highest number of reports were published in 2017 and 2021 with 7 reports in each year. This may be due to more aggressive treatment and standardization of care in the last decade in spine surgery. In one of the largest series of patients at a single center, Ruggieri et al have reported their experience at the Istituto Ortopedico Rizzoli comprising of 13 patients [20]. The highest number of patients reported in single study is of cervical affection (n= 11) by Du et al [21]. The exact incidence of GSD remains unknown owing to the sporadic occurrence of the disease. The reported incidence have been between 20-30 years age with more male predilection [22]. In our review the most common age was 10 years (11.36%). This contradicts

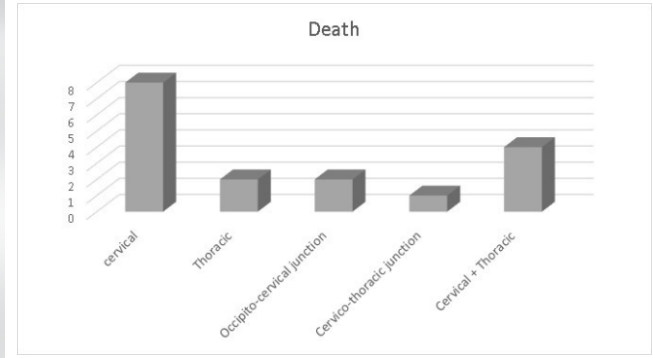

Figure 4: Bar diagram showing total number of deaths in the different affected regions of spine.

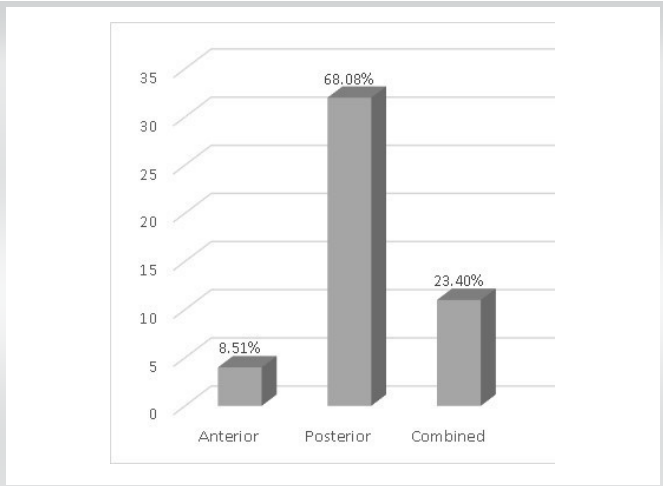

Figure 5: Bar diagram showing approaches used in surgical patients.

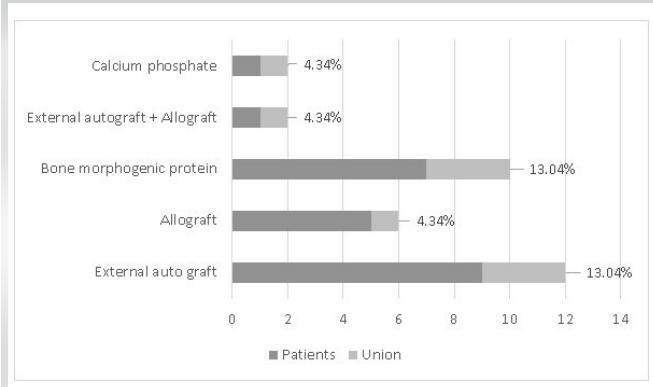

Figure 6: Stacked Bar diagram showing union achieved by additional bone graft / substitutes.

with previous reports. The gender ratio was in favor of males affection (67.4%) in the review.

The etiology of the Gorham stout disease is still unknown, it is not yet proved that whether this condition is hereditary or caused by other environmental or physiological factors [3-4, 6, 12]. Previous authors have reported that the process is cytokine driven which forms osteoclasts with high activity from monocytes and production of angiogenic factors [23–25]. The theories behind the development of the disease are related to the role of endothelial cells [6]. It has been postulated that endothelial cells of lymphatic channels secrete factors involved in osteoclastic activation and leading to bony osteolysis. The role of Osteoclasts in GSD is still unclear as some patients with GSD does not have osteoclast and some do [1, 2, 24-25]. Osteolysis is further divided into five types depending on the site involved and the genetic inheritance pattern as type I is hereditary multicentric osteolysis with dominant transmission, type II is hereditary multicentric osteolysis with recessive transmission, type III is nonhereditary multicentric osteolysis with nephropathy and type V is Winchester syndrome, defined as a monocentric disease of autosomal recessive inheritance [28]. It can be multicentric where radiological lesions can be different in different areas [5]. In another classification of international society for the study of vascular anamolies, GSD was found in simple vascular malformations, IIa-lymphatic malformation which helps in differential diagnosis [5, 29]. Monocytic cells producing osteoclastogenic factors such as factor B have been isolated in GSD patients [11, 24]. The bone that undergoes osteolysis is replaced by fibrous tissue [1]. The diagnosis of GSD is tough and demands a high-level accuracy of clinical suspicion passed through multiple diagnostic examinations. MRI, CT scan, X-ray, and bone scan are the most frequently used methods [3]. Radiology plays an important role for the diagnosis, but final confirmation should be done by biopsy to eliminate any infections, tumor, and necrosis [28-29]. The histology of GSD in spine shows irregular ecstatic vascular channels within the bony trabeculae. Bones have a thin cortex and a honeycomb like appearance but based on the histological examination diagnosis cannot be confirmed because the GSD lesions can be active or inactive. Therefore, diagnosis should be always concluded based on the clinical, histological, and radiology findings [6, 12–14]. The proliferation of the endothelial lining of the blood vessels is confirmed by the strong presence of D2-40 among all the cells in the pathological examination [6, 30-31]. In most cases, laboratory values are within normal limits [34–37]. Many Cytokine markers or related molecules in serum and tissue fluid have been measured experimentally to find markers of disease activity, but of the attempted markers only VEGF A and VEGF C have been proven effective [25, 38]. Osteolytic lesions in patients with GSD are visible as radiolucent foci in the radiographic images [6]. Classical radiological features are tapering bone ends or mouse tail appearance [39]. The vertebrae in GSD become weak and form biconcave deformities that further causes fracture of the bone and neurologic impairment [40]. GSD has been classically divided into early intraosseous stage that has sub-cortical radiolucency's and later extra-osseous stage that involves destruction, reabsorption, and disappearance of the bone [19]. The signal behavior varies on MRI because of the relative number of vascular structures and fibrosis. Inflammation and increased capillary permeability can

Sr. No	Year	Author	Number of Patients	Age	Sex	Follow-up	Visceral (+/_)	Appendicular skeletal affection (+/)	Number of Vertebrae	Region	Surgery(S)/ Conservative ©	A:Anterior/ P: Posterior/ C: Combined	Decompressio (D), D + Fixation(DF)	Bone graft (+/_)	Number of Surgeries	Medications Given	Union (Y,N, NC)	Stable spine construct (Y,N)	Remission (Y,N)
1	1983	Edawards et al[54]	1	8	M	72@	_	+	2	O, C	S	C	DF	_	4	NC	N	N	N
2	1983	Heflez et al[19]	1	13	M	12	_	+	6	O C Jn	C	NA	NA	_	_	RT	N	Y	N
3	1993	Dunbar et al[55]	3	I) NC	M	192@	_	_	3	C	S	NC	_	_	NC	RT	N	N	N
				II) NC	M	60	_	+	2	C	C	NA	NA	_	_	RT	NA	NC	Y
				III) 40	M	120	_	_	2	C	C	NA	NA	_	_	RT	NA	NC	Y
4	1994	Dominiguez et al[12]	1	6	M	72@	_	_	8	C T Jn	S	P	D	_	1	RT	NC	NC	N
5	1994	Drewry et al[56]	1	13	M	22	_	+	3	T, L	S	C	DF	+ Allo	2	RT	N	Y	N
6	1995	Pena et al[44]	1	40	M	52@	_	_	3	C	S	P	DF	+ BMP	1	RT	Y	Y	Y
7	1995	Foult et al[57]	1	32	M	48@	_	_	6	C	S	C	DF	+ EAG	3	NC	N	N	N
8	1996	Livesley et al[30]	1	5	M	36	_	_	6	T	S	C	D	+ EAG	2	NC	N	N	N
9	1997	Mawk et al[43]	1	6	M	6	_	+	3	O C Jn	C	NA	NA	_	_	RT	NA	N	N
10	1997	Hagberg et al[58]	1	19	M	19	_	+	3	C, T	S	NC	NC	_	3	RT, Bis, INTF	NC	NC	N
11	1997	Khosrovi et al[59]	1	62	M	24	_	+	2	O C Jn	C	NA	NA	_	_	RT	NA	NC	Y
12	2002	Lesniewska et al[60]	1	65	F	15@	_	_	4	C, T	S#	NC	NC	_	1	RT	N	N	N
13	2003	Chong Ng et al[48]	1	49	M	18	_	+	4	C	S	C	DF	_	2	NC	NC	Y	N
14	2005	Aizawa et al[46]	1	10	M	36	_		10	T	S	C	DF	+ EAG	1	Bis	N	Y	Y
15	2005	Duffy et al[61]	1	31	F	36	_	+	M	T, L	C	NA	NA	_	_	RT	NA	NC	Y
16	2005	Takahashi et al[62]	1	2	F	16	+	+	6	T, L	C	NA	NA	_	_	INTF	NA	NC	N
17	2006	Girn et al[63]	1	2	F	6@	_	+	7	C, T	S#	P	D	_	1	RT, Bis	N	N	N
18	2006	Kai et al*[64]	1	35	F	NC	_	_	1	C	S	A	DF	+ BMP	1	NC	NC	NC	NC
19	2006	Lekovic et al[65]	1	10	M	192	_	+	2	O C Jn	S	C	DF	_	1	RT	N	N	N
20	2009	Lehman et al[66]l	1	61	F	204	_	+	M	L	C	NA	NA	_	_	RT, Bis	NA	NC	Y
21	2009	Kose et al[67]	1	9	M	5.5	_	+	M	T, L, S	C	NA	NA	_	_	RT, INTF	NA	NC	N
22	2010	Mowry et al[68]	1	9	F	240	_	+	5	C	S	P	DF	_	1	NC	NC	Y	N
23	2011	Adler et al*[69]	1	7	F	6	_	+	M	L	C$	NA	NA	_	2	INTF, Bis	NA	NC	N
24	2011	Deveci et al[70]	1	6	M	4@	+	+	M	T	C	NA	NA	_	_	INTF, Bis	NA	NC	N
25	2011	Brodzki et al[38]	2	I) 2.5	M	24	_	+	M	NC	C	NA	NA	_	_	Bevacizumab, Octreotide, TAF, INTF, RT	NA	NC	Y^{Σ}
				II) 4	F	6	+	+	M	NC	C	NA	NA	_	_	Bevacizumab, Octreotide, TAF, INTF, RT	NA	NC	N
26	2011	Heyd et al[71]	6	I) 38	M	24	_		NC	NC	S	NC	NC	_	NC	NC	NC	NC	N
				II) 61	F	144	_		NC	NC	C	NA	NA	_		RT	NC	NC	N
				III) 24	F	46	_	+	NC	NC	S	NC	NC	_	NC	NC	NC	N	N
				IV) 30	M	38	_		NC	NC	S	NC	NC	_	NC	NC	NC	NC	N
				V) 44	M	54	_		NC	NC	C	NA	NA	_	_	RT	NC	NC	N
				VII)46	M	12	_		NC	NC	C	NA	NA	_	_	RT	NC	NC	N
27	2012	Sahoo et al[72]	1	21	M	NC	_	_	2	T	S	P	DF	_	1	NC	NC	NC	NC

Table 1: A short summary of the various published reports of Gorham Stout disease of spine, the type of surgical/medical management used and the outcome/remission of the included patients.

Sr. No	Year	Author	Number of Patients	Age	Sex	Follow-up	Visceral (+/_)	Appendicular skeletal affection (+/_)	Number of Vertebrae	Region	Surgery(S)/ Conservative ©	A:Anterior/ P: Posterior/ C: Combined	Decompressio (D), D + Fixation(DF)	Bone graft (+/_)	Number of Surgeries	Medications Given	Union (Y,N, NC)	Stable spine construct (Y,N)	Remission (Y,N)
28	2012	Noda et al[73]	1	15	M	NC	_	_	8	C	S	A	DF	_	2	INTF, octreotide, RT	NC	NC	N
29	2012	Zheng et al[74]	1	5	F	36	_	+	3	L	C	NA	NA	_	_	Bis	NC	Y	Y
30	2013	Sekharappa et al[4]	2	I) 15	M	12	_	_	4	T	S	P	DF	_	1	Bis	NC	NC	NC
				II) 23	M	20	_	_	2	T	S	P	DF	_	5	NC	N	N	N
31	2013	Barman etal[49]	2	I)23	M	13	_	+	NC	C, T	S	P	DF	_	2	Bis	NC	NC	NC
				II)15	M	NC	_	+	4	T	S	P	DF	_	2	Bis	NC	NC	NC
31	2013	Kilicoglu et al*[75]	1	35	M	108	_	+	2	O C Jn	S	P	DF		5	NC	N	Y	Y
32	2013	Huang et al[74]	1	34	M	NC	_	+	2	T, L	S	P	DF	+ EAG	1	RT, INTF	NC	NC	NC
33	2013	Esmailiejah et al[15]	1	32	M	60	_	+	1	L	S	A	DF	_	1	Bis, Chemo	NC	Y	Y
34	2014	Kakuta et al[47]	1	49	M	22	_	_	2	L	S	C	DF	_	1	NC	Y	Y	NC
35	2014	Maillot et al[76]	1	33	F	12	_	_	6	T	S	P	DF	+ BMP	2	NC	NC	Y	NC
36	2014	Suero et al*[77]	1	26	M	12	+	+	7	T, L	S	P	DF	+ Calcium Phosphate	1	INTF, Bis, Sir	NC	Y	N
37	2014	Nir et al[78]	1	19	F	24	_	+	3	T	C	NA	NA	_	_	Bis, INTF, BB	NC	Y	N
38	2015	Kohno et al[79]	1	27	M	84	_	+	2	O C Jn	S	P	D	_	5	RT, Bis	N	Y	Y
39	2015	Ganal et al[80]	1	44	F	144@	_	+	2	C, T	S	C	DF	+ Allo	5	Bis	N	N	N
40	2015	Carbo et al[81]	1	10	M	48	+	+	17	T, L	S^	NC	NC	_	1	RT, Bis, INTF	NA	NA	Y
41	2015	Kim et al[82]	1	12	M	21@	_	+	M	C	C	NA	NA	_	_	RT, Bis, INTF	NA	NC	N
42	2015	Gedam et al[83]	1	13	M	120	_	+	M	C	C	NA	NA	_	_	Bis	NA	NC	NC
43	2015	Rossler et al[84]	2	I) 14	M	48	_	_	M	S	C	NA	NA	_	_	Sun & Paclitaxel	NC	Y	Y
				II) 7	M	84@	_	_	5	T	C	NA	NA	_	_	Sun & Paclitaxel	N	N	N
44	2016	Schell et al[85]	1	31	F	72	_	_	4	C	S	C	DF	+ EAG, + Allo	1	NC	Y	Y	Y
45	2017	Tateda et al[13]	1	15	M	60	_	_	5	C	S	A	DF	+ EAG	1	NC	Y	Y	Y
46	2017	Srivastav et al*[86]	1	17	M	19	_	+	M	T	S	P	DF	+ Allo	2	RT, Bis	N	Y	N
47	2018	Mo et al[52]	1	14	M	24	_	+	8	C, T	S	P	DF	_	1	Sir	Y	Y	Y
48	2018	Liu et al[31]	1	31	M	24	_	+	3	L, S	S^	_	_	_	1	INTF, Bis	N	Y	N
49	2018	Jaccard et al[87]	1	23	F	24	_	+	2	T	S	P	DF	_	1	NC	NC	Y	Y
50	2019	Wang et al[88]	1	14	F	24	_	_	4	T	C	NA	NA	_	2	Bis	NA	NC	N
51	2019	Koto et al[11]	1	77	M	7@	+	+	1	T	C	NA	NA	_	NA	Bis, BB, RT	N	N	N
52	2019	Sanabria et al[39]	1	6	M	48@	_	+	3	O C Jn	C	NA	NA	_	1	Bis, BB, RT	NA	N	N
53	2019	Kim et al[89]	1	22	M	12	_	+	9	C, T	S	C	DF	+ Allo	1	NC	NC	Y	N

Table 1: A short summary of the various published reports of Gorham Stout disease of spine, the type of surgical/medical management used and the outcome/remission of the included patients.

Sr. No	Year	Author	Number of Patients	Age	Sex	Follow-up	Visceral (+/_)	Appendicular skeletal affection (+/)	Number of Vertebrae	Region	Surgery(S)/ Conservative ©	A:Anterior/ P: Posterior/ C: Combined	Decompressio (D), D + Fixation(DF)	Bone graft (+/_)	Number of Surgeries	Medications Given	Union (Y,N, NC)	Stable spine construct (Y,N)	Remission (Y,N)
54	2019	Du et al[8]	11	I) 5	M	L	_	_	16	C,T, L	C	NA	NA	_	_	Bis	NA	NC	NA
				II) 2	F	36	_	+	9	T, L	S	P	DF	+ BMP	1	Bis	N	N	N
				III) 11	F	24	_	+	11	C, T	C	NA	NA	_	_	Bis	NA	N	N
				IV) 12	M	72	_	+	9	T,	S	P	DF		1	Bis	N	Y	Y
				V) 39	F	36	_	_	6	T	S	P	DF	+ BMP	1	Bis	N	Y	Y
				VI) 43	F	60	_	_	10	T, L	C	NA	NA	_	_	Bis	NA	Y	N
				VII) 12	M	60	_	+	11	T, L	C	NA	NA	_	_	Bis	NA	N	N
				VIII) 11	F	36	_	+	6	T, L	C	NA	NA	_	_	Bis	N	Y	N
				IX) 10	M	12	_	_	8	T	S	P	DF	+ BMP	1	Bis	Y	Y	N
				X) 12	M	48	_	+	9	C, T	C	NA	NA	_	_	Bis	N	Y	N
				XI) 10	F	24	_	+	15	T, L, S	C	NA	NA	_	_	Bis	N	Y	N
55	2019	Barbagli et al[90]	1	32	M	4@	_	_	2	C	S	P	DF	_	1	Sir	NC	Y	N
56	2019	Simon et al[91]	3	I) 3	NC	132	_	+	1	C	C	NA	NA	_	_	INTF, Bis	NA	N	N
				II) 10	NC	36@	_	+	2	C	S	P	DF	_	1	NC	NC	NC	N
				III) 5	NC	24@	_	+	7	C	S	P	DF		1	NC	NC	NC	N
57	2020	Chang et al[92]	1	22	M	18	_	+	9	O, C, T	S	P	DF	_	1	RT	NC	Y	Y
59	2020	Yokoi et al[93]	1	14	F	10	_	+	4	T,	S$	P	DF	_	1	Bis	NC	NC	N
60	2021	Gui et al[94]	1	25	M	6	_	_	6	T	S	P	DF		1	NC	NC	NC	N
61	2021	Momanu et al[5]	1	18	F	NC	+	+	4	C, T	S	P	DF	+ EAG	3	NC	N	N	N
62	2021	Gronroos et al[7]	1	23	M	36	_	+	2	T	S	P	DF	+ EAG	2	RT, Bis, INTF	NC	N	Y
63	2021	Toga et al[95]	1	26	F	12	+	+	4	T	S	C	DF	+ EAG	3	INTF, Bis, BB	Y	Y	N
64	2021	Gezercan et al[96]	1	37	M	96	_	+	M	O C Jn	S	P	DF	+ EAG	M	NC	Y	Y	N
65	2021	Evsyukov et al[97]	1	58	M	36	_	+	3	C	S	P	DF	+ BMP	1	Bis	Y	Y	N
66	2021	Thompson et al[98]	1	60	F	3@	_	+	2	O C Jn	S	NC	NC	_	NC	Sir	NC	N	N
67	2022	Krishnan et al[33]	1	12	F	60	_	_	3	L	S	P	DF	+ Allo	1	Teriparatide, calcitonin, Bis, Sir	Y	Y	Y^{Σ}

@: Death, ^: Verteboplasty, $:Dural Fistual Repair, #: Failed Per-operative reconstruction/execution, * Added as per author's Email Reply , Present(+),Absent(-), NA : Not Applicable, NC: Not classified/ unavailable, EAG: External autograft (Iliac crest, Fibula or other stut graft), Allo(Allograft) BMP (Bone morphogenic protein) BIS (Bisphosphonate),RT (Radiotherapy), Sir(Sirolimus), Chemo (Chemotherapy), INTF (Interferon), BB(Beta-blocker), Sun (Sunitinib), TAF (Tafoxiparin), ∑:Objectified remission, Y:Yes, N:No

Table 1: A short summary of the various published reports of Gorham Stout disease of spine, the type of surgical/medical management used and the outcome/remission of the included patients.

increase the signal intensity on MRI, and hypointense zones are due to fibrosis [8]. GSD shows a low signal intensity on the T1 weighted images , but in active disease T1 and T2 weighted images both are hyperintense [12, 38-39]. MRI is thus useful in differentiating between early, active, and later stages by demonstrating changes in signal intensity over time, therefore the role of MRI is not to provide a specific diagnosis but rather to demonstrate the progressive nature of this disorder [41]. MRI is used to define the extent of spinal canal encroachment, vascular formation, and soft tissue involvement [42]. CT scan with 3D reconstructions is used for precise evaluation of the range of osteolysis. Radiographic features of GSD have four stages: 1) Bony deformity, 2) loss of bone mass, 3) Endothelial invasion into adjacent tissues, 4) Shrinkage end of affected bones giving it "sucked candy appearance" [15]. GSD affecting thoracic vertebrae can directly involve the extension of the lymphatic fluid into pleural cavity [43]. The manifestations of GSD are progressive and according to the musculoskeletal system affected. Even though GSD is progressive and does not metastasize, it's progression can stop suddenly [44], but in some cases lesions remained stable for longer duration without re-ossification [18, 45]. Common clinical features of GSD in spine patient include localized pain, fracture, paresthesia, and functional impairment, neurological defects, paralysis,

Sr.no	Medical management	Basic Mechanism	Limitations/side effects
1	Bisphosphonates	It attaches to hydroxyappetite crystals and inhibit the resorption of the bone by osteoclast.	Severe musculoskeletal pain, ocular inflammation, Osteo-necrosis of jaw, over suppression of bone turnover, and subtrochanteric atypical femoral fractures, increased incidence of atrial fibrillation
2	Radiotherapy	Radiotherapy may arrest endothelial cell proliferation and limit the progression of disease.	Healing Issues. Failure Bone-graft Incorporation.
3	Interferon alpha 2b	It impacts the cellular metabolism and differentiation possessing antitumor activity & interfere with the cancer cells multiplication. It also stops the growth of Osteoclasts.	Fever, rigors, chills, neutropenia, thrombopenia
4	Sirolimus	It is an immunosuppressive agent that directly target the mTOR (Malignant target of rapamycin) and thus decreasing the growth of tumour cells.	Mouth and lip ulcers, diarrhoea, abdominal pain, nausea, sore throat, headache, dizziness, elevated cholesterol, and leg swelling. Healing Issues. Sirolimus being FGF (Fibroblast Growth Factor) inhibitor may delay healing and is to be kept in mind before undertaking a revision surgery.
5	Beta-blockers	Down regulates the vascular endothelial growth factor (VEGF) which leads to vascular proliferation; It can also inhibit the proliferation and migration of lymphatic endothelial cells.	Bradycardia, orthostatic hypotension
6	Sunitinib + Paclitaxel	. Inhibits cellular signalling by targeting multiple receptor tyrosine kinases which play a role in tumour angiogenesis and tumour proliferation. . Paclitaxel promotes the assembly of microtubules and stabilizes microtubules preventing depolymerisation.	Hypothyroidism, hypertension, fatigue, yellow skin discolouration, neurotoxicity, bone marrow suppression, mucositis.
7	Calcitonin	Bone resorptive cells have surfaces for calcitonin. After activation the cells shrinks from the bone surface and stop bone resorption	Flushing, nausea, headache, vomiting.
8	Heparin/Tafoxiparin	Transport proteins across cellular barriers.	Thrombocytopenia or coagulation disturbances
9	Sclerostin inhibitors	Reduces the stimulation of osteoclastogenesis factor, thus downregulating Rankl Inhibitors	Headache, Arthralgia
10	Bevacizumab (VEGF Antibody)	VEGF is highly selective for vascular endothelial cells and induces angiogenesis by serving as a potent endothelial cell mitogen.	Haemorrhage, Clots in arteries

Table 2: Medical management modalities with their respective mechanism of action and side effects/limitations

respiratory distress and failure [5]. Aizawa et al have reported 28 cases of GSD involving the spine in the literature, stating that the cervical and the thoracic vertebrae are frequently affected, only one case was reported involving the lumbar vertebrae [46]. In our review, thoracic vertebrae was the most common region affected in spine with 25.92% (n= 21). Junctional affection was more common at Occipito-cervical junction (n= 9, 11.11%). Kakuta et al revealed a unique feature of partial disappearance of the aorta, which was supported by the tumor mass, a cage of harvested bone was inserted into the dead space following the tumor resection [47]. In our review overall junctional affection was noted in 10(12.34%) cases. Multiple vertebrae affection was noted in 79(74.26%) cases. Affection being multiple leads to deformity and instability needing stabilization in most of the cases. In the review though only 33 cases were managed conservatively. Out of these only 8 cases had stability maintained with average follow-up of 36 months. 25 cases (75.76%) lost stability in due course suggesting the need for surgical stabilization.

Chylothorax is a reported complication of GSD in 17% of patients and carries poor prognosis, further extension of lymphangiectasia to the surrounding structures results into hemothorax or chylothorax, Chylothorax develops due to the leakage of the chyle from penetration of the lymphatic dysplasia [3, 6, 47-48]. Its management is complex and complicated and with repeated interventions [31]. In severe cases of GSD involving spine, visceral functions are damaged and can be life threatening, higher mortality rate is seen in 13.3-20% of patients due to chylothorax [11, 50]. Patients with spinal & visceral involvement can have a mortality rate exceeding 50% [49]. But in our review, only 3 dead patients had appendicular skeletal affection. Visceral involvement (n= 8) is not a poor prognosticator in the current review analysis, as only one patient had mortality. Death in 17 patients (18.88%) were noted with cervical association (n= 8, 8.88%) in our review (Figure 4). Spinal GSD treatment includes three major

options: 1) Medical management, 2) Radiation Therapy and 3) Surgical stabilization [3]. Spine surgery is usually required in view of the progressive deformity. Any compromise in the stability of the spinal column can give rise to severe mechanical pain and predisposes the neural structure to damage [3, 6]. Radiation therapy is often used alone or with the combination of the surgery, the surgical intervention is mainly used for serving the purpose of the skeletal stabilization [6]. The effect of the radiotherapy yet remains unclear to prove whether it arrests the progression of the osteolytic changes or not. Radiotherapy at a decided dosage can eliminate the endothelial proliferation of the lymphangioma from the spine. Radiotherapy combined with medications are getting better to reduce the bony destruction [11, 13, 51]. The use of radiotherapy is mentioned both as a part of conservative management and post-operatively to maintain remission of disease. The surgical interventions are performed according to the size of the lesion, namely resection of the smaller lesions and long fusions for the larger lesions. If the disease is asymptomatic or spine is stable, then it can be managed with medications and radiotherapy but the ones presenting with deformities or neurological affection requires surgical interventions [4]. Less invasive procedures like vertebroplasty can be done in early affections, and dural infiltration may require duroplasty in some cases. Failure of executing a global stable reconstruction per-operatively, needing even abandonment of the surgery was noted in our review in two (2.22%) patients, highlighting the extensive destruction that can occur in GSD. So careful preoperative planning is needed with multiple surgical inventory/ instrumentation. The types of surgical treatments pertaining to spinal GSD varies from stabilization by posterior or anterior approaches or combined methods. Surgery is needed in most of the cases. The posterior approach was the most common in our review with 32 (28.89%) patients (Figure 5). Dural infiltration can occur needing duroplasty which has been needed and reported in (n= 2; 2.22%) cases. In 35 cases stable reconstruction of spine was successfully documented. Stability was non-maintained in 30(52.63%) cases. Nonunion and instability in spine necessitates multiple surgeries in many cases (n=21, 23.33%). Thus, surgical complex reconstructions, multi-rod systems with anterior reconstructions if needed are advised in all cases. Though questionable, the surgery can be done after medical treatments when the osteolysis have stopped. Delayed Timing of surgical interventions as a strategy has been advocated by some, as the grafted bone resorbs if surgery were performed before disease regression [13].

Calcium, vitamin D and pro nutritive additions for healing are being used generously. The outcome of the chemotherapy agents such as nitrogen mustard and steroids has been proven ineffective [12]. In medical therapy, bisphosphonates and/or sirolimus are advised to improve the stabilization of the bone post-operatively. Bisphosphonates are also used with the combination of alpha 2b interferon and other chemotherapeutic agents [13, 47, 52]. Other pharmacological agents suggested for the treatment of the GSD are androgens and propranolol [3]. A study conducted with sirolimus for vascular anomalies showed promising results for patients with tuberous sclerosis or lymphangioleiomyomatosis involving the PI3K/AKT pathway [52]. In our review with the treatments given, Outcomes with Radiotherapy is promising as the number of remissions were higher (n= 6). Till now no United states Food & Drug administration (USFDA) medical approval has been reported or in process for treating GSD [11]. Brodzki et al suggested that low molecular weight heparin and tafoxiparin therapy should be considered for severe pediatric GSS with anticipated risks as heparin-induced thrombocytopenia, an allergic reaction or coagulation disturbances [38]. A summary of current treatment modalities, their actions , caveats and effectiveness in our review of patients is tabulated (Table 2). But looking to the majority of used medical management, bisphosphonates, interferon and sirolimus form the mainstay of medical therapy. There is no conclusive line of treatment medically. Also, Pre-surgical medical optimization through neoadjuvant therapies targeting lymphangitic tissue has shown enhanced surgical outcomes [52].

In the long-term follow-up analysis, four year follow up of 26 patient inclusive of 2 years follow up of 19 patient is available. The average follow-up period has been reported as 47.12 ± 48.90 (3-240) months. The lesser number of available cases with longer time follow-ups suggests that the most effective way of stabilization surgery also cannot be recommended. This itself shows the complexity of the spinal affection in GSD which needs surgical reconstruction method to be optimized on case-to-case basis. The status of union is also not reported in most of the literature, all being short duration follow- up. Remission is the purpose of most medical treatment and achieving stability is the surgical goal. Morselized grafting of posterior elements is a standard technique. But it has been insufficient and a reason for failure of union. The use of bone graft substitutes/analogues doesn't guarantee union but a logical step to add to a favorable outcome in complex extensive GSD. Union evades GSD, and documented union was obtained in only 10 cases, out of which 8 cases were supplemented with a bone graft or substitute other than local autograft (Figure 6). HLA matched allograft achieving a stable union has been used in 1 case by Krishnan et al with favorable outcome. In the same case union can be enhanced by off label use of teriparatide and remission achieved with

bisphosphonate and sirolimus at 4 years follow-up [33]. Remission is the most important target in the therapy. Only 23 patients had remission in the review of which majority (n= 21) were inferred remission. Surprisingly though, obtaining objectified remissions is not reported in most of the literature. This would exactly be the reason why so many numbers of patients have multiple surgeries and failures. Of the attempted markers only VEGF A and VEGF C have been proven effective to demonstrate remission [25, 38]. The disease remission and osteolysis arrest can be confirmed by the MRI findings: the disappearance of GSD enhancement (hypointensity in T1 and T2 sequences) and fatty degeneration of the vertebral bodies [53].

Limitations of this review exist. The study does not conclude the recommended methodology of surgery or remission treatment. This is because there are smaller number of patients of GSD and multiple subgroups are many making it heterogeneous for statistical analysis. Also, the long-term follow-ups are not available. All these articles have considered published literature and follow-up duration, but recommendations are not standard in them as well. Our study has discussed all modalities of treatment and has tried to get the latest follow-up status of the patients in previous literature through email communication. There was a limitation of e-mail response from corresponding authors, and we could only get response from 5 authors. So, more long-term data could not be pooled. So, it may be inferred that the true follow-ups and outcome may be even more inferior. Standardization of medical therapy looks less likely due to sporadic presentation, unconventional treatment, off-label medications with unpredictable evolving sequela. Most cases are limited to anecdotal case reports and short case series.

Conclusion

Surgery would be needed in most cases of spinal GSD. Failure of fixations and repetitive surgeries are needed. So, achieving a global strong reconstruction with union should be expediated with use of bone graft analogues. Remission is daunting and "off label" therapies are the dictum. Radiotherapy has been used more frequently with or without bisphosphonates. Although, promising medical treatment are evolving (sirolimus and alpha 2B Interferon) and focus of treatment is directed towards anti-angiogenic, anti-osteolytic and anabolic therapy. Strikingly no consensus evolves and no standard treatment recommendations can be made out from the existing literature.

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