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Systematic Review

Impact of Intestinal Urinary Diversion on the Risk of Fracture and Loss of Bone Mass: A Systematic Review

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Abstract.
BACKGROUND: Patients undergoing intestinal urinary diversion (IUD) may have a higher risk of osteoporosis and risk of fractures due to metabolic acidosis and decrease of intestinal absorption surface.
OBJECTIVE: We performed a systematic review of the available literature on the impact of IUD on bone demineralization.
METHODS: We systematically searched PubMed®, for original articles published before April 2020. Primary end points were the risk of fracture and loss of bone density. Secondary outcomes were the metabolic changes in biochemical and urine parameters related to calcium metabolism and histological changes.
RESULTS: Our electronic search identified a total of 2417 articles. After a detailed review, we selected 11 studies that addressed the impact of IUD on bone health in 10369 patients. The risk of bone fracture was studied in 3 articles, showing a higher risk in the IUD population. Of the 9 articles evaluating the relation between intestinal urinary diversion and bone density, 5 did find a positive association. One article evaluated the bone metabolism at a cellular level after IUD showing a decrease in bone turnover in this population. Three of the eight studies reporting data on serum parameters related to calcium and phosphate metabolism showed differences. Finally, a correlation between concentration of pyridolines in urine and loss of bone density was found in two of the three studies.

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CONCLUSIONS: Although published data on BMD are contradictory, patients undergoing IUD seem to be at higher risk of bone fractures. Our finding support the need to implement accessible strategies on osteoporosis screening and prevention in IUD patients.

Keywords: Urinary Bladder Neoplasms, cystectomy, urinary diversion, acidosis, metabolic diseases, bone fracture, osteoporosis

INTRODUCTION

Urinary tract reconstructions using intestinal segments are performed in patients undergoing cystectomy for bladder cancer (BCa) or benign terminal bladder dysfunction. The majority of intestinal urinary diversion (IUD) are created using the terminal ileum as it has the advantage of a lower rate of intra- and postoperative adverse events than other intestinal segments [1, 2]. This implies the exclusion of this part from the gastrointestinal tract affecting the absorption of certain nutrients [1, 3].

The contact of urine with the absorptive surface of the intestinal mucosa in IUD cause metabolic derangements owing to the reabsorption of urine solutes [4]. In normal situations, the ileum and the colon absorb urinary chloride and excrete bicarbonate into the intestinal lumen. When exposed to urine, bicarbonate moves into the lumen of the IUD while chloride (Cl) and ammonium are absorbed leading to chronic hyperchloremic acidosis [5]. In response to metabolic acidosis, bone buffers the excess of protons and release calcium, resulting in hypercalciuria, without a concomitant increase on intestinal calcium absorption: acidosis suppresses the activity of osteoblasts at the same time that the synthesis of the receptor activator of nuclear factor kappa B ligand (RANKL) increases, which stimulates osteoclastic activity and recruitment of new osteoclasts promoting bone resorption to buffer the proton load [6]. Metabolic acidosis, therefore, is associated with an increase in urine calcium excretion [7]. Moreover, ileal resection compromises calcium absorption because calcium is mostly absorbed in the ileum. Therefore, patients undergoing an IUD are at considerable risk of bone demineralization.

Also, age-related bone loss is progressive and can lead to osteoporosis [8] increasing the risk for fractures. It is known that patients experiencing low impact fractures secondary to osteoporosis are at significantly higher risk for death than their non-osteoporotic counterparts, and this persists for several years post-fracture [9, 10].

The current literature in this field is scarce with only a few studies assessing the impact of IUD on bone metabolism [11–13]. Most of the publications focused on different outcomes related to bone health with inconsistent results. Two recent big population-based studies, however, suggested that patients undergoing IUD are at higher risk of fracture [14, 15]. Therefore, the purpose of this systematic review is to provide an analysis of the available literature on the impact of IUD on bones including the risk of fracture, bone mineral density and other indirect measurements of bone demineralization.

MATERIAL AND METHODS

Evidence acquisition

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [16]. The detailed PICO (Population, Intervention, Comparison and Outcomes) design is provided in the Section Inclusion Criteria.

Literature Search

PubMed database was searched in April 2020 to identify reports on the impact of IUD on bone health published between January 1990 and April 2020. The keywords used in our search strategy were: ((urinary diversion) OR (ileal conduit) OR (neobladder) OR (urinary reservoir)) AND ((fracture) OR (osteomalacia) OR (osteopenia) OR (osteoporosis) OR (bone mass) OR (bone mineral density) OR (bone mineralization) OR (bone metabolism) OR (complication)).

The primary outcomes of interest were the risk of fracture and loss of bone mass density (BMD). The secondary outcomes were the metabolic changes in laboratory parameters related to calcium metabolism as well as in urine and histomorphometric changes in bone architecture histological changes, such as trabecular bone volume (TBV).

Initial screening was performed independently by two investigators (CP and KR) based on the titles and abstracts to identify ineligible reports, and reasons for exclusions were noted. Potentially relevant reports were subjected to a full-text review and the relevance of the reports was also confirmed after the data extraction process. Disagreements were resolved via consensus with a third investigator (BP).

Inclusion and exclusion criteria

Studies were included if they investigated adult patients with trauma, neurogenic bladder or bladder cancer (Patients) undergoing IUD (Intervention) as compared with those not having that surgery (Comparators) to assess the impact on bone fractures or loss of bone mineral density (Outcome) in nonrandomized observational or cohort studies. Animal models, children undergoing urinary diversion were excluded. We also excluded reviews, letters, editorials, meeting abstracts, replies from authors, and case reports. No language restrictions were applied. In cases of duplicate publications, the most recent publication was selected. References of included manuscripts were further scanned for additional studies of interest.

Data extraction

Two investigators (CP and KR) independently extracted the following information from the included articles: first authors name, publication year, recruitment country, period of patient recruitment, number of patients, age, study design, the reason for urinary diversion, type of urinary diversion, control group in case there is one, follow-up duration, median age and type of test to determine bone health. All discrepancies regarding data extraction were resolved by consensus with a third investigator (BP).

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies following the Cochrane Handbook for systematic reviews of interventions for included non-randomized studies [17, 18]. The scale rates following three factors: Selection (1–4 points), Comparability (1–2 points) and Exposure (1–3 points), with total scores ranging from 0 (lowest) to 9 (highest). Studies with scores of more than 6 were identified as "high-quality" choices.

EVIDENCE SYNTHESIS

Literature search and characteristics of the included studies

Our initial search identified 2417 records, and after elimination of duplicates, 2411 articles were available (Fig. 1). A total of 2392 articles were excluded after screening the titles and abstracts, and a full-text review was performed for 19 articles. After applying the selection criteria, we identified 11 articles with 10369 patients for qualitative evidence. Table 1 summarizes the extracted data from the 11 studies, including the type of urinary diversion and number of patients. The median age and follow-up duration ranged from 50 to 72 years, and from 28.4 months to 8 years, respectively. Seven out of the 11 studies included only male patients. The studies had a median NOS score of 7 (4–7), as shown in Appendix 1.

Outcome 1: Risk of fracture

Three studies reported data on bone fractures in 10116 patients who underwent IUD [14, 15, 19]. Table 2 summarizes the results of these studies.

Two population-based studies reported a significant increase in the risk of fractures in a population with BCa who had IUD in comparison with their counterparts without IUD [14, 15]. Additionally, Richard et al. reported a higher risk of fracture not only in a BCa population but also in non-BCa patients who also had an IUD [15].

Although it was not the primary objective of the study, Campanello et al. reported three patients with IUD who had a lumbar spine fracture out of 30 patients who underwent a plain X-Ray of the thoracolumbar spine [19].

In those studies, IUD seemed to be associated with an increase in risk fracture. Moreover, there was no statistical difference regarding the indication for the cystectomy.

Outcome 2: Bone mineral density tests

Nine studies, comprising a total of 267 patients undergoing IUD, analyzed the potential loss of bone mass in comparison with those without intervention [12, 13, 19–25].

Four studies reporting on 117 patients with IUD, did not find significant differences on BMD when compared with matched healthy population [13, 19–21]. Two of these groups reported no significant differences in bone mineral content (g/cm) using

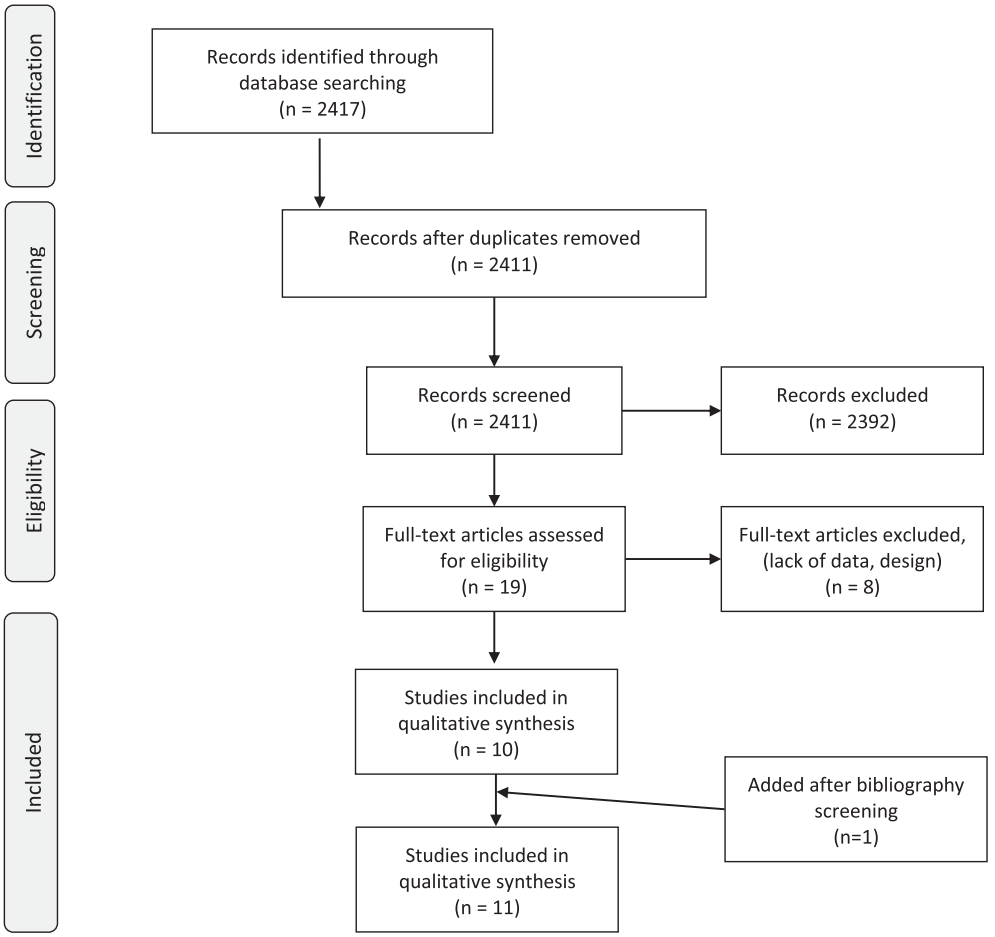

Fig. 1. PRISMA Flow Chart of the studies included.

single-photon absorptiometry (SPA) and dual-energy x-ray absorptiometry (DEXA) [13, 21]. Similarly, the other two groups, did not find significant differences in bone mass density (g/cm^2), between patients undergoing IUD and control, using either SPA or DEXA [19, 20].

On the contrary, five studies, comprising 150 patients, found an association of bone loss after IUD [12, 22–25]. Sevin et al compared a group of patients with neobladder using exclusively ileum segment ($n = 17$) and a group undergoing Indiana pouch, using ascendant colon ($n = 10$) with healthy controls ($n = 14$) [12]. They concluded that metabolic changes occur whenever bowel segments are interposed in the urinary tract, as alkaline phosphatase levels were elevated in both neobladder groups compared to the control, but only the ileal neo-bladder group had a significant decrease bone density. A study including Stanford pouch ($n = 9$) and ileal conduit ($n = 8$) showed no differences in the Stanford group compared to the control group ($n = 19$), whereas patients with ileal conduit were osteopenic after IUD revealing a significant difference with the control group (Table 3) [25]. No difference in BMD or bone metabolism parameters were observed between the two diversion groups. Another study reporting on 46 patients with different types of IUD, found that patients with IUD and metabolic acidosis presented a significantly lower BMD [22]. The type of diversion did not result in a significant difference in metabolic acidosis or bone resorption. Patients undergoing Vesical Ileal Padovana reconstruction ($n = 25$) presented a significantly lower BMD in the femoral region compared to the control group[23]. Fujisawa et al. also found demineralization in spine and femur in men undergoing orthotopic neobladder using different intestinal segments ($n = 23$) as compared with the age-matched population [24].

Table 1
Characteristics of the included studies

Author	Journal	Year Publication	Country	Study type	Recruitment	*n* Total	♂:♀	*n* Study cohort	Urinary diversion	*n* Diversion Group	Control Cohort	*n* Control	Media age study cohort (years)	Median Follow up (years)	Outcome: Risk of Fracture	Outcome: BMD tests	Outcome: Serum markers	Outcome: Urin markers	Outcome: Histoiogical findings
Campanello M.	J Urol	1996	Swedan	Longitudinal prospective	NA	48		48			NA		NA		✓	✓	✓		
							16:8		Kock reservoir	34			56	6,5					
							3:11		Bricker	14			72	6,1					
Davidsson T.	Urology	1995	Swedan	Longitudinal prospective	NA	39		39			NA					✓	✓		✓
							15:5		Ileal or colonic conduit	20			52	15,0					
							16:3		cecal reservoir	19			50	9,0					
Fujisawa M.	J Urol	2000	Japan	Longitudinal prospective	NA	33	100% male	33	Orthotopic neobladder	23	NA		62.8	2,4		✓	✓	✓	
									sigmold	23									
									lleocolic	8									
									asc colon	2									
Gannini S.	J amor Soc Nephrol	1997	Italy	Longitudinal prospective	1987–1995	41	100% male	25			Aged matched	16	62.7	3,9		✓	✓	✓	
									Padovana	25									
Gupta A.	JCO	2014	USA	population based-cohort	2000–2007	50520	37633:12887	4878			Bca w/o IUD	45642	NA*>66	3,4	✓				
									continent	721									
									incontinent	3892									
									unknown	265									
Incel N.	Int Urol Nephrol	2006	Turkey	Longitudinal retrospective	1994–2001	38	100% male	19			Matched control	19	64			✓	✓		
									Standford pouch	11			60	4,9					
									Ileal conduit	8			68	3,0					
Kawakita M.	J. Urol	1996	Japan	Longitudinal retrospective	1984–1993	359	100% male	46			Matched control	313				✓	✓	✓	
									Knock pouch	20			58	5,2					
									indiana	15			63	3,0					
									Ileal conduit	11			61	5,3					
Poulsen A.	BJU	1997	Denmark	Longitudinal prospective	NA	48	100% male	32			Healthy	16	67	2,0		✓			
									kock reservoir	32			62						
Richard P.O.	J. Urol	2019	Canada	population basedcohort	1994–2014	25894		5208			No IUD	20686			✓				
							1020:3281//76:24		Bca&IUD	4301	Bca&No IUD	16772		(1,79–6,69					
							363:544//40:60		IUD & No Bca	907	Healthy	3914		(5,57–7,8)					
Sevin G.	Eur Urol	2002	Turkey	Longitudinal retrospective	NA	41	100% male	27				14				✓			
									Indiana	10			59.5	4,7					
									Ileal neobladder	17			58.6	2,8					
Tschopp A.	J Urol	1995	Switzerland	Longitudinal retrospective	1985–1988	14	100% male	14			NA		72.4	(5–8)		✓			
									Neobladder	14									

BMD: Bone mineral density; NA: not available; ✓ present.

Table 2
Outcome 1: Risk of fracture on IUD patients

Author	Cohort	*n*	Follow-up (years)	*n* events	% events	Median time to fracture (months)	Incidence/ 100 person-year	HR fracture any site
Gupta 2014	IUD			792	16	16,6	6,55	**1,21**
	Control			10080	22	21,8	6,39	REF
Richard 2019	Bca + IUD	4301	1,79	647	15,04		4,41	**1,48**
	Bca w/o IUD	16772	6,69	3373	20,11		2,63	REF
	IUD	907	5,57	336	37,05		5,57	**1,48**
	healthy	3914	7,80	1140	29,13		3,51	REF
Campanello 1995	Kock	20		1				
	Bricker	10		2				

IUD: Intestinal urinary diversion; Bca: bladder cancer; w/o: without; REF: Reference.

Outcome 3: Histology

Only one study analyzed bone metabolism at a cellular level after IUD [21]. Histomorphometric analysis was carried out after bone biopsy in 33 patients with IUD and compared with biopsies of 70 healthy patients. Trabecular bone volume (TBV), osteoid volume, osteoid surface, resorption surface and appositional rate were assessed. The analysis revealed greater TBV compared to normal values in the patient with a continent reservoir, but not in the conduit group. The mineral appositional rate (a measurement of the linear rate of new bone deposition), was significantly less in the two patients group than in the normal subjects, although there were no differences between both groups. These results may indicate a decrease in bone turnover in this population, with resulting reduction of osteoid formation. Osteoid volume and surface in this study tended to be rather on the low side, although within the normal range.

Outcome 4: Serum markers for bone metabolism

Eight studies including 239 patients with IUD, reported data on serum parameters related to calcium and phosphate metabolism, such as osteocalcin, PTH, vitamin D, calcium or alkaline phosphatase [12, 19–25]. The mean values were within the normal ranges in five of the studies, as summarized in Table 4.

Subgroup analysis showed significant differences in three of the studies [12, 23, 25]. Incel et al. found statistically significant higher PTH values in patients with Stanford pouch (which were not found in the ileal conduit group) compared to control subjects [25]. Alkaline phosphate or bone alkaline phosphate levels were significantly higher in patients undergoing IUD [12], as well as reported by Incel et al. in the subgroup of Stanford pouch (and not in the ileal conduit subgroup) [25].

Outcome 5: Urinary markers

Pyridinoline and deoxypyridinoline are pyridinium crosslinks which stabilize the collagen chains within the extracellular matrix. They are released during the breakdown of mature collagen and excreted in the urine, and therefore, are used as specific bone turnover markers [26]. However, the clinical role is still controversial, due to the high biological variability [27, 28].

Three studies comprising 120 patients, analyzed the relation between the BMD and pyridolines in patients undergoing IUD [22–24]. Correlation between concentration in urine of these markers and loss of BMD was found in two of them, suggesting that acidosis may be attributed to the decrease in bone mineral density [22, 24].

However, in the study by Giannini et al. these differences were found when these urine parameters were evaluated at different time after surgery [23]. Particularly, patients with a shorter time after surgery (< 36 months) presented higher urine hydroxyproline values, corresponding with the period in which a more severe metabolic acidosis.

DISCUSSION

Patients experiencing low impact fractures secondary to osteoporosis are at significantly higher risk for death than their counterparts, and this persists for several years post-fracture [9, 10]. Nonhip, nonvertebral fractures also were associated with premature mortality [10]. The main interest to analyze the fractures after urinary diversion, is that such a surgery is mostly performed in patients with BCa, an aged

Table 3
Oucome 2: Bone mineral density on IUD patients

Author	Cohort	*n* Cohort analysed	SPA	DPA	DEXA	BMD Forearm	BMD Femoral	BMD Ward	BMD Lumbar	BMD whole body	Z-score Forearm	Z-score Femur	Z-score Lumber	T score Femur	T Score Lumber	T score < 2.5 Femur	T score < 2.5 Lumber
Campanello 1996			✓		✓												
	Knock reservoir	34				98 ± 19%	92 ± 15%		101 ± 17%	98 ± 6%		–0.28 ± 0.25	–0.17 ± 0.26				
	Ileal Conduit	11*				105 ± 20%	104 ± 14%		101 ± 17%	101 ± 9%		–0.21 ± 0.34	0,62 ± 0.47				
Davidsson 1995			✓		✓												
	Conduit (ileal and colonic)	18									0.08 ± 1.145	–0.217 ± 0.93	–0.089 ± 0.68				
	cecal reservoir	15									–0.157 ± 0.839	–0.485 ± 1.065	–0.399 ± 1.058				
Fujisawa 2000	orthotopic neobladder				✓							–.82 ± 0.99	–0.35 ± 1.031				
	sigmoid	23															
	ileocolic	8															
	ascendent colon	2															
Giannini 1997	Padovana	25			✓												
	Padovana	25					**0.74 ± 0.03***	0.52 ± 0.03								36%	32%
	Control						0.84 ± 0.03	0.61 ± 0.04									
Incel 2006					✓												
	Standford pouch	11					0.99 ± 0.11		1.11 ± 0.14					–0.63 ± 0.82	–0.9 ± 1.18		
	Ileal conduit	8					**0.90 ± 0.11***		**1.02 ± 0.13***					**–1.43 ± 0.86***	**–1.76 ± 1.14***		
	control	19					1.02 ± 0.25		1.19 ± 0.16					–0.21 ± 1.04	–0.27 ± 1.30		
Kawakita 1996					✓												
	knock pouch	20										0.52 ± 0.19	0.19 ± 0.22				
	indiana	15										0.61 ± 0.37	0.30 ± 0.30				
	ileal conduit	11										0.22 ± 0.20	0.31 ± 0.36				
Poulsen 1997			✓		✓												
	ileal conduit	25				NA					NA						
	control	16															
Sevin 2002				✓													
	control	14						0.9 ± 0.1	1.2 ± 0.2			–0.6 ± 0.5	0.6 ± 1				
	ileal neobladder	17						**0.77 ± 0.2***	**1 ± 0.1***			**–1.3 ± 0.5***	**–1.5 ± 1.1***				
	Indiana pouch	10						0.8 ± 0.2	1.1 ± 0.4			–0.8 ± 0.9	–0.9 ± 1.1				
Tschopp 1995					✓												
	ileal neobladder	14										0.24 ± 0.255	0.3 ± 0.27				

Table 4
Outcome 4: Serum markers for bone metabolism

Study	Cohort	*n* Cohort analysed	Osteocalcin	1.25 (OH)2 D3	25 (OH)2 D3	PTH	PTH intact	FA	FA-bone specific	Ca total	Ionized Calcium
Campanello 1996			µe/L	pg/mL	ng/mL	ng/L			µg/L		mmol/L
	Kock reservoir	27	9.2 ± 0.5	35 ± 3	24 ± 2	39 ± 5			10.8 ± 0.9		1.28 ± 0.01
	Bricker	13	8,6 ± 0.6	27 ± 3	27 ± 3	48.6 ± 7.1			10 ± 1.4		1.25 ± 0.01
Davidsson T			µg/L	pmol/L	nmol/L		pmol/L	µcat/L		mmol/L	mmol/L
	Conduit	17	3.2 ± 1.6	53 ± 12	63 ± 18		4.4 ± 3.0	3.5 ± 0.8		2.33 ± 0.08	1.26 ± 0.04
	Reservoir	18	3.7 ± 1.1	69 ± 29	57 ± 24		2.9 ± 1.1	3.0 ± 0,7		2.31 ± 0.09	1.24 ± 0.05
Fujisawa					NA		NA	U/L	NA	mg/L	NA
	Orthotopic neobladder	33	NA(↑2)	NA(↓2)		NA (normal in 33)	NA	237 ± 76	NA	9.3 ± 0.4	
Giannini S			NA		NA	NA	pg/mL	NA	U/L	mmol/L	mmol/L
	Padovana	25		33.09 ± 2.5			33.3 ± 2.7		**45.4 ± 4.4**	2.25 ± 0.02	**1.27 ± 0.01**
	Control	16		35.8 ± 1.6			28.3 ± 1.4		20.7 ± 1.5	2.27 ± 0.02	1.24 ± 0.01
Incel et al			NA	NA	NA	pmol/L		U/L		mg/dL	
	Standford pouch	11				**4.56 ± 2.67**		**98.27 ± 53.69**		9.15 ± 0.51	
	Ileal conduit	8				4.00± 1,79		110.37 ± 112.36		9.26 ± 0.61	
	Control	19				3.03 ± 0,96		71.05 ± 15.90		9.25 ± 0.55	
Kawakita			NA	NA	NA	NA	NA	IU/L	NA	mg/dL	
	kock pouch	20						227 ± 9.6		8.7 ± 0.06	
	Indiana	15						264 ± 53.5		8.7 ± 0.11	
	Ileal conduit	11						216 ± 22.9		8.6 ± 22.9	
Sevin et al			NA	NA	NA	pe/dL	NA	U/L	NA	mg/dL	
	Indiana	10				47.3 ± 9.5		**121.4 ± 43.6**		9.3 ± 0.6	
	Ileal	17				44.7 ± 18.1		**113.4 ± 79.2**		9.4 ± 0.5	
	control	14				59.1 ± 25.5		84.8 ± 15.1		9.3 ± 0.5	
Tschopp et al			NA	pg/mL	ng/mL	NA	pg/mL	U/L		mmol/L	
	Ileal neobladder	14		34.6(13.4–60.8)	20.8 (8.7–27.3)		37 (32–43)	81(52–96)		2.4 (2.09–2.54)	

population who is already at higher risk of bone fractures due to aging and an add risk of pathological fractures in case of developing bone metastases [29].

In the current literature, just two studies, addressed this question using the risk of fractures in patients undergoing urinary diversion as the endpoint [14, 15]. Regarding the findings, the studies looking at the risk of fracture showed a clear association to the presence of IUD, whatever the indication (oncological or benign condition). The risk of fracture was around 21–48% higher in patients undergoing a IUD compared with their health counterparts.

However, most of the articles included in this review used the subrogated variable BMD as their primary outcome. Although the measurement of BMD is an indirect risk of fracture marker, the use of tools which can help to screen patients at risk of fracture is of utmost importance [30]. Therefore, the FRAX (Fracture Risk Assessment Tool) score, which includes BMD, estimates the individualized 10-year probability of hip and major osteoporotic fracture and can identify patients at high risk. Due to the large timeline of the included studies and the change in the techniques used to assess BMD, the results were heterogeneous and could not be compared. The results of current literature on the effect of IUD on BMD are insufficient to provide clear and robust conclusions.

Moreover, other bone resorption parameters as pyridiniums, serum parameters as well as histological bone architecture, have been studied with no strong repercussion in this field. The lack of robust literature using these variables and the contradictory results, complicates to make any statement related to them.

Regarding the kind of diversion, there are studies based on small simple size, which reported higher metabolic acidosis rates in patients with continent diversion compared to those with ileal conduit. It is postulated that patients are at especially high risk for metabolic acidosis when the intestinal segment is exposed to urine for long periods since longer contact with mucosa leads to more reabsorption [2]. However, in our systematic review, several studies found no difference between conduit, continent bladders and control groups related to BMD [19, 21]. Despite the expectations due to the lower reabsorption period and ratio, one study found significant differences in the ileal conduit group but not in the continent group compared to the control [25]. However, age difference is considered a potential explanation for these results.

Several studies assessed the difference between the intestinal segment used (colonic or ileal), founding no significant difference in metabolic acidosis and bone demineralization [21, 22]. On the contrary, Sevin et al. reported a decrease BMD in patients with ileal bladder and no changes in those with an Indiana pouch [12].

It is to note, that patients with renal insufficiency are less likely to eliminate de acid load and therefore this could be a confusion factor. Nevertheless, most of the studies excluded patients with renal insufficiency.

Unfortunately, the quality and heterogeneity of the reported data, as previously mentioned (number of patients, primary outcomes, diagnostic tests, measurements...) made not possible to meta-analyze the results.

LIMITATIONS

This systematic review presents relevant and important findings. Additionally, no language restriction was applied in order to prevent the language bias. However, the study also presents several limitations. First of all, inherent limitations associated to the population studies based on administrative databases (SEER Incidence database, Ontario Cancer Registry, Registered Person database, Canadian Institute for health Health Information, Discharge Abstract Database and Ontario Health Insurance Plan). Second, the use of a BMD as surrogate variable for bone fracture in most of the studies. Although BMD is an indirect risk of fracture marker, tools for predicting risk of fracture, like FRAX score (in which BMD is also included) are of utmost importance [30]. Third, most of the article included had a small sample size with retrospective design and limited follow-up duration. Fourth, in a high number of publications, female patients were not included because of the potential effect of menopause and hormonal changes on bone mineral metabolism. Likewise, some studies exclude patients with renal impairments due to the effect on osteoporosis introducing significant selection bias, whereas others include them.

To conclude, patients undergoing IUD seem to be at higher risk of bone fractures than their counterparts. Although data concerning BMD are not conclusive, the higher risk of fracture on these patients support the need to implement strategies for the prevention of osteoporosis in patients with IUD. Fracture risk algorithms which combine BMD and clinical risk factors such as FRAX score can be used to guide treatment decisions. However, a wise strategy to detect patients at high risk of bone fractures and

who benefit the most from a prophylactic treatment still need to be explored.

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AUTHOR CONTRIBUTIONS

Carmen Pozo: conception, performance of work; interpretation or analysis of data; writing the article. Benjamin Pradere: performance of work; interpretation or analysis of data; writing the article. Katharina Rebhan: performance of work; interpretation or analysis of data; writing the article. Cao Chao: performance of work, writing the article. Lin Yang: performance of work, writing the article. Mohammad Abufaraj: interpretation or analysis of data; writing the article. Shahrokh F. Shariat: conception, interpretation or analysis of data, writing the article.

ETHICAL CONSIDERATIONS

This study, as a literature review, is exempt from any requirement for Institutional Review Board approval. No human or animal research was involved in the elaboration of this manuscript.

CONFLICT OF INTEREST

Shahrokh F. Shariat owns or co-owns the following patents: Methods to determine prognosis after therapy for prostate cancer, granted 2002-09-06; Methods to determine prognosis after therapy for bladder cancer, granted 2003-06-19; Prognostic methods for patients with prostatic disease, granted 2004-08-05; Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma, granted 2010-07-20. He is also an advisory board member of Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda and Urogen.

Carmen Pozo, Benjamin Pradere, Katharina Rebhan, Cao Chao, Lin Yang and Mohammad Abufaraj have no conflicts of interest to declare.

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Appendix 1
NOS Score of 11 studies included

Title	Selection	Comparability	Outcome/Exposure	
Campanello M., 1996	***	**	**	7
Davidsson T., 1995	***	*	***	7
Fujisawa M., 2000	**	*	*	4
Giannini S., 1996	***	*	***	7
Gupta A., 2014	***	*	**	6
Incel N., 2006	****	*	**	7
Kawakita M., 1996	**	*	***	6
Poulsen A., 1997	***	*	**	6
Richard O., 2019	****	*	**	7
Sevin G., 2002	***	*	*	5
Tschopp A., 1995	***	*	***	7