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Appendectomy Impact and Associated Disease: Systematic Review of Literature. Call for Awareness to All Physicians

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Abstract

Background: Appendectomy is one of the most common emergency surgical procedures, but the long-term consequences have not been fully explored and the physiological function of the human appendix has not been completely understood. Several hypothesis have been made. It could act as a "priming station" with an immune-modulatory function or as "safe house" for saprophytic gut bacteria, thus leading to certain diseases when removed.

Methods: A systematic review was performed according to PRISMA guidelines. Articles with appendectomy and post operative implication were screened and those with pertinent information were evaluated.

Results: Appendectomy resulted associated with several disease, among them: ulcerative colitis (UC), Crohn disease (CD), cardiovascular disease, type II diabetes, Clostridioides Difficile Infection (CDI), Parkinson Disease (PD), malignant neoplasia, Primary Sclerosing Cholangitis (PSC) and a miscellaneous of other.

Results: Showed a highly probable association between appendectomy and the development CDI, PD and CD. A possible association was found for cardiovascular disease, gallstones and malignant neoplasia.

An unlikely association was found for type II diabetes, PSC and UC.

Conclusions: Correlation between appendectomy and development of certain disease exist but it doesn't implies cause. Common environmental, immunological and genetic factors can also account for the development of the disease, more than the appendicitis itself. However, the appendix may have an important role in preventing those disease, and for this reason, if confirmed, a paradigm shift towards a conservative approach should be considered.

Keywords: Emergency surgical; Appendix; Bacteria; Diseases; Crohn disease.

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Background

Appendectomy is one of the most common emergency surgical procedures, it has been performed for centuries and it still is nowadays, but the long-term consequences have not been fully explored yet [1].

The human appendix has been described as a vestigial organ by Charles Darwin in "the descent of the man" in 1871. It was thought to have unknown or no function and even be detrimental, from its ability to cause death when inflamed.

Modern studies of comparative anatomy [2,3] identified homologous structures in the ceca of different species: some species have a proper appendix, while others have a cecum with the same histological structure and the same aggregation of lymphoid tissue, and because of this they are also hypothesized to have the same function. Apparently, some species lost the appendix during evolution and regained it back in a subsequent period, while others preserved it for millions of years: this aspect of evolutionary biology points out the importance of this anatomical structure, which if it wasn't so important, probably wouldn't have been preserved for so many years and by so many species.

However the physiological function of the appendix has not been demonstrated yet, despite several hypotheses have been made. It contains abundant lymphoid tissue, as demonstrated by microscopic findings, so it could be an important part of the immune system, such as a priming station [4]; another interesting and important theory is the "safe house" hypothesis: It has been demonstrated to contain different species of bacteria, hence it could be a reservoir of commensal flora, providing a continuous source of "good bacteria" to restore the balance of the gut microbiome when necessary [5]. To strengthen this theory, it has been observed that patients who underwent incidental or prophylactic appendectomy [6,7] had a lower level of richness and diversity of their gut microbiota. Gut microbiota has also been identified to be important for the metabolic homeostasis of the host [8,9]: It could hence contribute to metabolic diseases such as diabetes and chronic heart disease.

The aim of this systematic review is to identify the association between antecedent appendectomy and subsequent development of other diseases, which could be due to the lost "safe house" function of the appendix such as in C. Difficile infections, or to immune role dysregulations such as in systemic lupus erythematosus, rheumatoid arthritis, and cancers and other diseases. In the light of this insight, and of the modern understanding of the natural history of acute appendicitis, which doesn't necessarily evolve into its perforated form [10], it is crucial to change the perspective for acute appendicitis treatment and take into account the potential benefit of a conservative approach that "saves" a useful appendix when possible.

Materials and methods

A systematic review was performed according to the PRISMA guidelines [11]. All comparative studies analyzing the relationship between appendectomy and various diseases (IBDs, cardiovascular disease, type II diabetes, Clostridioides Difficile, Parkinson's disease, malignant neoplasia, primary sclerosing cholangitis and miscellaneous topics sush as TBC, ELS, cholelithiasis) were included. Patients >18 years who underwent appendectomy were comparated with similar populations who did not, and development of a specific disease was assessed in most studies.

An informatic search was conducted by the principal author in several database (Medline, Scopus, Embase) using the terms "appendectomy" OR "appendicectomy" AND "ulcerative colitis", "crohn disease", "IBD", "colitis", "pancolitis", "proctitis", "colorectal cancer", "rheumatoid arthritis", "cardiovascular disease", "cholecystitis", "diverticulitis", "parkinson", "diabetes" and combination of those terms with synonymous and MeSH terms; additionally hand searching of journals was conducted and references lists of pertinent papers was screened. RCT, cohort studies, clinical trials, guidelines, systematic reviews, meta-analysis, case-control and clinical series were included; editorials and narrative reviews were also analyzed to perform a reference list search but were not included in the results as well as case reports.

Restrictions regarding dates of publications were not used, and only articles written in English were selected.

Two authors, (M.I. and M.T.) reviewed the literature to assess the papers which matched the inclusion criteria, when no agreement was found, a third author opinion (L.A.) was sought.

Results

A total of 402 articles were found. Among them 62 studies were identificated after record excluded. Of the 62 studies included in this systematic review 2 were post mortem studies, 1 was a prospective study, 10 were self-reported questionarie based studies, 33 were case control studies, 5 were meta-analisis, there was 1 systematic review and 10 cohort studies (Figure 1).

As for association with specific disease, 2 studies were found that investigated association between appendectomy and cardiovascular disease; 7 studies with Clostridioides difficile; 8 with Parkinson disease; 1 with tuberculosis; 1 with systemic eritematous lupus; 2 with gallstones; 7 with primary sclerosating cholangitis; 23 with inflammatory bowel disease (among them, 10 indagated both Crohn disease (CD) and Ulcerative colitis (UC), 8 indagated UC alone and 5 indagated CD alone); 2 with diabetes and 9 with colorectal, ovarian and hematologic cancer (Table 1-7). Extensive results are reported in the supplementary results section, while discussion is reported below.

R. Andersson et al.	2003	Cohort	212.218 vs 212.218	Appendectomy vs controls	Positive (app-CD)	CD	-Appendicitis: 2.11 (CI 1.21-3.79) -Perforated: 1.85 (CI 1.10-3.18)	-Specificity of diagnosis partially verified -no informations about smoking	If app<10y ↓ risk of CD	22
Kaplan et al.	2007	Cohort	709.353	Appendectomy vs general population	Positive (app-CD)	CD	app-CD: SIR 1.52 (1.45-1.59)	Smoking	If app<10y no risk of CD (SIR1.00;1.80-1.25)	26
Kaplan et al.	2008	Meta-analysis	-	-	Positive (app-CD)	CD	App-CD: RR 1.61 (1.28-2.02)	-	After 5y risk to the baseline	27
Frish et al.	2009	Cohort	709.353	Appendectomy vs "expected"	Negative (app-UC)	UC	App-UC: SIR 1.04 (0.95-1.15)	-databases not for research purposes -specificity of dg partially verified -milder cases of UC not considered -smoking	↓ risk only when app for acute appendicitis and <20y	28
Andersen et al.	2016	Cohort	7.132.317	"Exposed" vs "unexposed"	Negative (appendicitis-UC)	UC	Appendicitis before age 20-UC: RR 0.90 (0.86-0.95)	-genetic and environmental factors	Appendicitis in a first-degree relative ↓ risk	29
Myrelid et al.	2017	Cohort	63.711	Appendectomy vs colectomy	Negative (app-colectomy) Positive (app-colectomy)	UC	Appendectomy <20, before UC dg ↓ risk of colectomy: HR 0.44 (0.27-0.72) Appendectomy after UC dg ↑ risk of colectomy: HR1.56 (1.20-2.03)	-milder cases of UC not considered -few details for patients	-	30
Chen et al.	2018	Case-Control	402 vs 402	Appendectomy vs controls	Neutral (app-UC)	UC	app-UC: 2.74% vs 3.98%, P=0.442 NS	-small number of patients	-	32
Piovani et al.	2019	Meta-analysis	-	-	Positive (app-CD)	CD	App-CD: RR 1.61 (1.28-2.02)	-	-	33
Chen et al.	2019	Systematic review	-	-	Positive (enviromental factor-CD) Negative (enviromental factor-CD)	CD	5 enviromental factors-CD: ↑ risk 4 enviromental factors-CD: ↓ risk	-	-	81
Stellingwerf et al.	2019	Meta-analysis	73.323	-	Positive (app-colectomy)	UC	App-colectomy: OR 2.85 (1.40-5.78)	-	50% of colectomies for CRC	35

IBD: inflammatory bowel disease; app: appendectomy; UC: ulcerative colitis; CD: Crohn disease; MC: microscopic colitis; UP: ulcerative proctitis; CI: confidence interval 95%; SCCAI: simple clinical colitis activity index
*see details in the text

Table 1: Appendectomy associated IBD.

Author	Year	Type	N° of Pt	Populations	Correlation	Disease	Detail corr.	Potential bias	Note	R.
Gilad et al.	1987	Multi centric Retrospective / Self reported	499 vs 998	IBD vs controls	Negative (app - UC) Positive (app - CD)	UC & CD	app-UC:OR 0.27 (CI 0.07-0.81) p<0.001 app-CD: OR 1.64 (CI 1.03-2.62)	CD: disease related laparotomies lead to ↑ App	Patients younger than 20 y	26
Gent et al.	1994	Multi centric Retrospective / Self reported	364 vs 364	IBD vs controls	Negative (app - UC) Neutral (app - CD)	UC & CD	app-UC: OR 0.3 (CI 0.1-0.6) app-CD: OR 1.4 (CI 0.6-3.4)	Recall	CD: ↑ in high hygene	13
Rutgeerts et al.	1994	Case-control	174 vs 161	UC vs controls	Negative (app - UC)	UC	OR: 0.02 (CI 0.01-0.06)	Controls had 25.4% rate of appendectomy (higher than expected)	Non-App ↑↑ than non-smoking as RF for UC	16
Wurzelman et al.	1994	Retrospective / Self reported	503 vs 403	IBD vs controls	Neutral (both)	UC & CD	app-UC: OR 0.3 (CI 0.1-1.1) NS	-	-	17
Smithson et al.	1995	Case-Control	314 vs 243	IBD vs controls	Negative (app - UC) Neutral (app - CD)	UC & CD	app-UC: OR 0.2 (CI 0.07-0.53) app-CD: OR 0.93 (0.39-2.18)	-	-	14
Breslin et al.	1997	Case-Control	311 vs 18i9	IBD vs controls	App - Neutral (both)	UC & CD	app-UC: OR 0.52 (CI 0.24-1.12) app-CD: OR 1.42 (CI 0.79-2.56)	-	Smoking ↑ CD but ↓ UC	15
Minocha et al.	1997	Case-control	193 vs 394	UC vs control	Negative (app - UC)	UC	OR: 0.25 (CI 0.13-0.5)	-	-	18
Russel et al.	1997	Case-Control / self reported	441 vs 602	IBD vs controls	Negative (app - UC) Neutral (app - CD)	UC & CD	app-UC: OR 0.36 (CI 0.15-0.8) app-CD: OR 1.65 (CI 0.96–2.91)	Recall; other confounding	UC: app protective only in pancolitis	19
Duggan et al.	1998	Case-Control / self reported	333 vs 337	IBD vs controls	Negative (app - UC) Positive (app - CD)	UC & CD	app-UC: OR 0.2 (CI 0.1-0.4) app-CD: OR 1.28 (0.7-2.3) NS	-	If app in <20y effect on UC ↑	20
Koutroubakis et al.	1999	Case control	210 vs 210	IBD vs controls	Neutral (app-UC) Positive (app-CD)	UC & CD	app-UC: OR 0.37 (CI 0.12-1.18) NS app-CD: OR 3.57 (1.32-9.67)	-	-	21
R. Andersson et al.	2001	Cohort	212.963 vs 212.963	Appendectomy vs controls	Negative (app - UC)	UC	-Appendicitis: 0.75 (0.62–0.90) -Perforated: 0.59 (0.34-0.99) -Incidental: 1.34 (0.77–2.38)	High number of UC patients and control excluded within 1 y from appendicitis	sig. only in <20y; *NS* in incidental app.*	25
Frish et al.	2001	Prospective	154.434	Appendectomy vs "expected"	Neutral (app-UC) Positive (app-CD)	UC & CD	app-CD RR: 2.88 (CI 2.45-3.39)	41% of the cases incidental appendectomy	After 5y lost correl. app-CD	23
Frish and Gridley	2002	Case-Control	10.498 vs 52.926	Appendectomy vs controls	Positive (both)	UC & CD	app-UC: OR 1.6 (CI 1.3-2.1) app-CD: OR 2.5 (2-3.3)	Populations: (only man, mean>50y)	-	24

Table 2: Appendectomy associated cardio.

Author	Year	Type	N° of Pt	Populations	Correlation	Disease	Detail corr.	Potential bias	Note	R.
Janskzy et Al	2010	Case-Control Cohort	54.449 vs 272.213	Appendectomy vs *controls*	Positive	AMI	HR 1.35 (CI 1.07-1.7)	Common misconosciute RF	HR positive only in >20 y*	37
Chen et Al.	2015	Case-Control Cohort	5.413 vs 16.239	Appendectomy vs *controls (*30d excluded)*	Positive	IHD	HR 1.58 (CI 1.32-1.89)	Common misconosciute RF; survelliance bias	HR positive in all age groups	38

AMI=acute myocardial infarction; IHD= ischemic heart disease, *see details in the text

Table 3: Appendectomy associated diabetes.

Author	Year	Type	N° of Pt	Populations	Correlation	Disease	Detail corr.	Potential bias	Note	R.
Wei et al.	2015	Retrospective Matched-cohort	31.512	Appendectomy vs matched controls	Positive	DM	Adj HR 1.3	Common, unknown risk factor	HR increases w/ perforation	39
Lee et al.	2018	Retrospective Matched-cohort	10.954 vs 43.815	Appendectomy vs matched controls	Neutral	DM	Adj HR 1.37(<30y) 2.45(<20y)	Common, unknown risk factor	Positive correlation for age<30	40

DM: type II Diabetes, *see details in the text

Table 4: Appendectomy associated clostridium.

Author	Year	Type	N° of Pt	Populations	Correlation	Disease	Detail corr.	Potential bias	Note	R.
Fujii et al.	2010	Retrospective Case-control	386	App. vs *controls*	No correlation	CDI *severity* OR *recurrence*	OR 1.2(relapse) 0.8(severity)	No data on first infection *	Appendectomized patients -> longer diharrea	42
Im et al.	2011	Retrospective Case-control	254	App. vs *controls*	Positive	CDI *recurrence*	adj-RR 0.398 if app present	Lack of transversal follow-up; appendix presence detected by TC	Appendix protective for recurrence	43
Merchant, al.	2011	Retrospective Case-control	257	App. vs *controls*	Negative	Toxin test positive	-11.6% rate CD + in appendectomized	No correlation w/ clinical signs; no diagnostic criteria	Appendix potential protective*	44
Ward et al.	2013	Retrospective	102	App. vs *controls*	Absent	CDI	No difference	//	//	45
Khanna et al.	2013	Retrospective	355	App. vs *controls*	Absent	CDI *severity* OR *recurren.*	No difference	//	//	46
Yong et al.	2015	Retrospective	507	App. vs *controls*	Positive	CDI requiring colectomy	OR 2.1 (risk of colectomy for appendectomized)	//	Appendix protective for colectomy	47
Franco et al.	2019	Retrospective	250	Appendectomy vs *controls*	Positive	CDI *Recurrence*	Recurrence 51% vs 44.3%	High rate of relapse in general	Appendix protective for hospitalization	48

DM: type II Diabetes, *see details in the text

Table 5: Appendectomy associated parkinson.

Author	Year	Type	N° of Pt	Populations	Correlation	Disease	Detail corr.	Potential bias	Note	R.
Mendes et al.	2015	Retrospective cohort / self reported	295	Appendectomized	Negative	PD	HR 0.63 CI 0.41-0.98 p=0.04	Recall bias	Affect onset, not progression	49
Marras et al.	2016	Cohort prospective / dataset	42.999	Appendectomy vs cholecistectomy vs controls	Neutral	PD	HR unchanged	10 years follow up	//	50
Svensson et al.	2016	Cohort prospective / dataset	265.758	Appendectomy vs controls	Positive	PD	HR 1.14 CI 1.03-1.27	Common risk factor	Follow up 20y	52
Yilmaz	2017	Retrospective case-control	1625	PD & Parkinson-like & controls	Neutral	PD	//	Recall bias, small "event" sample	//	51
Palacios et al.	2018	Cohort self reported / prospective	121.000 & 51.000	Self reported appendectomy	Neutral	PD	//	Unability to assess date of appendectomy	HR increased in appendicitis vs incidental	53
Killinger et al.	2018	Datasets, cohort mixed + immunoistochemical essays	1,6 million	General population & PD	Negative	PD	-19.3% incidence of *sporadic* PD in appendectomized	//	A-syn rich appendix; ↑in rural; ↑ 3.6 years onset	54
Hai-tao Lu et al.	2020	Meta	5 studies	//	Neutral	PD	RR 1.02,CI 0.87–1.20, p= 0.789	High variability (I2 = 83.1%)	//	55
Mohammed et al.	20xx	Dataset	62 million	Appendectomized,PD and general	Positive	PD	HR 3.19 (CI 3.1-3.28 p=0.001)	6 months washout*	largest, U.S. dataset	60

*see details in the text

Table 6: Appendectomy associated cancer.

Author	Year	Type	N° of Pt	Populations	Correlation	Disease	Detail corr.	Potential bias	Note	R.
McVay	1964	Postmortem	914	Colon cancer/vascular disease/other neoplasia	Positive	Cancer	24.2% vs 11.7% p<0.006	Post mortem data; presence of incidental appendectomy	colonic, and noncolonic 60y -> increased correlation	56
Howie et Al.	1965	Quest- retrospective	152	Cancer VS healthy controls	No	Cancer	/	No information on "healty-controls"		57
Howard Bierman	1967	Retrospective/ postmortem	1.409	122 leukemia/lymphoma and 1287 post mortem	Positive	Cancer	35% vs 24.3% p<0.001	Post mortem data; presence of incidental appendectomy	Ovarian, colon and breast + corr.*	3
Cassimos, Al.	1973	Retrospective	1.000	500 cancer vs 500 healthy contriols	Mixed(details in text)	Cancer	Man: 18.7% vs 10.4% p<0.01	No information on "healty-controls", no info on timing	Ovarian and breast positive correlated	2
Friedman et Al.	1990	Cohort	167.561	Multifasic questionnaires + national database	No	Cancer	RR 0.8 to 0.9	10 year median follow up		6
Mellemkaer et Al.	1997	Cohort	82.157	Appendectomy *vs general population*	No	Cancer	SIR 1.05	10 year median follow up	Increasing years of follow up incresed SIR	23
Wu et Al.	2014	Cohort	75.979 vs 303.640	Appendectomy vs no-appendectomy matched cohort	Positive	Cancer	14% higher in appendecomy patients*	unexplained absence correlation in women	HR 12.9 in men >60y	58
Song et Al.	2015	Cohort	480.382	Appendectomy vs *general population*	No	Cancer	SIR 0.98 to 1.03	*SIR in high prevalence disease		59
Lee et Al.	2018	Cohort	707.663	Appendectomy & Cholec. *vs general population*	No	Cancer	SIR 1.43 for appendectomy	*SIR in high prevalence disease; 13 y followup	Lose sign. When extended period	60

*see details in the text

Table 7: Appendectomy associated miscellaneous.

Author	Year	Type	N° of Pt	Populations	Correlation	Disease	Detail corr.	Potential bias	Note	R.
Lai et al.	2014	Case-Control (Cohort)	11.366 vs 45464	Tubercolosis vs control	Positive (appendectomy)	TBC	app: adj OR 1.4 (1.13-1.75)	Retrospective nature	//	61
Chung, Lin et Hsu	2018	Case-Control (Cohort)	80.582 vs 323.850	Appendectomy vs control	Positive	LES	Adj HR 2.04 (1.52–2.76)	Not transversal on population*	aHR for women<49y: 2.27	62
Chung et Al.	2016	Retrospective Cohort	4916 *vs* 4916	Appendectomy vs matched controls	Positive	Gallstones	HR 1.79(CI 1.29-2.48) p<0.001	Common risk factor high likely	Positive correlation for woman	63
Kim et Al.	2020	Retrospective Cohort	14955 *vs* 59820	Appendectomy vs matched controls	Positive	Gallstones	1.4% vs 0.8%; HR 1.77 (CI 1.51-2.08) p<0.001	Common risk factor high likely	Loss of positive correlation after 1 year	64
Van Erpecum et al.	1996	Case-Control	59 vs 130 vs 197	PSC vs UC vs Control	Absent (appendectomy)	PSC	OR 1.44 (CI .67-3.12)	Small sample size	Smoking ↑ appendicitis but ↓ PSC	65
Mitchell et al.	2002	Case-control /Self reported	170 per group	PSC vs UC vs Control	Absent (appendectomy)	PSC	OR 1.11 (95% CI 0.57–2.2)	Small sample size	//	66
Florin et al.	2004	Case-Control	90 vs 450	PSC/IBD vs controls	Absent (appendectomy)	PSC	25.8% vs 23.2% (p=0.69)	Small sample size	Data corrected for smoking; appendectomy delays onset PSC	67
Andersen et al.	2014	Case-Control / Self reported	240 vs 245	PSC vs control	Absent (appendectomy)	PSC	app: 17% vs 13% (NS)	Small “event” sample size	//	68
Eaton et al.	2014	Multicentric / Self reported/ Case-control	1000 vs 663	PSC (PSC+IBD *and* PSC-IBD) vs control	Absent (appendectomy)	PSC	OR 1.1 (0.8-1.6) p=0.52	//	Correlation present with all PSC considered*	69
Boonstra et al.	2016	Case-Control / Self reported	343 vs 232	PSC vs control	Absent (appendectomy)	PSC	13% vs 13% (NS)	Small “event” sample size		70
Wijarnpreecha et al.	2018	Meta-Analysis	2432	PSC vs control	Positive	PSC	1.37 (95% CI 1.15—1.63)	Publication bias	//	71

*see details in the text

Discussion

Inflammatory bowel disease

Up to 2000, several studies tried to evaluate the effect of appendectomy on development of IBD, with great success in linking appendectomy to UC with an inverse rapport. Russel et al [12] expanded the research on both UC and CD and they found that appendectomy was only protective when UC was manifesting as pancolitis (OR, 0.2; 95% CI, 0.02–0.7).

Confounders could be acting, but they should not have a strong impact. One potential confounder is smoking. It is known to lower the incidence of UC and to increase the incidence of acute appendicitis [13]: smoking patients could develop more frequently appendicitis, undergo appendectomy, keep smoking and never develop UC. Several studies took this potential confounder into account [12,14-19] and did not find it to minimize the effect of appendectomy on UC.

Another concern regarded the time relationship: did the appendectomy result in less UC, or did the diagnosis of UC prevent appendectomy? [20] Given that, several studies excluded patients who had been diagnosed with UC prior to appendectomy, this eventuality seems highly unlikely [21,14,22].

Two hypotheses seem to be the most likely: either appendectomy is protective for UC, or some biological factors exist that predispose for acute appendicitis and at the same time are protective for UC.

Appendix is a T-helper organ. According to the first hypothesis, its removal could affect the balance toward a prevalent suppressor T-cell function, limiting the development of UC. This was also supported by a study that examined the effect of appendectomy in developing IBD on genetically engineered mice (in whom a mutation predisposing to IBD was induced). In that study, if a mice had an appendectomy performed, it would develop IBD in 3.3% of the cases, conversely it would develop it in the 80% [23].

If the second hypothesis is real and some factors which leads to appendicitis are protective for UC, it could be reasonable to expect that the reverse association with UC would emerge only in true acute appendicitis and would not be observable when the appendix is removed “incidentally”. This is what Andersson et al. [22] found in their cohort study: when patients who underwent incidental appendectomy were analyzed, no correlation with UC was found. This appeared to be the state of the art until Frisch et al [24], some months later, fearing that those retrospective case-control studies were threatened by methodological implication, conducted a large and well-designed prospective study that demonstrated no association between appendectomy and UC. They concluded that this random relationship was reflecting difficult differential diagnosis in abdominal pain, such as patients with abdominal pain who underwent appendectomy only to discover later that there was no acute appendicitis at a histological level and were correctly diagnosed with UC or CD with a follow-up diagnostic workup. Among all their appendectomies, the 41% were incidental, hence without a real acute appendicitis. However, the hypothesis that abdominal pain would confound the diagnosis may be unlikely: if it was so, it would be expected for “incidental appendectomy” to carry the higher risk of UC, instead the opposite was observed.

Frisch et al [25] conducted later a wide cohort study in Sweden and Denmark to assess if the lower risk of UC observed in patients after appendectomy could be related to the surgery itself or directly to the disease. They found out that the significant reduction of the risk was correlated with appendectomy done for appendicitis before age 20, therefore in presence of inflammation of the appendix. The surgery done without underlying inflammation did not reveale the same result, in fact there was no reduction of UC after appendectomy. Similar results came out from the analysis of those with affected relatives: appendectomy without inflammation did not modify risk of UC and surgery for acute appendicitis decreased the risk. For this reason, they stated that prophylactic appendectomy should not be performed in patients at risk of developing UC.

A constitutional immune hypothesis has been proposed: factors associated with a predisposition to a Th1 or a Th2 immune response may be different in patients with UC from those with acute appendicitis. Th1 proinflammatory response seems to be higher in acute appendicitis, while Th2 response is predominant in UC.

Cheluvappa et al [26,27] tried to investigate the link between appendectomy and colitis in a deeper way. They examined determined gene sets to better understand the pathological mechanism of IBDs and investigate the changes made on distal colitis. They created a murine experimental model of appendicitis and appendectomy (AA) to study which chemokines were involved in colitis amelioration.

Given that appendectomy reduces UC pathology somehow decreasing the intensity of CD, and that chemokine are known to induce chemotaxis in adjacent cells with specific receptors, they analyzed chemokines gene expression to find potential targets to use to improve colitis pathology in animal models, and later they may be a resource to use for human IBDs too.

Despite all the studies conducted about IBDs until that moment, the relationship between appendectomy and CD remained unclear. Kaplan and colleagues tried to clarify this connection carrying out a population-based cohort study in Sweden and Denmark [28]. They tried to assess the risk of CD after the removal of the appendix. Two-thirds removed the appendix because of acute appendicitis (perforated and non-perforated), the remaining ones had macroscopically normal appendixes: all appendectomies performed in patients older than 10 years were associated with an increased risk of developing CD for both sexes, especially in the first year. The higher risk was found with the perforated form and with non-inflamed appendix.

They also performed a meta-analysis [29]: it showed a significantly elevated risk of developing CD, which was higher in the first year post-surgery and slowly fading in five years as already demonstrated by Friesch et al [24] and their previous study [28]. The higher risk during the first year may be a diagnostic bias of CD presenting with right lower quadrant abdominal pain similarly to acute appendicitis or it may rarely involve the appendix and precipitate appendicitis. Counfouder factors such as smoking, the stronger genetic influence in juvenile onset of CD and the involvement of the appendix itself could not be assessed because this study did not take them into consideration. Smoking is a known risk factor for CD, the adult form of CD appears to be more influenced by environmental factors than the juvenile one and the

involvement of the appendix may lead to a perforation causing a severe form of appendicitis.

So far, appendectomy has been reported to be associated with a lower risk of UC in individuals who underwent surgery before age 20 [30-32].

The effect of surgery on the course of the disease seems to lead to less relapses and less need for immunosuppressant therapy in individuals who have had appendectomy before UC diagnosis. Lastly, it seemed to lead to a lower risk of colectomy when appendectomy was performed in early life prior to UC diagnosis and vice versa a higher risk of colectomy when performed after UC diagnosis.

At this point, the idea of appendectomy as a valid treatment for patients suffering from UC started to be attractive. Among the first ones to suggest this optionwere Bolin and colleagues [33], who conducted a prospective study with a cohort of 30 patients to determine if appendectomy may be proposed as a valid therapeutic alternative, specifically for patients suffering from ulcerative proctitis. After surgery, the amelioration was significant: 27 out of 30 patients clinically improved, and 40% (12 out of 30) were even able to interrupt medical treatment thanks to a complete resolution of the symptoms.

The delayed time between appendectomy and the amelioration of symptoms of ulcerative proctitis is the same observed in immunomodulating therapies usually used for the disease: this may suggest that the appendix acts as a priming station for the immune response in the mucosa of the intestine, which contributes to the pathogenesis of UC.

According to this study, the therapeutic role of appendectomy for UC is a promising and valid option, however deeper investigation is still needed.

Felice et al [34] conducted a review in which they identified influencing factors of the clinical outcome of UC to evaluate the possible therapeutic role of appendectomy. Despite contrasting results came throughout their literature analysis, a possible therapeutic role of appendectomy for UC patients is present.

However, the evidence is not strong enough to make the procedure a routinely used treatment. Some factors need a deeper investigation, for example the risk of colorectal cancer and colectomy after appendectomy in UC patients. This is what Stellingwerf et al [35] analyzed in a systematic review and meta-analysis. They analyzed 891 studies, the overall result was that colectomy rate were not significantly different in patients who underwent appendectomy from the ones who did not. Patients who were appendectomized after the diagnosis of UC had a slightly higher risk of colectomy compared to the ones who were appendectomized before the diagnosis of UC, as already shown by Myrelid et al [36]. and Felice et al. [34], however this difference was not statistically significative.

They also noticed a slightly longer duration of UC in appendectomized patients, this may be explained by the fact that appendectomy itself slows down the clinical course of the disease, but it does not completely remove the inflammation from the gut mucosa. This long-lasting inflammation could eventually promote tumor turnover, cell overgrowth, genomic instability and neoangiogenesis. Therefore, a postponed colectomy may eventually lead to colorectal cancer.

For this reason, colectomy performed due do colorectal cancer was significantly higher after appendectomy.

When analyzing those results, possible confounders for CRC need to be taken into consideration: longer duration of UC disease, less use of medications, primary sclerosing cholangitis and family history of CRC.

Those studies need to be continued, the clinical improvement of patients suffering from UC after appendectomy has been demonstrated but the possible risk of CRC must be investigated before considering appendectomy as a routinely used therapeutic procedure.

In the work of Radford-Smith [37] the importance of appendectomy in the natural history of IBDs is discussed.

Regarding UC, a highly significant inverse relation with appendectomy related to the age has been established: appendectomies performed at a younger age are protective. Appendectomized patients also need lower doses of immunosuppresants, they have better prognosis with a milder clinical presentation and less use of immunosuppreant therapies. In addition, the inflammatory activity of the appendix and colon was analyzed by Sahami et al [38]. using biopsies from patients before and after appendectomy: 28/30 patients had an inflamed appendix, and the reduction of inflammation was observed in 46% of biopsies done after appendectomy. The inflammatory infiltrate was predominantly formed by CD4+ T lymphocytes in both specimens, confirming similar inflammatory pathways in both appendicitis and colonic inflammation. Those findings are encouraging for a possible therapeutic role of appendectomy in UC patients, however, in addition to the previously mentioned studies, it is important to keep in mind that the appendix may be a “skip lesion” in UC.

On the other hand, the relationship between appendectomy and CD is not clear yet. It may be confounded by the similar clinical presentation of the two diseases: both presenting with right lower quadrant abdominal pain. This could be the reason for surgeries performed on patients with macroscopically normal appendixes, who were then diagnosed later with CD, only when a subsequent diagnostic work up was done. Moreover, the appendix is infrequently involved in the inflammation of CD, despite its location near the ileum.

Regarding the natural history of CD, a more extensive but clinically milder colitis was identified in patients who underwent appendectomy.

Only a minority of studies did show a positive association between appendectomy ad CD, the rest of them did not.

The effect of appendectomy on the natural history of CD is not clear. It seemed to delay the presentation and diagnosis of the disease and to be associated with an increased risk of intestinal resection when appendectomy is performed due to perforated appendicitis. This last finding may be suggestive of a meaningful variation in both genotype and phenotype of patients with perfo-

rated and non-perforated appendicitis.

Cardiovascular disease

It is possible that the association between cardiovascular disease and appendectomy lies in the increased risk of AMI in patient who had undergone surgery, compared with patient that did not. Janszky et al [39]. suspected this bias in their study and offered another "control group" composed by patients who had undergone hernia repair to indagate if the surgery itself would be a risk factor for AMI. When analyzing the appendectomy group vs "non-surgery" it was noted that the risk of increased AMI would manifest only if patients who underwent appendectomy were younger than 20 years: this due to the pathophysiology of the association. Vermiform appendix is thought to exercise to the maximum his immunomodulation in the early 10-20 years of life, this would explain why the effect would only manifest in that sub-group. Hernia surgery group, in contrast, apart from sharing known risk factors for AMI, (smoking, obesity) did not manifest this change in the effect over year. In every-age group there was an elevated HR for hernia surgery and AMI. If surgical intervention would itself constitute a risk factor, it would have been the same even in patients older than 20 years at the index operation.

When comparing appendectomized patient to a non-surgery group, surveillance bias must be addressed. In order to reduce this bias, Chen et al [40] excluded in their study all the patient that developed an heart disease in the 30 days after the appendectomy (those patients whose heart disease could be unmasked from an hospital admission due to appendicitis but unrelated to it), when such an analysis was performed, HR would remain significant (1.58 $p<0.001$).

If there is a common factor between cardiovascular disease and appendicitis, this could be smoking [13], moreover in studies when this was indagated the association resulted to be stronger with women, which therefore we would expect manifesting in a women to man ratio in cardiac event after appendectomy, which in the studies of Chen and Janszky did not happened.

Diabetes

If appendix can modulate immunity, and type II diabetes as thought can find its pathogenesis as inflammatory disease [41], it is reasonable to look for a link between type II Diabetes insurgence and appendectomy. Wei et al. and Lee et al. [42,43] found this correlation in their well designed and powered studies but Lee et al. failed to demonstrate an association on the general population, and found that DM would only develop more frequently in appendectomized patients younger than 30 year, suggesting that there is a specific timeset in which the appendix performs its immune and modulatory functions. Wei, observed that the risk of developing Type II diabetes were even higher in patients who suffered from perforated appendicitis compared with uncomplicated appendicitis.

Recent data supports the hypothesis that perforated appendicitis is not the natural evolution of acute non-complicated appendicitis but that the two are separate pathological entities, given that from a 30 years analysis of incidence it had been proved that the trend in the two pathologies was untied [44].

It has been proposed that development of perforated appendicitis could be related to a polymorphism of IL-6 gene that causes a deeper inflammation leading to perforation [45] and that signaling pathways of IL-6 could be implicated in development of type II diabetes as well [46]. If those speculations are real, it is possible that a common risk factor exist for development of acute perforated appendicitis and development of type II diabetes, in such scenario, the removal of the appendix would probably not determine development of diabetes itself but would be a consequence of a common risk factor. The relationship between *uncomplicated* appendicitis and development of diabetes and, as suggested by other studies [47] chronic kidney disease associated to diabete, remains evident and unexplained.

Clostridioides difficile

CDI infection is a worldwide problem, as well as recurrence after first episode, which can occur up to the 20-30% of the cases [48]. First recurrence usually occurs after 2 weeks of termination of antimicrobial therapy and the risk of recurrence is increased for each recurrence (e.g. after one recurrence risk rises up to 40%, after two recurrence risk of another recurrence is 60%) [49].

Although Fujii et al [50] in their study didn't demonstrate any association in severity and recurrence, their work did not indagate the insurgence of a first episode of CDI, nor is reported the specific on the duration of diarrhea which was found to be longer in Appendectomized patients – this itself, could partially validate the theory that appendix is a "safe house" for saprophytic gut bacteria that repopulate GI tract after infective colitis. Im et al. [51] one year after, with a similar designed study, found a strong relationship between CDI recurrence and presence of appendix. Merchant et al [52] and later Ward and collegues [53] with their studies denied those results, but their work was biased by the absence of clinical signs of disease: CDI is definite by a positivity stool test along with clinically relevant diarrhea (3 or more loose stools in 24 h) [54,49]. In their study, Merchant et al. did not searched for CDI patients, given that the clinical status wasn't stated, instead they searched for patients with positive stool samples unregardless of presence or absence of clinical symptoms.

Recent data suggest that asymptomatic carriers of some non-toxigenic strains of C. Difficile may actually be protected from development of the disease [55,56], with this in mind, having appendix removed and testing negative for C. Difficile in absence of clinical signs, may actually increase the risk of developing future infection from a more virulent strain of CD.

Khanna et al. [57] took into account the presence of symptoms defining CDI, and still wasn't able to demonstrate any correlation between severity or recurrence of CDI and appendectomy status. Clanton et al (7c) as well as Yong et al (8c) demonstrated a strong association between absence of appendix and need for total colectomy, leading to the idea that the presence of appendix could be protective for the insurgence of fulminant CDI.

Franko et al. [58] pointed out that appendectomized patients more frequently need hospitalization for CDI recurrence. This could itself be an indicator of a more severe disease in appendectomized patient; additionally they found a little increase in the recurrence nevertheless authors concluded that appendix status appear unrelated to CDI recurrence, we disagree on this and giving that their rate of recurrence appears slightly higher compared

to the general rate of recurrence which is about 30% [49] (vs 45.6% in their work) we suspect that some "non-appendectomy" patients who didn't experienced recurrence may be lost, or that some "non-appendectomy" patients may have developed a paucisymptomatic form of CDI and therefore haven't been clinically identificated, as already proposed by prof. Yong and collegues (8c).

Parkinson disease

A modern proposal on the pathogenesis of PD implies that initiating events could spread from an organ outside the brain, like GI tract [59]. This could resonance with the evidence that GI symptoms are frequent and can even precede neurological impairment in PD [60]. The immune reactivity as well as the quantity of aberrant alpha-synuclein appear to be relevant thoughout the GI tract, especially into the appendix [61]; additionally appendix receives a dense vagal innervation – and it has been demonstrated that truncal vagotomy reduces PD insurgence [62], this in turn gave birth to several speculation towards a role of appendix in the development of PD. Mendes et al. in their study concluded that surgical removal of appendix could delay (but not stop) the insurgence of PD [63], removing a potential area where pathologic a-syn can build up and than migrate to the brain. They didn't find difference in PD clinical symptoms or drug dosage in appendectomized vs non-appendectomized patients and concluded that even if appendix could affect PD onset, it wouldn't affect progression.

Marras et al. and Palacios et al [64,65] refuted those results with their large, cohort and questionnaire based study (respectively).

Palacios et al found no correlation, while Marras found a slightly increase in PD detection in patients underwent appendectomy when compared with non-surgery group, but this would fade when comparing with cholecystectomy group underlining that the surveillance bias more than the real implication was responsible for the rise in PD rate. Yilmaz et al [66] failed to find any association between appendectomy and PD, but in their cohort of PD only a total of 69 patients had undergone appendectomy, therefore their results resulted unpowered.

Those studies are denied by Svensson: given that PD is a slow developing degenerative disease, and many years must pass before enough substantia nigra is damaged in order to show symptoms, a 10 years follow up (as in the work of Marras et al.) wouldn't be long enough to investigate association between appendectomy and PD; moreover Palacios et al. didn't have access to the date of appendectomy and couldn't speculate how much time would have pass from the index operation to PD diagnosis. Svensson [67] with a longer follow-up trial, showed no benefit in delaying onset of PD with appendectomy; PD incidence was slightly increased by appendectomy, suggesting some link between the two entities.

This would also match with the results by Palacios' research team who found an increased risk of developing PD only in patient underwent appendectomy for appendicitis compared with removal of healthy appendix [65].

At least one common risk factor is known for both pathologies, and it is smoking [13,68], but interestingly it should increase risk of appendectomy and decrease risk of PD [69], therefore it is hard to imagine that the same factor would lead to increase in both pathologies.

Up to 2016, Svensson results seemed to lead the scene, until two years later when, with their work Killinger et al. [70] disowned their results. They demonstrated, with a large database of 1.6 million patients, a reduced risk of PD in appendectomized patients (-19.3%) with a 52 years follow up. In addition, they conducted immunohistochemical analysis that showed elevated quantity of aberrant alpha-synuclein in the appendix of patients who had appendectomy who *didn't* have PD; they concluded that removal of appendix can somehow reduce the risk (or at least slow down) of PD by removing a pathogenic area where a-syn can accumulate. While fascinating, this is in contrast with a recent research conducted by Mohammed and Cooper [71] with an even higher dataset of 62'218'050 patients: they found that the RR of developing PD was 3.19 (CI 3.10-3.28 $p<0.001$) in patients appendectomized compared with non-appendectomized patients. Authors withheld enthusiasm given the principal flaw of their study, that is a washout of only 6 months between appendectomy and PD diagnosis that, as seen, could bias results, but in the light of the finding of Killinger et al. that alpha-syn accumulates are found in "healty", non-PD patients as well, it was proposed that surgical manipulation of an hot spot of a-syn such as the appendix during appendectomy, could lead to increased rate of PD. All the studies aforementioned, with the exception for two (one because unpublished, the other because unrepresentative) [71,63] were included in a recent meta-analysis [72] that found no association between appendectomy and PD. As we already stated, there were high heterogenicity between the studies, mainly attributable to the high differences in follow-up length. In our opinion, the arguably most reliable study [70] with the longer follow-up should be taken into account while assessing the possibility of an interaction between appendectomy and PD, until time-analysis of ongoing studies are available [71].

Malignant neoplasia

Initial postmortem trials showed a strong, sed suspicious correlation between appendectomy and cancer [1]. Postmortem material can frequently be biased because if a patient have had an autopsy she must have been ill enough to be hospitalized, therefore many cases could be missing if the death has occurred at home. Another bias is that in the past (and still up to this day) appendectomy was sometimes incidental to the laparotomy: if a surgical exploration of the abdomen was performed (for every reason), appendectomy was performed. This would result in two effects: 1) some appendectomy of the postmortem data did not happened during acute appendicitis, but this fact does not interfere with our search for a protective or harmful effect of maintaining an healty appendix; 2) some patients who had to be operated on for oncological purpose (e.g. open colorectal excision or open gynecological procedures) would have their appendix removed therefore biasing the results in favor of an apparent protective effect of appendix.

In many studies an higher incidence of appendectomy is noted in woman compared to men, this is due to incidental appendectomy which is more frequent in woman given the gynecological procedure to which are exposed.

Another issue is the high prevalence of appendectomy in patients with colon cancer: Did the patient had a previous appen-

dectomy related with the insurgence of the cancer or the appendix have been removed along with the colonic cancer at the index operation? This confounding effect could also bias the data on ovarian cancer but there is no way we can imagine how this could bias data on breast cancer, which appear to be relevant.

After the initial enthusiastic reaction to the potential correlation between appendectomy and colonic cancer, some epidemiological studies started to emerge. Among them, the study of Moertel et al. (non ancora trovato) with 1770 patients had the biggest cohort for its time. They showed lack of correlation between appendectomy and incidence of new cancers. The lack of correlation was also demonstrated by friedman et al [73] and late by mellemkaer [24]. Those studies led the initial enthusiastic response fade, although all of them had a potential bias: their median follow up was around ten years, which in our opinion could be too short for observing the carcinogenic effect expected of the removal of the appendix.

It have been argued that the increase in colorectal cancer seen in appendectomized patients derives from a common (sed unidentified) risk factor that could increase the incidence of both pathologies. If this was the case, epidemiological studies would have shown a correlation for all age populations and all time long follow-up, sed frequently this isn't true. In (5) we observe 53 colorectal cancer in the appendectomized cohort of 80'000 patients and 54 expected cancer in the general population with a SIR of 1, additionaly in the same study, while the incidence of cancer (unregard less of the location) would increase in response to appendectomy, when analyzing a longer follow up period, this wasn't standing for the colorectal cancer alone in which the SIR would remain 1. In our opinion it is unlikely that a common risk factor for appendicitis and colorectal cancer would not manifest in a 10 year period of follow-up (at least for the appendicitis which is a disease common to the young people), but it is possible to show that appendectomy is a risk factor for cancer if a follow up period of 20/30 year is observed. This theory of ours is contradictory with the largest trial that positively correlate appendectomy and colorectal cancer [3]. In that trial a trend towards increased colorectal cancer was observed in appendectomized group but it was observed in the first 3.5 years of follow-up, later the increase in colorectal cancer in response to appendectomy would fade, suggesting that the effect of appendectomy on cancer pathogenesis should be more incisive in the first years after the index operation: this observation relates quite badly with the theory of carcinogenetic effect of appendectomy. For this 3.5 year time of increase colonic cancer after appendectomy we must consider the possibility that this relates to some form of surveillance/detection bias [74]. This option is further corroborated from the net effect that we see in older people compared to young patients: it is usual for older patient to get a preoperative CT scan or a follow-up colonoscopy after appendectomy that could show a neoplasia that would have gone undetected. On the other hand it must be noted that in order to mitigate this effect Wu et al. excluded all the patients of their cohort that had a diagnosis of cancer after 18 months from the appendectomy, therefore the reason for the increased incidence only in the first 3.5 years remains unexplained. Lee et al [75] conversely, showed that *if* the cases of colorectal cancer that occur after 3 years from appendectomy are excluded, the correlation between appendicitis and colorectal cancer disappears with a non-significant SIR – thus corroborating the idea of existence of some form of detection bias. Although the population of more than 700.000 patients it extremely large, Lee et al had a low number of events: ("events" is here referred to occurrence of colorectal cancer) 69 in the total 13 years period. When analyzed further, we find that 56 of those events (81%) happened in the first 5years, and the amount of colorectal cancer in the ">5 years" group follow-up is 13: quite unremarkable number to make assumptions on the long term effect of appendectomy.

"Standardized incidence ratio" is a calculated surrogate of the relative risk (RR) of developing a disease (e.g. colonic cancer) of the exposed population (e.g. appendectomized) compared with the "*general population"* rates. This measure does not takes into account that patients exposed to the presumptive causative factor, *are* themselves part of the general population to which are compared to, therefore for high incidence disease (such as appendectomy) [76], the real RR may not be reflected from the SIR. Existence of this bias was demonstrated in a study which considered SIR for developing Kaposi Sarcoma (KS) and other cancers in persons with HIV/AIDS (PWHA) [77]. The authors retained that SIR would under estimate the incidence of those specific cancers (KS, etc.) in the PWHA, therefore compared the incidence of cancer with some "corrected" SIR in which from the general population was *removed* all the PWHA patients; with this adjustment, RR was found to be very higher. (SIR of developing KS: 117; SIR of developing KS with the SIX-"excluded" method: 657).

The established correlation between PSC and IBD [78], among with the relationship between appendectomy and UC led several authors to the investigation of correlation between appendectomy and PSC. The first work between 1996 and 2016 were unable to find any direct correlation with the ecception of Eaton et al. [79] and Boonstra et al. [80], who found a correlation between appendectomy and PSC only when the PSC group included those who had synchronous IBD, conversely, when "pure" PSC were compared with healthy controls, appendectomy would remain consistent between groups.

Recently, a meta-analysis by Wijarnpreecha et al. [81] found a correlation, but they were unable to separate the cohort of patients with "pure" PSC and PSC-IBD, additionally their excellent work highlighted a publication bias on the topic, making the results unreliable to draw definitive conclusions.

Miscellaneous topic

If the vermiform appendix has the ability to act as immunological barrier [82], its removal could accelerate bacterial translocation into the venous circulation of the bowel (which is the hepatic portal circulation), therefore potentially affecting the ability of liver cells to secrete bile acids [83] and increment the rate of gallstones formation as suggested from Chung and Kim [84,85]. The main criticism to this causative relationship would be the existence of common risk factors for development of cholelithiasis and appendicitis (and therefore appendectomy), which moreover is already known to exist. Those risk factors are obesity, smoking, alcohol, and dietary habits [86,87]. If this is the case, thus, we would expect also other pathologies related to those risk factors to be correlated with appendectomy such as hypertension, diabetes, dyslipidemia, etc. Conversely, in their large cohort, Kim et al [84] observed a similar rate of those pathologies in both groups and a slight increase in ischemic heart disease in appendecto-

mized (4.1% vs 3.4%), whose potential motivation are further explained elsewhere in this paper.

In the other large work on the topic, Chung [88] concluded that removal of the appendix could be responsible, through an immune-system disarray, to development of SLE in young woman. With their study they found that up to 41.5% of the SLE occurring in their cohort could be eliminated by eliminating the "appendectomy" factor.

In our clinical scenario where appendectomy is liberal, "white" appendectomy rate is still high and safe options exist to treat the majority of acute appendicitis without recurring to surgery [89] the implication of this 41.5% reduction would be great for clinical practice. However in their cohort the results were not longitudinally applicable: in male patients, low income patients and patients living at a mid/low urbanization level, appendectomy didn't show to have a role in developing of SLE, moreover it was noted that when dividing the cohort in the subgroup of patients who developed SLE within 1 year from the appendectomy or after 1 year, the rate was higher in first subgroup (adjusted HR 4.86 vs 1.69) suggesting that either appendectomy was part of the first manifestation of SLE or the appendectomy lead to a hospital recovery in which SLE was discovered.

Despite potential confounding, the correlation still would persist when the subgroup ">1 year" was analized (adj HR 1.69; CI 1.21 - 2.37).

The established correlation between PSC and IBD [78], among with the relationship between appendectomy and UC led several authors to the investigation of correlation between appendectomy and PSC. The first work between 1996 and 2016 were unable to find any direct correlation with the ecception of Eaton et al. [79] and Boonstra et al. [80], who found a correlation between appendectomy and PSC only when the PSC group included those who had synchronous IBD, conversely, when "pure" PSC were compared with healthy controls, appendectomy would remain consistent between groups.

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Conclusion

Inflammatory bowel disease

Appendectomy decreases the risk of UC; the more probable hypotheses are a T-cell suppression which acts as a protective factor agaist UC or a common biological factor which is at the same time responsible for the onset of acute appendicitis (and subsequent appendectomy) and protective for the development of UC.

Appendectomy increases the risk of CD, probably because of genetic factors that acts together with environmental exposure leading to the developement of the disease.

Cardiovascular Disease

It is reasonable to suspect that appendectomy somehow increases long term cardiovascular risk, even if this effect would manifest from the surgical intervention itself rather than from the removal of the appendix, we suggest to take into account the impact of appendectomy on cardiovascular disease when addressing therapeutic options.

Type II Diabetes

Appendectomy increases the rate of DM development in the subsequent years, especially when considering perforated appendix and in a younger age range. This points out the possible immunological implication and a common risk factor such as an IL-6 gene polymorphism, therefore we conclude that it is unlikely that surgeon behavior in regard to a liberal approach to appendectomy can positively or negatively affect development of DM, without excluding this hypothesis completely.

Clostrioides difficile

We believe that the removal of the appendix can negatively impact the severity, the rate of recurrence, the need for hospitalization and for total colectomy for CDI. Prospective studies and dedicated meta-analysis are needed to definitively address this topic, given the contrasting result emerged from our research.

Parkinson disease

Epidemiological, anatomical, biological and immunological evidence that appendix and PD are correlated, exist. The most plausible explanation is that some exogenous insult initiate the pathological aggregation of alpha-synuclein in the appendix (and in all the GI tract) and than by vagal nerve this is brought to substantia nigra where, in a "prionic" fashion, the spread eventually contributes to the development of the disease in a decade-taking process. Whether this is accelerated by appendectomy (by manipulation during surgical intervention), or delayed by it (by eliminating a potential "hotspot" for a-syn accumulation) is still a mater of debate.

Malignant neoplasia

Consistent evidence of a correlation between appendectomy and cancer development are lacking. Several studies showed the absence of such a correlation but those are flawed either from a short follow-up time or methodological issues (such as SIR-based analysis). We believe in a biological validity of the thesis that appendectomy is somehow related to an immune disarray that impairs host defense against colonic microorganism, and that this could eventually lead, in predisposed individual, to insurgence of neoplasia, but with the evidence available we can not validate neither reject this hypothesis.

Miscellaneous topic

There is no apparent correlation between appendectomy and PSC, apart from the potential confounder of the concomitant IBD which instead can be influenced.

Appendectomy could impact the rate of development of gallstones and correlated pathologies.

To prove statistical correlation between appendectomy and a certain disease (e.g IHD; Type II Diabetes, Cancer, etc…) it is not enough. As already stated, correlation does not imply *cause* and it is absolutely possible that there are some common risk factors that affect both the development of acute appendicitis (leading

to appendectomy) as well the disease on study (Table 8). Now that some years have passed from the implementation of the conservative therapy for acute appendicitis, we could design studies to address if the real incidence of increased pathologies is due to the *removal of appendix itself* or to some common risk factor between appendicitis and the disease of study by comparing incidence rate in appendectomized patients compared with patients who suffered acute appendicitis but underwent conservative management.

If our hypothesis - that the human appendix has a role in the *prevention* of some diseases - would be confirmed, surgeons should aim to the conservation of this organ whenever possible. A complete paradigm shift would then manifest, where conservative treatment would no longer be an alternative to operative management but would be the preferred option, not over the immediate outcome of the single patients, but even as a matter of public health.

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