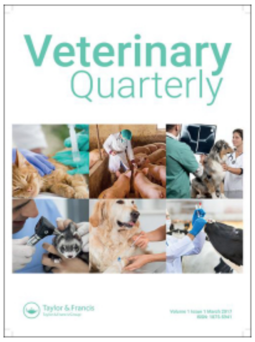

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Exploring thyroid function in main domestic ruminants: a scoping review of physio-anatomy, diseases and diagnostic tools

Justine Eppe[a], Patrick Petrossians[b], Frédéric Rollin[a], Sandrina Vandenput[c] and Hugues Guyot[a]

[a]Clinical Department of Production Animals, Fundamental and Applied Research for Animals & Health Research Unit (FARAH), Faculty of Veterinary Medicine, University of Liège, Liege, Belgium; [b]Department of Endocrinology, University Hospital of Liege, University of Liege, Liege, Belgium; [c]Health Sciences Library, University of Liege, Liege, Belgium

ABSTRACT

While thyroid physiology has been studied in domestic ruminants, many uncertainties remain. In fact, this metabolism is rarely assessed in routine veterinary practice, and diseases of the thyroid gland or its metabolism are poorly documented in domestic ruminants. This scoping review aims to summarize current knowledge in anatomy, physiology, diseases, and diagnostic methods related to thyroid function in domestic ruminants. A structured research methodology was followed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews. Four databases were used: CAB Abstracts, Embase, PubMed and Scopus. Selection and screening process of the identified studies, as well as data extraction, were managed using Covidence software. Finally, 206 studies were included. Most studies involved cattle ($n = 104$), followed by sheep ($n = 65$) and goats ($n = 28$). The main study topic was on thyroid physiology ($n = 127$), followed by diseases ($n = 48$), diagnostic methods ($n = 22$) and histology ($n = 9$). Although many studies addressed the anatomy and physiology of the thyroid gland, few confirmed the euthyroid status (having a normally functioning thyroid gland) of these animals, warranting cautious interpretation of the results. Hypothyroidism is the most documented thyroid disease in ruminants, predominantly caused by iodine deficiency. The physiology of the thyroid gland has been extensively studied in relation to heat stress, reproduction, animal production and nutrition. However, there is much less literature available on diseases described in domestic ruminants and their diagnostic methods. Diagnostic tools for assessing thyroid metabolism in ruminants include assays for total thyroxine, total triiodothyronine, bovine thyroid stimulating hormone, total serum iodine, milk iodine, urine iodine, and plasmatic inorganic iodine.

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thyroid gland; cattle; sheep; goats; diagnostic imaging

1. Introduction

Endocrinology, including thyroid physiology, has been extensively studied in humans (Dighe et al. 2017a, 2017b; Song et al. 2023; Zamwar and Muneshwar 2023; Chen et al. 2024), as well as in dogs (Taeymans et al. 2007; Liles et al. 2010; Müller et al. 2014) and cats (Peterson 2006; Paepe et al. 2008; Barberet et al. 2010). Thyroid diseases have been described in these species, along with diagnostic methods and treatments. Additionally, the role of the thyroid metabolism in maintaining health, thermogenesis, promoting growth and development, enhancing immunity, influencing in cognitive development and homeorhetic changes during different physiological stages in these species has also been recognized (Amino et al. 2002; Huszenicza et al. 2002; De Luca et al. 2020).

For a long time, numerous studies have focused on various aspects of metabolism in ruminants. Iodine deficiency, hypothyroidism, and hyperthyroidism are diseases that have been described and sometimes experimentally induced (McCoy et al. 1997; Zagrodzki et al. 1998; Thrift et al. 1999). Thyroid lesions discovered in

CONTACT Justine Eppe justine.eppe@uliege.be Clinical Department of Production Animals, Fundamental and Applied Research for Animals & Health Research Unit (FARAH), Faculty of Veterinary Medicine, University of Liège, Avenue de Cureghem 7A7D, 4000 Liege, Belgium.

slaughterhouses have also been reported (Alipourzamani et al. 2011; Darakhshesh et al. 2011). Diagnostic tools such as hormone assays (Gueorguiev 1999; Livesey et al. 2014; Steinhoff et al. 2019) and imaging techniques have been tested (Metzner et al. 2015; Pankowski et al. 2020; Eppe et al. 2023). However, few of these tools have been validated for routine use. The thyroid function plays a key role in ruminants' production of milk, meat, and hair fiber (Steinhoff et al. 2019). Before advancing further with research, it is advisable to take stock of the current knowledge to identify future research directions.

Veterinary medicine for ruminants is evolving significantly, and thyroid physiology can no longer be ignored in their medical management. This scoping review aimed to concisely outline the three primary focal points emphasized in the literature regarding ruminants: understand the thyroid anatomy and physiology, exploring thyroid diseases, and assessing diagnostic methods for thyroid-related conditions to identify what is still unknown in these areas for the ruminant species. The use of a scoping review was particularly appropriate in this case, as it allows for a comprehensive exploration of broader themes and the identification of gaps within the existing literature (Munn et al. 2018). Although research in this area is limited, it remains understudied and warrants further investigation. To our knowledge, this is the first scoping review on thyroid function in domestic ruminants.

2. Methods

This scoping review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for scoping reviews (PRISMA-ScR) checklist (Tricco et al. 2018). Since this study did not involve animals or humans, no ethical protocol was required. However, the presence or absence of an ethical protocol was noted in the extraction of data from the studies. Studies with poor methodology (study with a poor experimental design, such as no sorting by breed or physiological condition to describe thyroid disease with a small number of animals) or lacking ethical protocol were removed. Studies with a good methodology but no ethics protocol, because the latter was not yet mandatory, were retained. In fact, removing studies without ethics protocols meant that we lost a significant amount of information, as many articles date from before the 2000s.

2.1. Eligibility criteria

The eligible studies had to meet all of the following criteria: (1) published papers related to thyroid physiology (function, dysfunction and/or assessment) in the target population of domestic ruminants, including sheep, goats, and cattle; (2) any study design, including reviews (narrative or systematic), experimental, observational, or descriptive studies, (3) published in English or French, (4) no time limit on publication date.

We excluded studies that used ruminants as models for human research but provided no discernible impact or contribution to knowledge in ruminant medicine.

2.2. Information sources

Four electronic databases, selected with the assistance of an information scientist (SV), were searched to achieve comprehensive coverage of the subject: CAB Abstracts (EBSCOhost, 1973 onwards), Embase (Elsevier interface, 1974 onwards), Medline (PubMed, 1966 onwards), and Scopus (Elsevier interface, 1996 onwards).

2.3. Search strategy

To ensure the novelty of our study, a preliminary investigation was conducted, querying PubMed and CAB Abstracts, to verify that no literature reviews had yet been published on the topic.

The search strategy was developed with the assistance of an information scientist (Sandrina Vandenput). An initial exploratory search of Medline (*via* the PubMed interface) was undertaken to identify some relevant articles on the topic. The terminology used in these relevant articles was analyzed and used to develop a comprehensive search strategy for PubMed and the other databases. The search strategy,

Table 1. Search queries for identifying studies in Medline (PubMed), Embase, Scopus and CAB abstracts.

Database	Search ID	Search queries (keywords and thesaurus terms)	Results (n of studies)
Medline (Pubmed)	#1 #2 #3 #4 #5 #6 #7	"Cattle"[Mesh] OR "Goats"[Mesh] OR "Sheep"[Mesh] OR Cattle OR cow OR cows OR calf OR calves OR bovine OR goat OR goats OR caprine OR ewe OR ewes OR sheep OR lamb OR ovine OR ruminant OR ruminants OR bull OR bulls OR heifer OR heifers "Thyroid Hormones"[Mesh] OR "Thyroxine"[Mesh] OR "Triiodothyronine, Reverse"[Mesh] OR "Triiodothyronine"[Mesh] OR "Thyrotropin"[Mesh] OR "Thyrotropin-Releasing Hormone"[Mesh] OR "Thyroid Diseases"[Mesh] OR Thyroid OR hypothyroidism OR hyperthyroidism OR thyroxine OR thyrotropin OR triiodothyronine ("Thyroid Gland"[Mesh] AND "Diagnostic Imaging"[Mesh]) "Mice"[Mesh] OR mice OR mouse #1 AND (#2 OR #3 OR #4) #6 NOT #5	8967
Embase (Elsevier interface)	#1 #2 #3	('cow'/exp OR cows OR calves OR cattle OR bovine OR heifer OR heifers OR bull OR bulls OR goat OR goats OR sheep OR 'calf (bovine)'/exp OR 'goat'/exp OR 'bovine'/exp OR 'sheep'/exp OR ewe OR ewes OR lamb OR cow) ('thyroid gland'/exp OR 'thyroid disease'/exp OR 'thyroxine'/exp OR '3,3',5' triiodothyronine'/exp OR 'thyrotropin'/exp OR 'protirelin'/exp OR 'thyroid hormone'/exp OR (thyroid AND stimulating AND hormone) OR 'hyperthyroidism' OR 'hypothyroidism') #1 AND #2	8222
Scopus (Elsevier interface)	#1 #2 #3	Cattle OR cow OR calf OR calves OR bovine OR goat OR caprine OR ewe OR sheep OR lamb OR ovine OR ruminant OR bull OR heifer Thyroid OR hypothyroidism OR hyperthyroidism OR thyroxine OR thyrotropin OR triiodothyronine #1 AND #2	9437
CAB Abstracts (EBSCOhost)	#1 #2 #3	DE "cattle" OR DE "beef cattle" OR DE "bulls" OR DE "calves" OR DE "cows" OR DE "dairy cattle" OR DE "dual purpose cattle" OR DE "feral cattle" OR DE "freemartins" OR DE "heifers" OR DE "steers" OR DE "sheep" OR DE "ewes" OR DE "lambs" OR DE "rams" OR DE "wethers" OR DE "goats" OR DE "feral goats" OR DE "kids" OR cattle OR cow OR calf OR calves OR bovine OR goat OR caprine OR ewe OR sheep OR lamb OR ovine OR ruminant OR bull OR heifer ((DE "thyroid gland") OR (DE "thyrotropin" OR DE "thyrotropin releasing hormone" OR DE "thyroxine" OR DE "D-thyroxine" OR DE "L-thyroxine")) OR (DE "thyroid diseases" OR DE "autoimmune thyroiditis" OR DE "cretinism" OR DE "goiter" OR DE "hyperthyroidism" OR DE "hypothyroidism" OR DE "thyroid cancer") OR (thyroid OR thyroid disease OR thyroxine OR triiodothyronine OR thyrotropin OR thyrotropin releasing hormone) #1 AND #2	4738

This table lists the search questions adapted according to the chosen search engine. The table identifies "search IDs" as search items for an idea. The search language is adapted according to the search engine as well. The last column mentions the results obtained.

including all identified keywords and thesaurus terms, adapted for CAB Abstracts, Embase, PubMed, and Scopus is available in Table 1. The queries were similar across the database but adapted to meet the specific requirements of each, with one adjustment made for PubMed. This adjustment involved excluding the term 'mice' to increase the specificity of the results. This was necessary due to PubMed's focus on human medicine and the significant number of trials involving mice and bovine hormones. This adjustment was not necessary for the other databases. No language or research limits were imposed.

An initial step in validating the search equations was to conduct a quality control check of the queries formulated using the identified keywords and thesaurus terms. This quality control process aimed at assessing the accuracy of the queries by reviewing the resulting references to confirm the inclusion of the 10 relevant articles previously selected by the authors.

This quality check confirmed that all 10 articles were present in the results provided by Scopus and CAB Abstracts databases. For PubMed and Embase, only 8 out of these 10 articles were present in the results provided. However, a verification revealed that the two missing references were not present in these databases. This quality control conducted across all four databases allowed us to validate the search queries before proceeding further.

After completing the quality control check, the databases were searched, and all records were imported into Covidence software (Veritas Health Innovation, Melbourne, Australia) in June 2022, with an update in March 2024. The software automatically removed duplicates.

2.4. Selection of sources of evidence

The two stages of the selection process were carried out independently by two of the authors (JE and HG). Furthermore, to prepare for the selection task, these two authors independently tested 20 records to ensure their understanding of the selection criteria and refine them if necessary.

The final inclusion criteria were studies related to:

1. Domestic cattle, sheep, goats
2. Thyroid physiology, diagnostic imaging, thyroid diseases, thyroid hormones, thyroid hormone assays, or thyroid metabolism.

Studies were excluded if they focused on:

1. species other than domestic ruminants, including wild ruminants,
2. human subjects,
3. objective unrelated to ruminant outcomes,
4. in vitro research.

The selection process occurred in two stages: first, solely by screening title and abstract, and then, for selected records, by reviewing the full text.

If there was a discrepancy in the selection decision between authors for certain records, it was resolved through discussion and consensus to determine whether to include or exclude the document from the analysis.

In the second part of the selection process, reasons for exclusion were specified. References for which the full text could not be found were also rejected.

2.5. Data charting process and data items

The selected studies were extracted using Excel (Excel 2023, v. 2310, Microsoft Corp.). A data extraction questionnaire was developed by two of the authors (JE and HG), pilot-tested on 10 randomly selected articles. The 10 papers selected were of different types (2 cohort study, 2 randomized controlled trial, 1 case series or case report, 2 non-randomized controlled trial, 1 precision of diagnostic tests, 1 narrative review and 1 descriptive study) and were not known by the authors before the articles were selected and the full texts were read. Points were awarded based on correct information. A 95% concordance result was obtained after reading these 10 articles. The questionnaire was therefore judged by JE and HG to have been correctly formulated and adapted to all the studies included in this scoping review. After finalizing the data extraction questionnaire, one reviewer (JE) performed the data extraction for the rest of the included papers.

A range of information was collected with this questionnaire to characterize the studies included:

- Study identifiers and characteristics of the study: title, first author's name, publication date, continent where the study was conducted, and study design;
- Participants characteristics: species studied, breed (if applicable), type of production (milk, meat, hair fiber (wool, cashmere, mohair)), and the number of animals included in the study;
- Summary of results: covering physiological and pathological aspects, as well as diagnostic and histological approaches while appropriate;
- Additional information: potential declaration of a conflict of interest, presence or absence of an approved ethical protocol.

2.6. Synthesis of results

The screening process was described using the PRISMA flowchart, automatically generated by Covidence software. Data extraction was performed using Excel software, which was also used to analyze the results and generate the graphs and tables.

3. Results

3.1. Selection of sources of evidence

Details of the selection are shown in Figure 1. A total of 31,364 records were imported into Covidence from bibliographic database searches. Additionally, 10 records were included through citation searching within the bibliographies of relevant studies. Among these 31,374 records, 14,429 duplicates were identified (by Covidence or manually). The first step of screening (based on the title and abstract) led to the elimination of 14,817 records. Of the 2,128 selected records, 875 full texts could not be retrieved (41.1%). Out of the remaining 1,253 papers, 1,047 were rejected for the following reasons: the main ones being that the study of thyroid physiology was not the central focus of the article (30%), the study had a wrong setting (insufficient number of animals, bias, etc.) (7%), or the reference was incomplete (for example, only the abstract was available) (5%). Finally, there were some *in vitro* studies (Figure 1; wrong study design; 4%) that were removed. The remaining 206 studies were considered eligible for this review.

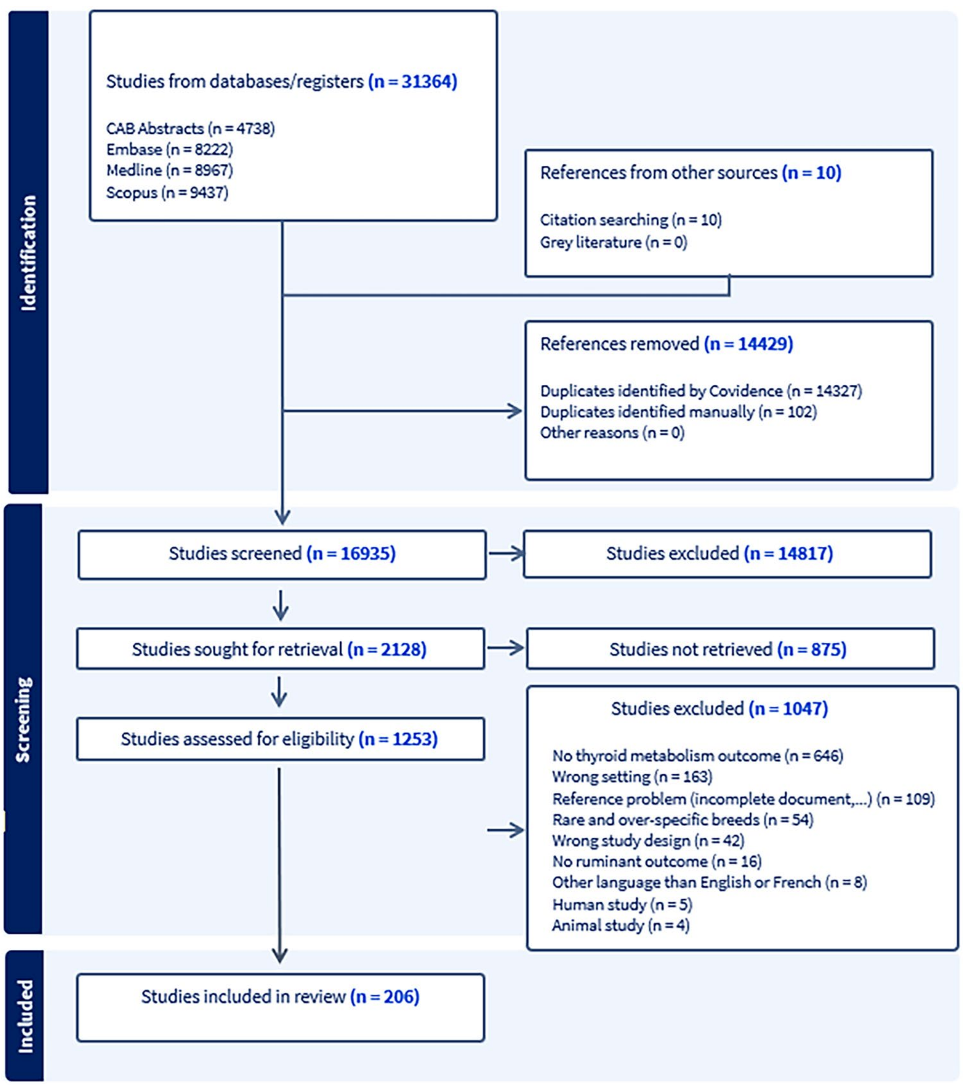

Figure 1. PRISMA flowchart describing the number of records identified, included, and excluded, and the reasons for exclusions through the screening process of the scoping review. The left-hand identification box represents records identified by search from May 22, 2022, to March 29, 2024. The chart format was adapted from (Page, 2021). Studies extracted from databases and those from other sources, such as citation searches, were included in the articles to be screened. Duplicates were removed either automatically by the Covidence software or manually by our two reviewers. Once the studies had been screened for title and abstract by our two reviewers, the full texts were downloaded and the studies were read to verify their eligibility. After reading, studies were rejected for various reasons, which will be explained in the results.

3.2. Characteristics of the studies included

The included studies spanned from 1957 to 2024. Over half of them ($n = 109$; 53.0%) were conducted before the year 2000. The included studies came from all five continents: Europe ($n = 89$; 43.2%), America ($n = 50$; 24.3%), Asia ($n = 41$; 20%), Oceania ($n = 17$; 8.2%), Africa ($n = 9$; 4.3%).

The study designs were as follows: cohort study ($n = 74$; 35.9%), randomized controlled trial ($n = 62$; 30.1%), case series or case report ($n = 30$; 14.7%), non-randomized experimental study ($n = 12$; 5.8%), precision of diagnostic tests ($n = 12$; 5.8%), narrative review ($n = 11$; 5.3%), and descriptive study ($n = 5$; 2.4%).

3.3. Critical appraisal within sources of evidence

None of the selected studies had declared a conflict of interest. However, only 32 studies explicitly stated that they received ethical approval. Given the types of studies selected from our 206 articles, ethical protocol approval would have been expected for 160/206 studies.

3.4. Results of individual sources of evidence

Most of the studies focused on cattle ($n = 104$; 50.4%), followed by sheep ($n = 65$; 31.5%), and goats ($n = 28$; 13.6%). Only 4.5% ($n = 9$) of the studies addressed multiple ruminant species. Seventy-eight out of 206 studies concerned dairy ruminants, 54/206 beef ruminants, 7/206 wool ruminants, and 67 combined at least two different purposes. All the details are available in Table 2.

The main cattle breed represented in the studies was Holstein Friesian ($n = 48$), followed by buffalo ($n = 10$). The breed of sheep was not mentioned in 14/65 studies. The most common breed of sheep was Merino ($n = 9$), followed by Suffolk ($n = 8$) and Welsh Mountain ($n = 5$). As far as goats are concerned, there was no single breed that predominates in the studies, which included Cashmeres and Angoras, as well as rarer breeds such as Black Bengal, Polish White or Fawn Improved.

The distribution of the study subject is described by species considered in Figure 2. The studies primarily focused mainly on physiology ($n = 127$), followed by thyroid diseases ($n = 48$), diagnosis ($n = 22$) and histology ($n = 9$) even though several studies ($n = 13$) addressed multiple aspects. Physiology studies covered many facets, from the exchange of thyroid hormones and the development of the thyroid gland in the fetus to the growth, reproduction, and milk/meat production of ruminants. They also looked at iodine metabolism, its absorption, and its use by the body. Studies regarding thyroid diseases focused mainly on goiter and hypothyroidism, even if other diseases such as iodine poisoning, hyperthyroidism, lymphocytic thyroiditis, or tumors were also described. Several studies have looked at thyroid gland lesions at slaughter. A summary of the lesions observed, and their prevalence can be found in Table 3. The studies on the accuracy of diagnostic tests described blood assay methods (for example ECLIA:

Table 2. Species, type, and cohort size according to the type of the study.

	Species (n of studies)				Type (n of studies)				Population size		
Type of study (n of studies)	Cattle	Goat	Sheep	> 1 species	Dairy	Meat	Fiber	More than 1	Mean ± SD	Min	Max
Randomized controlled trial ($n = 62$)	27	6	27	2	22	20	2	18	40 ± 40	5	170
Cohort ($n = 74$)	48	8	17	1	37	12	1	24	72 ± 120	2	591
Case series/ Case report ($n = 30$)	11	9	10	0	6	11	0	13	24 ± 46	1	199
Diagnostic test accuracy study ($n = 12$)	6	2	3	1	5	3	0	4	73 ± 92	10	330
Non-randomized experimental trial ($n = 12$)	6	0	6	0	3	5	0	4	42 ± 54	4	193
Review ($n = 11$)	4	0	2	5	3	1	0	7			
Qualitative research ($n = 5$)	2	3	0	0	0	1	0	4	148 ± 176	18	386
Total ($n = 206$)	104	28	65	9	76	53	3	74			

n, number; SD, standard deviation; "more than 1", more than one species or speculation in the study.

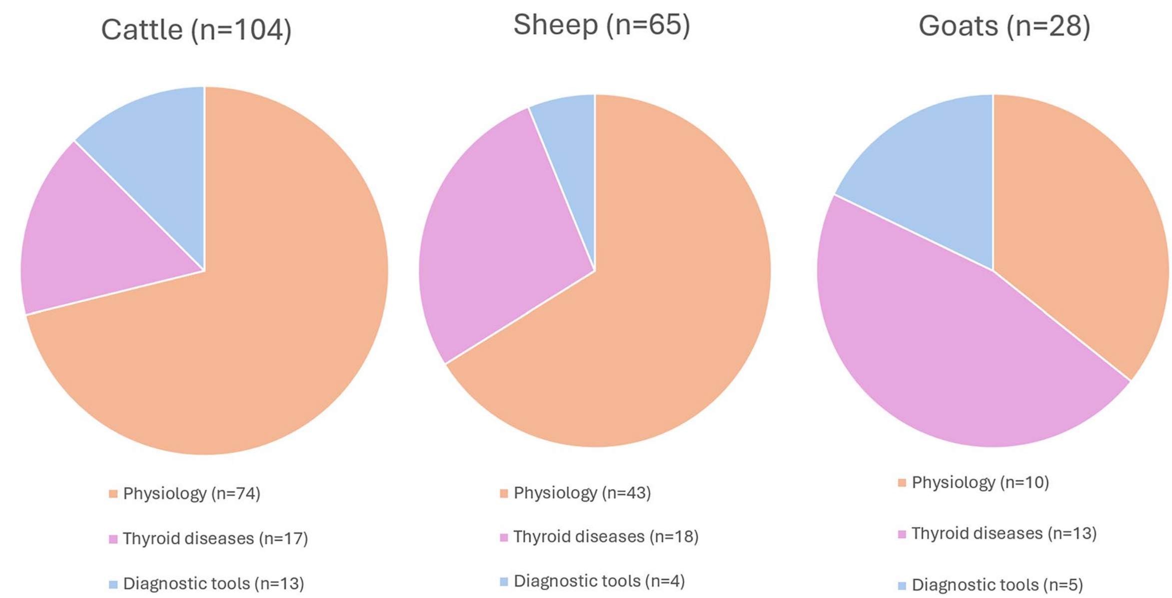

Figure 2. Breakdown of study subjects by species and study topic.

electrochemiluminescence immunoassay, CLIA: chemiluminescence immunoassay, RIA: radio-immuno assay, ELISA: enzyme-linked immunosorbent assay) for thyroid hormones (thyroxine, T4; tri-iodothyronine, T3; thyrotropin, TSH) and iodine (total iodine, inorganic plasmatic iodine) as well as imaging methods such as ultrasound and computed tomography-scan (CT-scan). A summary of blood tests available to assess thyroid function in ruminants is available in Table 4. The five qualitative studies were descriptions of histological slides from ruminant thyroids. Histological studies described both healthy thyroids and those affected by illness. The number of animals included in the study varied considerably from one type of study to another (1 to 591 animals). Species, type, and cohort are summarized in Table 2.

4. Discussion

Veterinary medicine is evolving, and little is known about thyroid physiology in ruminants. This scoping review was carried out with the aim of taking stock of what is known about thyroid metabolism in domestic ruminants. Two hundred and six scientific papers have been selected on this topic (Figure 1). The most studied subject is thyroid physiology, followed by thyroid diseases and - diagnostic tools in cattle and sheep (Figure 2). In goats, thyroid diseases are the most studied subject. The most represented species in the papers is bovine, followed by sheep. The goat is the least represented species in literature.

Sample sizes vary considerably for all types of study (Table 2). It is therefore not possible to make a firm statistical comparison between all these studies. It is the reason why it was preferred to carry out a review of the literature in this discussion.

Regarding the critical evaluation of the quality of papers, it should be noted that few studies included an ethics protocol (32/206). There are several possible explanations for this. First, ethics protocols were introduced in the 2000s in Europe and since the first journals imposed this protocol on scientific articles in early 2010s in Europe. Second, the period included in this review is broad (1957 to 2024) with a relatively homogeneous distribution of papers (about 50% above the 2000s), which may also explain the low number of studies with an ethics protocol. This criterion was not strictly observed, because otherwise a lot of records would have been lost.

4.1. Anatomical and histological characteristics of the thyroid gland in domestic ruminants

The results of 10/206 studies specifically report information on the anatomy or histology of the healthy thyroid gland. The two most common species in these references were cattle and goats.

During pregnancy in sheep, the fetus' thyroid gland develops with asymmetric lobes, a glandular isthmus, and an intensive vascularization between 32 and 36 days of embryonic development (Hájovská 2002).

Table 3. Summary of prevalences obtained in studies recording lesions at the slaughtered house.

Thyroid lesion	Reference	Species	Prevalence	Number of animals	Country, continent
Congenital goiter observed macroscopically, without histological diagnosis	George et al. 1966	Sheep (Merino, Dorset Horn, Crossbred)	Merino: 50% Dorset Horn: 44% Crossbred: 21%	349	Australia, Oceania
Colloid goiter	Shelke et al. 2009	Buffaloes	8.5%	290	India, Asia
	Salunke et al. 2008	Buffaloes	24.8%	250	India, Asia
	Alipourzamani et al. 2011	Sheep	4%	100	Iran, Asia
	Darakhshesh et al. 2011	Sheep	4%	100	Iran, Asia
	Mohajeri et al. 2012	Goats	1.3%	386	Azerbaïdjan, Asia
Hyperplastic goiter	Shelke et al. 2008	Buffaloes	0.9%	290	India, Asia
	Salunke et al. 2008	Buffaloes	5.2 %	250	India, Asia
	Alipourzamani et al. 2011	Sheep	27%	100	Iran, Asia
	Darakhshesh et al. 2011	Sheep	32%	100	Iran, Asia
	Mohajeri et al. 2012	Goats	18.4%	386	Azerbaïdjan, Asia
Nodular hyperplasia	Salunke et al. 2008	Buffaloes	0.6%	250	India, Asia
	Mohajeri et al. 2012	Goats	0.7%	386	Azerbaïdjan, Asia
Lymphocytic thyroiditis	Salunke et al. 2008	Buffaloes	8%	250	India, Asia
	Alipourzamani et al. 2011	Sheep	2%	100	Iran, Asia
	Darakhshesh, 2011	Sheep	3%	100	Iran, Asia
Suppurative thyroiditis	Darakhshesh, 2011	Sheep	1%	100	Iran, Asia
Fibrous thyroiditis	Shelke et al. 2009	Buffaloes	4.83%	290	India, Asia
	Mohajeri et al. 2012	Goats	1%	386	Azerbaïdjan, Asia
Idiopathic follicular atrophy	Mohajeri et al. 2012	Goats	2%	386	Azerbaïdjan, Asia
Parenchymental cysts	Salunke et al. 2008	Buffaloes	2.4%	250	India, Asia
	Mohajeri et al. 2012	Goats	2.6%	386	Azerbaïdjan, Asia
C-cell adenomas	Mohajeri et al. 2012	Goats	0.2%	386	Azerbaïdjan, Asia
C-cell carcinoma	Mohajeri et al. 2012	Goats	0.2%	386	Azerbaïdjan, Asia

This table lists the lesions found on the thyroids of ruminants at the slaughterhouse. Hypothyroidism can be characterized by lesions on the thyroid gland, that could be macroscopic (goiter, congenital goiter) or microscopic (colloidal goiter, nodular hyperplasia or hyperplastic goiter). Based on these results, it would appear that the histological expression of hypothyroidism differs between small ruminants (sheep, goats) and buffaloes. Small ruminants are more likely to develop hyperplastic goiter, while buffaloes are more likely to develop colloid goiter. In addition to this well-documented disease in ruminants, other lesions related to diseases known in other animal species have also been discovered: lymphocytic thyroiditis, suppurative thyroiditis, fibrous thyroiditis, idiopathic follicular atrophy, parenchymental cysts. Finally, thyroid cancers may also be found: C-cell adenomas, C-cell carcinoma. These lesions are much rarer than those associated with hypothyroidism, the rarest being cancers.

In all ruminants, the thyroid gland consists of two ellipsoid lobes connected by an isthmus. It is positioned under the larynx, on the first two or three tracheal rings (Baishya et al. 1991). The isthmus is glandular in calves but may be fibrous in adult cattle. There are few reports on the anatomy of the thyroid gland in sheep, but a glandular isthmus has also been described in this species (Hájovská 2002). In goats, the lobes are fusiform or oval and joined by a poor fibrous isthmus, like a thin band connecting the medial caudal edges of the two lobes (Pankowski et al. 2020). In calves, breed can influence the weight of the thyroid gland (Suuroja et al. 2003). There are several studies that have measured the thyroid gland (thickness, length, width, volume), but all involved calves of different ages and species, and it is difficult to compare the results between them (Baishya et al. 1991; Suuroja et al. 2003). These studies involve calves whose health and thyroid status had not been checked (Baishya et al. 1991), and even stillborn from other causes, which could have influenced the results obtained (Suuroja et al. 2003). The thyroid gland grows the most in the first week of life, then increases by around 0.5 g per month (Suuroja et al. 2003). The thyroid weight of a newborn calf can be calculated using the following formula:

$$Y = 0.348 * X^Z$$

where Y is the thyroid weight (g), X the weight (kg) of the calf, and Z a coefficient that varies between papers: $z = 0.944$ according to Hernandez et al. (1972) or $z = 1.076$ for Szuba et al. (1992). The differences in Z coefficients could be attributed to the different breeds of cattle used in these two studies and to the fact that no tests were carried out to ensure that the calves were euthyroid.

Table 4. Thyroid hormones and iodine reference intervals for adult and newborn (NB) cattle (in blue), sheep (in orange) and goats (in yellow) (according to validated references).

Marker	Matrix	Sample tube	Analysis method	Validation of the method	Deficiency Or Hypothyroidism	Excessive	Normal range	Unit
Total T3	Serum	Dry	RIA	Intra-study	-	-	1-2 [1] (buffalo bulls)	ng/mL
	Plasma	Heparin	RIA	Validated by laboratory	-	-	2.02-16.12[2] (NB)	nmol/L
	Serum	Dry	RIA	Intra-study	-	-	1.34±0.04[7] (DC early lactation)	
					-	-	1.24±0.04[7] (DC mid lactation)	ng/mL
					-	-	1.34±0.04[7] (DC late lactation)	
	Serum	Dry	RIA	Not validated for cattle[10]	-	-	4.18± 0.38[8] (extreme DM)	
					-	-	2.16±0.45[8] (moderate DM)	
					-	-	1.48±0.67[8] (normal DM)	
					-	-	Between 0.65±0.07 and 2.49±0.13[11] (DC)	
	Serum	Dry	RIA	Intra-study	0,62-12,37[12] (NB)	-	6,49-9,28[12] (NB)	nmol/L
					-	-	0,93-1,7[12] (DC)	
	Plasma	Heparin	RIA	Validated by laboratory	-	-	4.95-6.93[14] (NB)	nmol/L
	Serum	Dry	ELISA	Intra-study	-	-	1.56-4.76[4] (non-productive)	
	Serum	Dry	MEIA	Intra-study	-	-	1.56 ± 0.35[5] (non-productive)	
	Plasma	Heparin	CLIA	Validated[6]	-	-	1.81±0.6[6] (non-productive)	
	Plasma	Heparin	ECLIA	Validated[6]	-	-	2.33±0.8[6] (non-productive)	
	Plasma	Heparin	RIA	Validated[6]	-	-	1.4±0.4[6] (non-productive)	
	Serum	Dry	MEIA	Intra-study	-	-	1.58 ± 0.27[5] (pregnant ewe)	
	Serum	Dry	MEIA	Intra-study	-	-	1.26 ± 0.20[5] (lactating ewe)	nmol/L
	Serum	Dry	ELISA	Intra-study	-	-	2.20-3.60[4]	
Free T3	Serum	Dry	RIA	Intra-study	-	-	2.98-6.23[11] (DC)	pg/mL
					-	-	3.45-5.37[11] (DC in lactation)	
	Serum	Dry	ELISA	Intra-study	-	-	5.15-8.63[4]	pmol/L
	Serum	Dry	ELISA	Intra-study	-	-	3.85-12.14[4]	pmol/L
rT3	Serum	Dry	RIA	Intra-study	-	-	333±17[7] (DC early lactation)	pg/mL
					-	-	314±17[7] (DC mid lactation)	
					-	-	340±16[7] (DC late lactation)	
Total T4	Serum	Dry	RIA	Intra-study	-	-	20-40[1] (bulls)	ng/mL
	Plasma	Heparin	RIA	Validated by laboratory	-	-	25-95[2] (DC)	mmol/L
	Serum	Dry	RIA	Intra-study	-	-	50±1.9[7] (DC early lactation)	ng/mL
					-	-	55.2±2.3[7] (DC mid lactation)	
					-	-	61.5±1.6[7] (DC late lactation)	
	Serum	Dry	RIA	Validated[10]	-	-	67.7±5.8[8] (extreme DM)	
					-	-	47.2±6.8[8] (moderate DM)	
					-	-	58.6±5.9[8] (normal DM)	
					-	-	Between 39.16±3.13 and 88.5±4.41[11] (DC)	
	Serum	Dry	RIA	Intra-study	6-142[12] (NB)	-	232-373[12] (NB)	nmol/L
					-	-	64-116[12] (DC)	
					-	-	Between 58±0.08 and 119±4[13] (independent of iodine supply)	
	Serum	Dry	CLIA	Validated by laboratory	<40[15]	-	50.8-105[15]	
	Serum	Dry	ELISA	Intra-study	-	-	102.51-120.78[4] (non-productive)	nmol/L
	Serum	Dry	FPIA	Intra-study	-	-	40.88±18.05[5] (non-productive)	
	Plasma	Heparin	CLIA	Validated[6]	-	-	53.1±10.7[6] (non-productive)	
	Plasma	Heparin	ECLIA	Validated[6]	-	-	86.1±15.7[6] (non-productive)	
			RIA	Validated[6]	-	-	95.3±23.3[6] (non-productive)	
					-	-	42.66±17.04[5] (pregnant ewe)	
					-	-	43.48±18.18[5] (lactating ewe)	
	Serum	Dry	CLIA	Validated by laboratory	<40[15]	-	61.7-108[15]	
	Serum	Dry	ELISA	Intra-study	-	-	101.50-110.87 (non-productive)	nmol/L
Free T4	Serum	Dry	RIA	Intra-study	-	-	1.47-1.86[11] (DC)	ng/dL
					-	-	1.37-1.85[11] (DC in lactation)	
	Serum	Dry	ELISA	Intra-study	-	-	17.95-49.18[4]	pmol/L
	Serum	Dry	ELISA	Intra-study	-	-	12.77-33.39[4]	pmol/L
TSH	Serum	Dry	RIA	Validated [2]	-	-	1.3-13[2] (DC)	µU/mL
					> 35[9] (NB)	-	1.3-19.7[2] (NB)	
	Plasma	Heparin	RIA	Intra-study	-	-	2-5[3] (DC)	ng/mL
	Plasma	Heparin	RIA	Validated by laboratory	-	-	2-5[14] (NB)	µU/mL
	Plasma	Heparin	RIA	Intra-study	-	-	2-6[3]	ng/mL
PII	Plasma	Heparin	Sandell-Kolthoff ICP-MS	Validated[17]	<80[13] (pregnant DC)	>1000[19]	105-287[13] (pregnant DC)	ng/mL
					<30[19]	100-950[19]	30-40[19]	ng/mL
IT	Serum	Dry	ICP-MS	Validated	1-5[19]	70-300[19] 100-2500[19] (toxic chronic) >1000[19] (toxic acute)	10-40[19]	µg/dL
					2.5[19]	800-2600[19] 4000-30000[19] (toxic)	3-12.3[19]	µg/dL
					<5[19]	>50[19] 1200-5000[19] (toxic)	7-10[19]	µg/dL
	Milk	-	Sandell-Kolthoff ICP-MS	Validated[16]	8-25[19]	500-3500[19]	370±3[18] (DC) 30-300[19]	µg/L
					12-80[19]	1000-2000[19]	80-400[19]	µg/dL
					<25[19]	>500[19] 35000-47500[19] (toxic)	25-400[19]	µg/dL
	Urine	-	Sandell-Kolthoff ICP-MS	Validated[16]	-	>50[19]	18.7±19[18] (DC) 10-25[19]	µg/dL
	Allantoid	-	Ion-exchange chromatography	Validated[17]	66±27[22]	-	818±980[22]	µg/L -
	Amnios				157±75[22]	-	1605±1142[22]	µg/L
	Colostrum				87±21[22]	-	333±192[22]	µg/L
Weight	Thyroid	Fresh Thyroid	Scale	-	>30[21] (NB)	-	5-12[22] (NB)	g
					-	-	<0.4[20] (NB; thyroid/birth weight ratio)	g/kg

Microscopically, for cattle, goats and sheep, the thyroid gland is surrounded by a fibrous capsule and composed of secretory follicles surrounded by connective tissue containing parafollicular C cells. A follicle is a round structure surrounded by rectangular follicular cells and filled with colloid (Baishya et al. 1991;

Kumar et al. 2007; Igbokwe and Ezeasor 2015). These cells have a basal nucleus which may contain mitotic figures and, at their apex, toward the inside of the follicle, endocytosis vesicles are visible. If the follicle is inactive, the cells take on a cubic appearance with a dark nucleus and no mitotic figures. The colloid contains the precursors of thyroid hormones (Igbokwe and Ezeasor 2015). Thyroid follicles are largest in buffalo (79 µm), followed by zebu (73 to 284 µm) cattle (57 µm), goats (35 to 190 µm) and sheep (34 µm) (Ashok et al. 1993; Igbokwe and Ezeasor 2015; Menaka et al. 2022). Limited literature is available on thyroid follicle micrometry in certain species such as cattle and sheep.

Histological view of a healthy thyroid gland in cattle can be seen in Figure 3C in the silhouette of the gland (magnification x100, Haematoxylin-Eosin stain).

4.2. Physiology of the thyroid gland and aspects of the hypothalamic-pituitary-thyroid axis in ruminants

A total of 15/206 studies are used to summarize the general physiology of the thyroid gland in ruminants. Of these studies, 8/15 concern cows, 4/15 sheep and 1/15 goats. This section also includes two reviews of the literature of aspects of thyroid physiology on ruminants.

The hypothalamic-pituitary-thyroid axis works as follows: the hypothalamus secretes thyroid releasing hormone (TRH), which stimulates the pituitary gland to synthesize thyroid stimulating hormone (TSH), which in turn stimulates the thyroid gland to produce thyroid hormones (Todini 2007). During a TRH (Thyrotropin-Releasing Hormone) challenge, TSH rises within a few minutes of the injection of TRH, peaking at around 60 min and then falling slowly over several hours to a nadir, before gradually rising again (Klein and Fisher 1980; Chadio et al. 2006; Guyot et al. 2007b). The increase in TSH *ipso facto* induces an increase in T4 as well, in a delayed manner. A TSH injection stimulates the thyroid gland to increase 3,3′,5-triiodothyronine (T3) secretion (stimulation of intra-thyroidal conversion of T4 to T3) (Peeters et al. 1992).

The synthesis of thyroid hormones is illustrated in Figure 3C. Inside the thyroid gland, iodide is transported by the Na^+/K^+ ATPase pump (25–30% of total iodine) into the thyroid cell. Then, it is re-excreted in the follicular space for oxidation by the membrane-bound thyroperoxidase (H_2O_2 peroxidase produced from NADPH) and associated with tyrosil derivatives using thyroperoxidase enzyme. In this way, the tyrosil derivative can bind with one or two iodine atoms. This provides mono-iodotyrosine (1 iodine atom, MIT) and di-iodotyrosine (2 iodine atoms, DIT). The thyroglobulin is therefore covered with MIT and DIT (as on the peaks of a sea urchin), which, when coupled, give the hormones tri-iodothyronine (T3 = DIT+MIT) and tetra-iodothyronine or thyroxine (T4 = DIT+DIT). Once this coupling has been achieved, the 'urchin' is phagocytosed by thyrocytes and undergoes pinocytosis following the action of lysosomes. This digestion releases T3 and T4 hormones into the extracellular space. Much less T3 than T4 is synthesized by the thyroid gland; biologically active hormone T3 production is mainly due to T4 deiodination by peripheral 5′-deiodinase (DIO) enzyme contained in the various tissues (outer-ring deiodination) (Todini 2007; Capuco et al. 2008) and to a lesser extent by intra-thyroid T4 activation to T3 by an intra-thyroid deiodinase (Peeters et al. 1992). T4 can be considered as a pro-hormone (Todini 2007).

DIO enzymes are present in several tissues, mainly the kidneys and liver, which mainly express DIO type 1 (DIO1) (Chadio et al. 2006). The brain, lactating udder, skin, skeletal muscles, and brown adipose tissue mainly express DIO type 2 (DIO2) (Capuco et al. 2008). Finally, there is a DIO type 3 (DIO3) which is widely expressed in the body and plays an important role in oxygen consumption and thyroid hormones regulation but is also present in the placenta and regulates thyroid hormones in the fetus (Todini 2007; Capuco et al. 2008). DIO3 is only capable of degrading T3 and T4 hormones into 3-3′diiodothyronine or 3-5′-diiodothyronine (3-3′T2 or 3-5′T2) and 3,3′,5′-triiodothyronine or reverse T3 (rT3) (inter-ring deiodination). DIO2 is inhibited by rT3 (Todini 2007). The residual MIT and DIT are deiodinated by a 5′-DIO enzyme, releasing tyrosine and iodine (Todini 2007). The iodine can then return to the cycle (NRC, 2000). T3 and T4 can be deiodinated, with T4 being transformed into active T3 or inactive rT3 by a 5′-DIO (Todini 2007).

The T3 and T4 provide negative feedback to the hypothalamic-pituitary-thyroid axis, reducing the production of TRH in the hypothalamus and TSH in the pituitary. TSH also exerts negative feedback on the hypothalamus and thus on TRH secretion (Todini 2007). Thyroid hormones, especially T3, can have indirect effects,

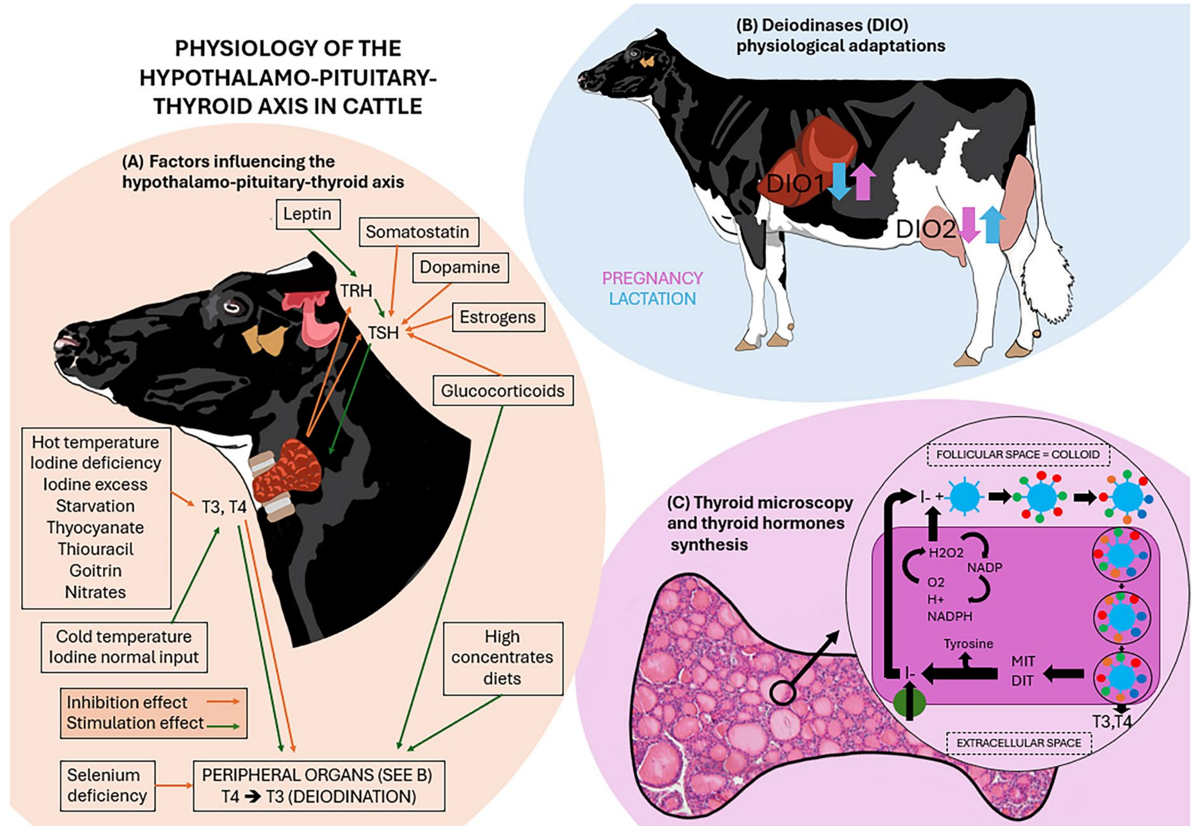

Figure 3. Illustration of thyroid physiology in ruminants (the cow was chosen to illustrate) inspired by Żarczyńska et al. (2022), Chen et al. (2022), Steinhoff et al. (2019), Weitzel et al. (2017), Tsuji et al. (2016), Huszenica et al. (2002), Paulíková et al. (2002), Anderson et al. (2002), Christopherson et al. (1979). The hypothalamic-pituitary-thyroid axis is illustrated in (A). The hypothalamus (dark pink) secretes TRH, which stimulates the pituitary gland (light pink), which in turn secretes TSH. TSH stimulates the thyroid gland (brown) to secrete the hormones T3 and T4. Thyroid hormones are in turn capable of providing negative feedback to the pituitary gland and hypothalamus. The thyroid gland straddles the trachea and cricoid cartilage of the larynx and the first two tracheal rings. Factors having effects on the hypothalamic-pituitary-thyroid axis are represented. Orange arrows indicate an inhibitory effect. Green arrows indicate a stimulatory effect. (B) The activation or inactivation of deiodinases 1 and 2 (DIO 1 and DIO 2) depending on the physiological status of the animal. DIO1 and DIO2 both activate T4 to T3. Thus, during pregnancy (pink arrows), it is the liver DIO1 pathway that is favored. During milk production (blue arrows), the udder route, DIO2, is favored. The thyroid gland is shown in (C). The histological structure of the thyroid gland is shown in the silhouette of the gland (magnification x100, Haematoxylin-Eosin stain). An arrow zooms in on a subunit of the thyroid gland: the secretory follicular cell. In the circle, the synthesis of the hormones T3 and T4 is represented. It all starts with the uptake of iodide from the extracellular space by the Na^+/K^+ATPase pump (in green) in the thyroid cell. Iodide is re-excreted into the follicular space to undergo oxidation (H_2O_2 peroxidase produced from NADPH) and to be associated with tyrosil derivatives using thyroperoxidase (localised at the membrane level). This provides Mono-iodotyrosine (in red, MIT), di-iodotyrosine (in green, DIT). Thyroglobulin (in light blue) is therefore covered with MIT and DIT like a sea urchin on its peaks, which, by coupling, give the hormones tri-iodothyronine (in orange, T3=DIT+MIT) and thyroxine (in dark blue, T4=DIT+DIT). Once this coupling is achieved, the "sea urchin" is phagocytosed by the thyrocyte and undergoes pinocytosis following the action of primary and secondary lysosomes. This digestion releases the hormones T3 and T4 which diffuse into the extracellular space and the residual MIT, DIT which will be deiodinated by a seleno-dependent deiodinase thus releasing tyrosine and iodide which can return to the cycle.

by binding to a nucleic receptor and causing RNA synthesis, or direct effects (Huszenicza et al. 2002). These effects are manifold and involve numerous organs such as the brain, heart, udder, adipose tissue, etc. Thyroid hormones, particularly T3, can be used as markers of stress and well-being in ruminants (Ferlazzo et al. 2018). Indeed, T3 concentration decreases under stress (Strath et al. 1982; Mancini et al. 2016; Ferlazzo et al. 2018). Almost 99% of thyroid hormones are transported in the blood by proteins (90% for T4; 9% for T3) (Guyot and Rollin 2007; Todini 2007). There are therefore two forms of thyroid hormone: total forms (free forms+bound forms) and free forms. The free forms (1%) are those that are biologically active (Guyot and Rollin 2007).

It is important to point out an important role of thyroid hormones in dairy cows' energy metabolism (Fazio et al. 2022). Thyroid hormones have an insulin-agonistic and antagonistic effect on different organs, and therefore a significant effect on glucose metabolism. Monitoring thyroid hormones in high-producing dairy cows can represent an important tool for evaluating anabolic or catabolic adaptations and anticipating excessive energy balance (Steinhoff et al. 2019; Fazio et al. 2022).

Although pulsatility in TSH secretion has been described in cattle (Thomas et al. 1974; Guyot et al. 2007b), some studies describe constant TSH concentrations over 24 h (Curtis and Abrams 1977). This may be linked to the time of sampling, which can vary from every 20 min to an hour. There is also a diurnal rhythm in T3 and T4 secretion (Bitman et al. 1984; Guyot et al. 2007b). T4 peaks sharply at night between 2 and 5 am and between 7 and 9 pm in the evening in fattening male buffaloes (Agarwal et al. 1983). The explanation for these peaks is unclear, and could be behavioral, sexual, temperature-related, or postural (Agarwal et al. 1983). T3 follows the fluctuations of T4 (Agarwal et al. 1983). T3 and T4 serum concentrations are similar between male and female goats (Madan et al. 2019). The seasonality of T3 and T4 hormone secretion is more explained in Section 4.6 and 4.10.

The hypothalamic-pituitary-thyroid axis is influenced by numerous factors linked to the environment, diet and hormones of ruminants. A summary of these influences is shown in Figure 3A. All these factors are explained precisely one by one in the following paragraphs. The hypothalamic-pituitary-thyroid axis is represented on Figure 3A with the negative feedback of thyroid hormones. The factors that influence this axis can interact directly on thyroid hormones (e.g. by desactivation of DIO or interferences in captation of iodine in the thyroid gland) or on pituitary or hypothalamic glands. These factors can be internal or external.

4.3. Iodine status in ruminants

Of the 16/206 studies on iodine and thyroid metabolism, 12/16 concern cattle, 2/16 sheep, 1/16 goats and one is a literature review on iodine in ruminants. Of these studies, 7 tested iodine supplementation.

In cattle, iodine is required for the synthesis of thyroid hormones (Chadio et al. 2006; Colston 2018). This trace-element is mainly absorbed in the rumen (70–90%), then in the omasum (10%), secreted in the abomasum (10%) and then reabsorbed (18 times more than secreted), secreted by the bile (30%), urine (40%) and absorbed to a lesser extent in the small and large intestines (Barua et al. 1964; Miller et al. 1975). Iodine is found in the form of plasma inorganic iodine (PII) in the blood. Then, PII is rapidly taken up by several organs, namely the thyroid gland (33%), the udder (8%) during lactation, and the uterus (and fetus) *via* amniotic fluids during pregnancy.

The daily iodine requirement of dairy cattle is calculated as follows:

$$\text{Dietary I, mg}/d = 0.216 \times \text{BW}^{0.528} + 0.1 \times \text{Milk}$$

where BW = body weight (kg), milk = the quantity (kg/day) of milk produced per day. In the case of non-ruminant calves, daily intake should be based on a diet of 0.8 mg I/kg DM (dry matter) (Subcommittee on Beef Cattle Nutrition; Committee on Animal Nutrition; Board on Agriculture; National Research Council (NRC) 2000). Iodine intake in pregnant ewes should be between 0.12 and 8 mg/kg DM iodine to avoid either depletion of the dam's iodine stores in the case of deficiency, or disruption of thyroid metabolism in the case of excess (Aumont et al. 1989).

The European Commission imposes a maximum of 10 mg/kg of iodine in feed for ruminants fit for human consumption (EU 1459/2005; European Commission 2005). A concentration of iodine exceeding 10 mg/kg in the diet caused a disturbance in thyroid metabolism in ewes (Aumont et al. 1989). Cattle meat contributes around 2% of human iodine needs, so it might be tempting to increase the high iodine content of food (>10 mg/kg in the ration) (Meyer et al. 2008). However, an increase of the iodine supplementation to a concentration of 8.31 mg/kg DM already tends to reduce the bulls' average daily gain and increase their thyroid gland weight (Meyer et al. 2008).

Iodine is also present in milk at a concentration varying between 25 and 400 μg/L (Hillman and Curtis 1980; Puls 1994), but attention should be paid to pre- or post-soaking with products containing iodine during milking. These products can greatly increase the concentration of iodine in the milk (Guyot and Rollin 2007). Certain dewormers, such as nitroxinil and closantel, and other iodide-based medications (sodium iodide, potassium iodide) can also overestimate iodine levels in cattle (Guyot and Rollin 2007).

Iodine supplementation has several reported effects. It increases in dairy goats' serum free T3 (fT3) concentration, fT3/fT4 ratio, glucose, total protein, RQUICKI (Revised Quantitative Insulin Sensitivity Check Index) and decreases BUN (blood urea nitrogen) (Nudda et al. 2013; Zebari and Salih 2023). The fact that T3 increases RQUICKI suggests that iodine supplementation improves tissue insulin sensitivity by decreasing insulin secretion (Nudda et al. 2013). It is consistent with the report in cows that thyroid hormones have an insulin-agonistic and antagonistic effect on different organs (Fazio et al. 2008). An improvement in the plasma IgG and PII concentration of the calves and sheep offspring and colostrum iodine concentration of the cow is observed when dams are supplemented with iodine (Aumont et al. 1989; Kerslake et al. 2010; Guyot et al. 2011). Iodine drenching (0.5 to 1 mg/day of iodine) of goats at the end of gestation (daily, 6 weeks before parturition) also improves the birth weight of kids (Zebari and Salih 2023). Iodine supplementation to cover requirements has several beneficial effects on the health and quality of dairy products in cows. It improves phagocytosis of neutrophils and improves cheese quality *via* the reduction of lipid oxidation (reduction in malondialdehyde levels) and milk somatic cells (Iannaccone et al. 2019). The PII concentration decreases and increases very quickly in cows when the diet's iodine concentration is changed, from a few hours after the change to a peak after 1 week (Hemingway et al. 2001).

The thyroid gland can be impaired by various goitrogenic substances that disrupt iodine metabolism and thyroid hormone synthesis (Figure 3A). Cyanogenic glucosides, found in plants such as white clover, millet, and flax seeds, are converted in the rumen into thiocyanates, which competitively inhibit iodine uptake by the thyroid gland (Żarczyńska et al. 2022). Goitrin and thiouracil, naturally occurring in rapeseed, turnips, and cabbage, inhibit both thyroperoxidase and deiodinases, key enzymes involved in thyroid hormone production and activation. *Leucaena leucocephala*, a tropical leguminous plant, contains 3-hydroxy-4(1H)-pyridone, a compound with well-documented goitrogenic effects. Additionally, excessive calcium levels in the diet or drinking water, as well as nitrate anions (NO_3^-), have also been shown to interfere with iodine absorption and thyroid function (Żarczyńska et al. 2022).

4.4. Selenium status in ruminants

In our search, 11/206 studies focus on selenium and thyroid physiology. Of the studies, 4/11 involve cattle, 3/11 goats, 2/11 sheep, and two studies involve several species at the same time.

The thyroid gland is one of the organs containing the highest concentration of selenium (Hefnawy and Tórtora-Pérez 2010). Selenium is an essential trace element that has numerous antioxidant functions in the body. Selenium is a constituent of DIO enzymes which transform T4 into active T3 and the thyroperoxidase (Hefnawy and Tórtora-Pérez 2010). When the thyroid hormone status of selenium-deficient ruminants is compared with that of ruminants with normal selenium status, the selenium-deficient ruminants have higher plasma T4 values and lower T3 values (Figure 3A). This phenomenon is explained because their conversion is no longer carried out properly (Arthur et al. 1988; Hefnawy and Tórtora-Pérez 2010; Guyot et al. 2011), but it's not always the case (Chadio et al. 2006).

Supplementing selenium-deficient pregnant ewes with iodine and selenium increases their selenium utilization but does not alter their thyroid hormone profile, whereas the thyroid hormone profile of their lambs will change in the first 30 days after birth (Konečný et al. 2015). Oral supplementation with 0.6 mg/kg of respectively selenium and iodine improves growth performance in goats (Aghwan et al. 2016). However, the concentration expressed in this study exceeds the European standard for selenium concentrations in animal feed, which is set at a maximum of 0.5 mg selenium/kg (EU 2019/804). Next to that, an another study has shown that selenium supplementation alone (0.5 mg/kg per day on average, *via* a bolus) improves growth weights and serum T4 concentration in Angora goats male kids, whereas iodine supplementation alone only increases serum T3. Moreover, the joint addition of iodine and selenium to goat diets enables greater selenium retention in muscles (higher selenium concentration in muscles) than if the ration had been supplemented with iodine or selenium alone (Wichtel, Craigie et al. 1996). Finally, the results of selenium supplementation in ruminants are contradictory, because it is influenced by the composition of the complementation. Some studies show no effect on thyroid hormones when selenium and vitamin E were added to the lamb ration (Naziroğlu et al. 1998), while others show an increase in T3 and T4 hormones and a decrease in TSH in cattle when selenium is added with iodine (Guyot et al. 2011). It is therefore complicated to interpret the effect of selenium alone in all these studies, since most of them combine other elements (iodine, vitamin E, etc.).

Selenium supplementation before and after parturition is essential to maintain selenium and T3 homeostasis during late gestation and the postpartum period in ewes and their lambs up to 8 weeks of age (Ghany-Hefnawy et al. 2007; Hefnawy et al., 2014). Considering calves not supplemented on grassland, many of the negative effects of selenium deficiency, such as growth deficiency, are explained by the malfunctioning of the thyroid metabolism (Wichtel, Thompson et al. 1996). When cows are fed a selenium-deficient (0.05 ppm DM) ration for around 100 days, there is very little change in thyroid hormones, namely a limited decrease in serum T3 concentration, but no effect on T4 (Contreras et al. 2002). This suggests the existence of selenium homeostasis in cattle (Contreras et al. 2002).

4.5. Thyroid physiology during the fetal and neonatal periods in ruminants

Many studies are focused on the physiology of the thyroid gland during gestation and in the newborn, as this section includes 24/206 references. This physiology is mainly studied in sheep and cattle with 11 out of 24 studies in sheep, 11/24 cattle and 1/24 goats.

The sheep fetus absorbs iodine from the 50th day of gestation (Barnes et al. 1957). There is transplacental passage of fetal T3 and T4 into maternal blood, where it is converted into rT3 and T2s (3,5 diiodo-l-thyronine), metabolites of the hormone T3 and T4 (Sack et al. 1975; Chopra et al. 1979; Wu et al. 2006). In the fetus sheep, there is naturally not a high concentration of T3, T4, and rT3, but the two metabolites of 'T2s' (3-3′T2 and 3-5′T2) are good parameters to get an idea of the thyroid status of the fetus (Chopra et al. 1979). There is also a transplacental passage of maternal iodine and selenium to the fetus in cattle (Guyot et al. 2011). In one experiment in sheep, it was shown that the placenta of ewes is impermeable to T4 to the fetus in the last 6 weeks of gestation, with the fetal thyroid taking over (Hopkins and Thorburn 1971). As T4 is a physiological regulator of O_2 use by the near-term sheep fetus, it is one of the mechanisms of action that explains the poor growth of a hypothyroid fetus (Fowden and Silver 1995). During the last third of gestation, the sheep fetal thyroid gland can produce its own thyroid hormones, but the fetus is less able than its mother to convert T4 hormones into T3 (Barnes et al. 1957; Fisher et al. 1972). T4 and rT3 hormones levels fall in fetuses' blood during the last third of gestation. It is suggested that the fetus has a change in deiodination pathway (Mathur et al. 1980). A T3 peak is observed in the sheep fetus 6 days before parturition. Fetal cortisol also increases during this period (Nwosu et al. 1978).

There is a neonatal reserve of thyroid hormones and a good capacity for the newborn to secrete thyroid hormones. Reducing the level of colostrum in calves has minimal effects on this (Stojic et al. 2002). Colostrum contains around 1.3 times more iodine than milk from the first week of lactation in ewes (Aumont et al. 1989). The amount of colostrum iodine is dependent on the amount of iodine in the bovine diet (Guyot et al. 2011). It is recognized that thyroid dysfunction can be linked to neonatal disease in calves (Cabello 1980). A combined injection of cortisone and thyrotropin-releasing hormone produced a 5-fold increase in surfactant protein A in alveolar washings from lambs (Ikegami et al. 1991). In terms of calves' biochemical parameters, there is a decrease in PII from birth to day 10 and a transient increase in T4 and T3 plasma levels during the first 6 h of neonatal life and an increase of the FT4/T4 ratio, while rectal temperature decreases slightly but significantly (Davicco et al. 1982; Cabello and Wrutniak 1986). This increase can be attributed to the TSH surge which occurs at birth. This TSH surge is caused by cold shock at birth and can be reduced if the animal is immersed in a 37–39 °C bath at birth. Changes in thyroid hormone activity before birth have implications for glucose homeostasis and energy availability in lambs. The T3 peak in response to endogenous or exogenous corticoids may have an important role in mediating the maturational effects of glucocorticoids on glycogen storage in the fetal liver and heart (Forhead et al. 2009). Plasma T4 and T3 levels then fall during the first week of neonatal life and remain stable until days 30–60 (Davicco et al. 1982; Sharma et al. 1985). There is a peak in T3 and T4 at 30 days of age in goats and sheep. T4 remains higher in growing goats and sheep than in those aged between 1 and 3 years (Novoselec et al. 2009; Madan et al. 2019). The TSH surge can be mimicked by injection of TSH and induces a higher rise in T3 and T4 in calves aged 21 days than in those aged 3 h (Davicco et al. 1982). In calves, there are positive correlations between weight gain and thyroid hormones concentration (Bobek et al. 1980; Kahl and Bitman 1983). The T3:T4 ratio does not vary throughout age. T3 and T4 together are negatively correlated with age (Sharma et al. 1985).

In Belgian Blue heifers, T4 concentrations may serve as indicators for assessing the effective growth of the animals, during the first year of life (Fabry 1983). Weaning is a stressful time for young animals and results in an adaptation of thyroid metabolism, with a decrease in T3 and an increase in T4 in lambs (Fazio et al. 2015). Stress, food deprivation, and physiological adaptation to weaning are all possible explanations for this phenomenon (Fazio et al. 2015).

4.6. Thyroid physiology during the reproductive cycle

Nine studies focus on understanding the physiology of the thyroid gland and its role in reproduction. Cattle is the subject of the study in 8/9 papers, and only one study concern sheep. Thyroid physiology is involved in the reproductive cycle of ruminants.

1. Thyroid hormones influence female ruminants' reproductive cycle in various ways, not all of which have yet been fully elucidated in these species. Thyroid hormones have both direct and indirect effects on the reproductive system of dairy buffalo (Ghuman et al. 2011). Sheep and goats are seasonal polyestrous animals, meaning that their ovulation cycles occur according to the season. As the days get shorter, melatonin production increases and stimulates the hypothalamus to secrete gonadotropin hormone (GnRH). In turn, GnRH stimulates the production of FSH and LH to initiate the animal's cycle. The seasonal decline in luteinizing hormone (LH) pulse frequency in ewe is due to thyroid hormones in absence of gonadal steroids during spring and summer (Anderson et al. 2002). Thyroid hormones play a crucial role in interpreting photoperiod and assimilating seasonal changes. There are indeed changes in DIO activation in the hypothalamus depending on the season. During long days, thyroxine stimulates DIO2 to synthesize more T3, contributing to GnRH secretion by the hypothalamus. During short days, thyroxine activates the DIO3 pathway and metabolizes thyroid hormones into T2, reducing T3 circulation and GnRH secretion (Ikegami and Yoshimura 2013). However, thyroid hormones are not necessary for the resumption of seasonal reproduction or for stimulating the amplitude of the LH pulse (Anderson et al. 2002). Cows with a prolonged luteal phase, delayed first ovulation or non-ovulation and a short luteal phase have a different serum thyroid hormone profile and an increased T4:T3 ratio compared to cows with a normal cycle (Kafi et al. 2012; Yari et al. 2023). Plasma TSH concentration is lower in cycling cattle than in non-cycling or non-pregnant cattle (Kesler et al. 1981; Ghuman et al. 2011). Thyroid hormones have a direct stimulatory effect on ovarian function, as low thyroid activity can suppress steroidogenesis in ovarian cells, which can induce anestrus and reduce estrus expression (Ghuman et al. 2011). To explain how hypothyroidism induces delayed puberty in humans, Gonadotropin-inhibitory hormone (GnIH) was recently discovered to be secreted by the hypothalamus and inhibited by thyroid hormones (Tsutsui et al. 2018). It remains to be determined whether GnIH also exists in ruminants. In heifers, induction of hypothyroidism by ingestion of 6-n-propyl-2-thiouracil (PTU) did not cause delayed puberty (Thrift et al. 1999). Although hypothyroidism paradoxically increases the ovarian response to superovulatory treatment, the fertility of these cows is impaired by hypothyroidism (reduced number of transferable embryos) (Bernal et al. 1999). Thyroid hormones enable pre- and post-implantation of the embryo in cattle (Ghuman et al. 2011).
2. In bulls, T4 correlates with seminal volume and sperm motility and T3 correlates with total sperm concentration and the percentage of live spermatozoa (Dixit et al. 1984). A study suggests that inducing hypothyroidism in neonatal calves from exceptional genetics (destined for reproduction) could result in larger testicles and better sperm production in adulthood, bearing in mind that thyroid hormones have the effect of reducing testicular volume in prepubertal bulls (Majdic et al. 1998).

4.7. Thyroid physiology during milk, meat, and fiber production

Several studies (22/206) shed light on the relationship between thyroid metabolism and production: milk (18/22), meat (2/22) and wool (2/22). For dairy production, it is the dairy cow, which is mainly studied, since there are only 1/18 studies on dairy sheep. For meat, one study in cattle and one in goats were found. Concerning wool, two studies in sheep and goats are used.

The behavior of thyroid physiology in dairy cows and buffaloes is widely described in relation to milk production. During gestation, TSH and T3 are lower on day 18 of pregnancy, compared to non-pregnant dairy heifers (Meyerholz et al. 2016). Thyroid hormones T3 and T4 decrease after calving and during early lactation (Kesler et al. 1981; Tiirats 1997; Fiore et al. 2015), but TSH and free T4 (fT4) increase during early lactation, whereas rT3 decrease (Steinhoff et al. 2019). The reduction in T3 and T4 hormones at the start of lactation is explained by their massive use during this period of high demand (Tiirats 1997). Higher T3 and T4 values are found during gestation rather than at the start of lactation (Fiore et al. 2018). TSH is correlated with milk production (Hassan et al. 1985; Fiore et al. 2018). While some studies recognize a negative correlation between T3 and T4 hormones and milk production (Vanjonack and Johnson 1975; Hassan et al. 1985; Gueorguiev 1999; Mohebbi-Fani et al. 2009), others show only a negative correlation between rT3 and milk production (Tiirats 1997). These studies focus on different species (buffalo, cattle), breeds and levels of milk production, which could explain the variations in these results.

T4 increases from the 200th day of lactation and 20 days before parturition and decreases around parturition in cows (Blum et al. 1983). T3 and T4 are lower in pluriparous cows and cows with the highest milk yield (18.9 to 23.5 kg/day) in comparison with primiparous and cows with the lowest milk yield (10.9 to 14.3 kg/day) (Blum et al. 1983). T3 and T4 show a negative correlation with body condition score (BCS) in cows (Natalija et al. 2013; Duru et al. 2021). T3 increases around 120 days of lactation and then decreases (Blum et al. 1983).

The transition from gestation to lactation is accompanied by a change in the abundance of transcriptomes for activating and deactivating DIOs, with a decrease in T3 and T4 conversion in the liver and an increase in this conversion in the udder (Figure 3B). DIO1 is the most important form expressed in the liver and its expression decreases with lactation (Capuco et al. 2008). DIO2 is the form most expressed in mammary tissue during lactation and the preferred pathway at this time. To a lesser extent, DIO3 is expressed in the liver and udder (Capuco et al. 2008). It is not yet known whether this thyroid depression at the start of lactation is the cause or the consequence of the decreased hepatic DIO concentration (Pezzi et al. 2003). Interestingly, it has been suggested that a cow has an adaptive capacity to its metabolic stage that depends, at least in part, on polymorphic variants of the DIO1 gene. This information could be used in the future to select cows that produce better and have better fertility (Kostyunina et al. 2023). In cows close to terms, free T4 correlates with triglycerides and very-low density lipoproteins (Mohebbi-Fani et al. 2009). Blood T3 concentrations are lower in lactating ewes compared to pregnant and non-pregnant (non-lactating) ewes (Novoselec et al. 2009). Serum T3 and rT3 are unchanged, but T4 and T3 in milk decrease significantly from early to mid-lactation but not from mid to late lactation in cattle. Reverse-T3 in milk does not change (Akasha et al. 1987). T3 and T4 concentrations in milk represent 4 to 5% of total calf maintenance requirements (Akasha et al. 1987). Very low or even undetectable levels of T4 are found in commercial milk products (Richardson and Mattarella 1977). Serum T4 is significantly lower at 100 days of gestation in heifers, with T4 being negatively correlated with milk production (Bitman et al. 1984). The same movements in thyroid hormones occur in lactating ewes, in which there are also significant variations between available energy and metabolic demand during the transition period (Ehrhardt et al. 2023). To compensate for this, insulin resistance and a reduction in circulating thyroid hormones can be observed during this period. A recent study has shown that the orchestration of these mechanisms is governed by the CNS-MC system (central nervous system-melanocortin), consisting of alpha-melanocyte-stimulating hormone (alpha-MSH) and agouti-related peptide (AGRP), which act respectively as agonist and antagonist on central MC receptors (Ehrhardt et al. 2023). The regulations leading to these changes are complex, and further studies are needed to understand their intricacies.

To produce meat, it is observed in bulls that serum T3 concentration is significantly influenced by the degree of expression of the double-muscled (DMU) trait, extreme DMU bull of breed Angus, Charolais and Limousin-Hereford, with higher T3 concentrations compared to low or moderate DMU subjects. DMU bulls also tend to have a higher T4 concentration. These DMU animals with higher serum T3 levels, a larger T3 pool size and a high metabolic rate suggest that they are relatively hyperthyroid (Strath et al. 1982). Use of T3 blood concentration in cattle and goats as a breeding selection criterion to promote feed efficiency and growth is discussed (Strath et al. 1982; Abdoun et al. 2018). Serum T3 is correlated with average daily gain (ADG), feed intake and feed conversion (Abdoun et al. 2018).

It has been demonstrated that temporary alterations in thyroid hormones (through T4 or T4 inhibitor administration) during ewe gestation can affect wool follicle development in lambs (McDowall et al. 2011). Administration of exogenous T4 reduces the number of primary, secondary, and total wool follicles. However, lambs from the T4-treated group ewe tend to have a higher proportion of secondary follicles and greater total follicle densities at 12 months of age. These variations did not influence fiber yield or fiber diameter (McDowall et al. 2011). The skin expresses DIO1 and DIO3, and the percentage of expression of these two DIOs varies according to the season, which could explain, in addition to the variations in thyroid hormone concentration during a year, the variations in wool growth in sheep. Thyroid hormones are correlated with wool growth in sheep and angora goats (Todini 2007). The serum T3 is positively correlated with cashmere growth in goats and must play an important role in hair germination and growth (Sun et al. 2018). Moreover, the daily administration of exogenous T4, and the induction of hyperthyroidism, has demonstrated in several studies, on sheep and angora goats, a higher quantity of wool produced and longer fibers' length with lower fibers' diameter (Todini 2007). However, none of these studies clearly describe the precise mechanism by which thyroid hormones are involved in wool production (Todini 2007).

4.8. Impact of nutrition on thyroid physiology

The nutrition and physiology of the thyroid gland (13/206 studies) was studied in sheep (7/13) and cattle (6/13).

Experiments were carried out on lambs to test the effect of overnutrition or undernutrition of their mother at the end of gestation, to find out whether it was possible to program the thyroid response in this way. The results showed, for overnutrition, no abnormality in the functioning of the hypothalamic-pituitary-thyroid axis in lambs (Johnsen et al. 2018). In over-fed ewes, the plasma concentration of T4 increases and T3 decreases in lambs (Caldeira et al. 2000). On the other hand, in lambs, undernourishment during late gestation unmanageably leads to hyperthyroidism associated with an increase of the expression of genes regulating the synthesis of thyroid hormones and the expression of DIOs in more than one of the target tissues - liver, cardiac muscle, *longissimus dorsi* - but reduces these activities in adipocytes (Johnsen et al. 2013). This effect is immediate at the start of life, even before changes in T3 and T4 concentrations. It is a permanent effect which becomes stronger in adulthood (Johnsen et al. 2013). Modifying the maternal diet, in terms of percentage of daily dietary requirements (60, 100 or 140% of the daily requirements) or selenium concentration (9.5 or 81.8 μg/kg BW), only has a slight impact on the functioning of the offspring's hypothalamic-pituitary-thyroid axis, *via* minimal changes in T3 concentration (Vonnahme et al. 2013). It is known that dietary restriction induces a reduction in hair follicle activity in cashmere goats. The exact mechanism is poorly understood and a difference in DIO activity is suspected (Rhind et al. 2006).

During a starvation period in rats, the drop in leptin can send a signal to the paraventricular nucleus (PVN) in the hypothalamus to suppress TRH expression (Huszenicza et al. 2002) (Figure 3A). TSH thus slightly decreases and T3 and T4 hormones decrease. In cattle, T4 decreases by 75% after food deprivation. The rate of secretion is 24% of normal (Tveit and Almlid 1980). T3 and rT3 decrease by 60% of normal (Tveit and Almlid 1980). There is no evidence of a T4 inactivation mechanism, contrary to what has been seen in humans. TSH decreased to 85% of normal (Tveit and Almlid 1980). The greatest decrease in thyroid hormones occurs within 24 h after an episode of starvation, making it a very rapid process. If dietary restriction occurs in early gestation, there are long-lasting adaptations in the expression of thyroid hormone receptors on the placentomes of pregnant ewes. If, on the other hand, this food restriction occurs at the end of gestation, the placentomes can adapt to nutritional restrictions during gestation (Steinhauser et al. 2021). Six hours after refeeding, TSH increases by 300% compared with a control group. T3 and T4 reach the zenith 12 h after refeeding (Tveit and Larsen 1983).

Regarding feed management, hearty colostrum meals in newborn calves are associated with higher plasma T4 concentrations for up to 1 week of life (Grongnet et al. 1985). An increased concentrate-to-hay ratio after weaning in calves increases thyroid hormones, insulin, blood glucose, ammonia, rumen propionic acid and average daily gain (Fernandez et al. 2012). A high level of concentrate feedstuffs in the ration in cows leads to an increase in thyroid hormones, which may alter glucose and lipid metabolism *via* activation of the thyroid hormone receptors mechanism (Chen et al. 2022). Thyroid hormones influence ruminal motility, the rate of passage of ruminal particles and the digestibility of DM (De Moraes et al. 1998).

Beside iodine and selenium, other minerals may be involved in thyroid metabolism such as copper and zinc (Sampaio et al. 2021; El-Tawab et al. 2022). It has recently been demonstrated that zinc has an action on DIOs (inhibitor and cofactor of these enzymes) T3 nuclear binding and on TSH synthesis in sheep (Sampaio et al. 2021). Zinc status should be determined in cases of hypothyroidism (Shulhai, 2024). In human medicine, interactions are well described, particularly for vitamin A, zinc, and magnesium. These elements play an indirect role through their antioxidant or immunity-related effects (Rabbani et al. 2021). Vitamin A deficiency causes a reduction in thyroid iodine uptake, thyroid hypertrophy, and impaired synthesis of thyroglobulin (Rabbani et al. 2021).

In human medicine, the interactions between thyroid metabolism and diet have been well studied. Iron is the main atom included in thyroperoxidase, so a deficiency could lead to thyroid disorders during periods of high iron demand, such as during pregnancy. Vitamin D supplementation, through the action of this vitamin on the immune system, appears to be effective for patients suffering from Hashimoto's thyroiditis. Finally, copper and magnesium are being studied for their potential role in thyroid cancer (Shulhai et al. 2024).

4.9. Implications of thyroid metabolism in ketosis in cattle

The study of thyroid metabolism in the context of ketosis was carried out in 13/206 studies in cattle.

Ketosis is an important disease in lactating cows where thyroid metabolism is involved. In early lactation cows, there is a positive correlation between serum T4 and serum beta-hydroxy butyrate (BHB) (Mohebbi-Fani et al. 2009; Kafi et al. 2012). Thyroid hormones play a key role in the etiopathogenesis of ketosis (Tiirats 1997; Huszenicza et al. 2002). There is T3 threshold for predicting the risk of ketosis; a T3 value < 1.23 nmol (ROC test; sensitivity $= 0.81$; specificity $= 0.93$) is associated with BHB > 1.1 mmol/L in 5 ± 3 days post-partum (Fiore et al. 2017). It has been shown that cows with severe fatty liver during early lactation were hypothyroid. Hypothyroidism can be both a risk factor and the cause of fatty liver (Šamanc et al. 2010).

Cows suffering from ketosis have lower concentrations of thyroid hormones T3 and T4 than healthy cows at the same physiological stage. This is logical since the reduction of these hormones is associated with a reduction in energy metabolism in favor of lipid metabolism, notably at the start of lactation, to allow high milk production (Tiirats 1997; Nikolic-Judith et al. 2001; Huszenicza et al. 2006; Djokovic et al. 2014). Ketosis also reflects the runaway nature of this metabolic pathway.

The increase in thyroid hormones at the end of gestation leads to a decrease in cholesterol (negative correlation). It is suspected that thyroid hormones have a direct effect on beta-hydroxy-beta-metylglutary l-CoA reductase, which decreases cholesterol synthesis. There is a negative correlation between thyroid hormones and cholesterol. The change in cholesterol levels is therefore not associated with milk production (Gueorguieva and Gueorguiev 1997).

Postpartum propylene glycol supplementation induces T4 to T3 conversion and increase the local hepatic leptin and short-form leptin receptor mRNA in the liver (Gyorffy et al. 2009). This phenomenon is not associated with a significant change in hepatic total lipid level but more a local defense mechanism to prevent fatty liver formation (Gyorffy et al. 2009). As explained before, at the start of lactation, there is a reduction in insulin-mediated glucose tissular availability, a reduction in plasma thyroid hormones and the accumulation of lipids in the liver. Leptin appears to attenuate all these phenomena (Ehrhardt et al. 2016). Monitoring leptin and thyroid hormones can be useful for reproductive management (Duru et al. 2021).

4.10. Involvement of thyroid metabolism in heat and cold stress in ruminants

The involvement of thyroid metabolism in heat and cold stress is a major theme that is well documented in the literature, including ruminants. During our research, there were numerous studies on heat stress, but only those that centrally studied thyroid physiology in the context of heat stress were kept. The studies retained (9/206) concerned 6/9 cattle, 2/9 sheep and 1/9 goats.

In cold weather, bulls kept outdoors at temperatures as low as −15 °C have higher T4 levels than those kept indoors (Christopherson et al. 1979). Increasing the feed intake of animals raised outdoor reduced the difference with those raised indoor (Christopherson et al. 1979). Increasing the energy levels of the diet increases the levels of T3 and T4 in the serum and increasing the ambient temperature decreases the concentrations of serum T3 and T4 (Christopherson et al. 1979; Güler et al. 2006) (Figure 3A). This is also confirmed in lambs. Those exposed to cold have an increased T3, but this hormone decreases if they are exposed to food restriction (Ekpe and Christopherson 2000).

Thyroid physiology adapts to ensure thermoregulation and basal metabolism (Ekpe and Christopherson 2000). Thyroid hormones are higher in calves born in winter than in summer (Bobek et al. 1980). In goats, it has been shown that the microscopic morphology of the thyroid gland differs between winter and summer: in winter, more thyroid hormones are secreted, so the follicular parenchyma is rectangular, with numerous endocytosis vesicles visible in the cell apex. In summer, on the other hand, the follicles tend to have flattened, non-secretory cells (Ali et al. 2020). FT4 and T4 are higher in autumn, lower in winter and intermediate in spring and summer. In winter, although thyroid hormone secretion increases, there is greater T3 and T4 tissue utilization which keeps concentrations low, especially if the cows are lactating. In fact, the stage of lactation has more influence on thyroid hormone levels than the seasons. FT3 and T3 show the same pattern (Nixon et al. 1988). Changes in photoperiod do not influence T4 in ewes (Fitzgerald et al. 1982). In goats, plasma T3 concentrations are similar between groups before parturition, likely due to equal metabolic demands, but are higher in the long-day photoperiod group from 10 to 40 days postpartum before declining between days 50 and 70 compared to the short-day photoperiod group in goats. This postpartum increase in long-day photoperiod goats may not be due to higher milk production demands but could result from a carryover effect of heat stress experienced during the dry period (Mabjeesh et al. 2013).

During the warm, humid season, the T4/T3 ratio is higher in cattle, indicating either that the degradation/use of T3 hormone is greater, or that peripheral conversion is reduced. It is recognized in humans that peripheral conversion is reduced or even eliminated in hot weather (Khurana and Madan 1986). Heat stress in lactating cows leads to a decrease in T3 and T4 (Figure 3A). It leads also to a reduction in hepatic sensitivity to thyroid hormones, *via* changes in the abundance of mRNAs that enable transduction to facilitate amino acid and fatty acid catabolism, as well as gluconeogenesis (Weitzel et al. 2017).

4.11. Assessment of the function and morphology of the thyroid gland in ruminants

Interpreting thyroid metabolism is quite complex, as it often requires repeated measures (Colston 2018). While many studies present the results of hormone assays, few have validated these methods of analysis beforehand or validate them using assays repetitions. As a result, in practice, veterinarians have access to few thyroid parameters in ruminants.

This part of the knowledge about ruminants is very limited. This is even more frustrating when these results are compared with those available in humans or other species in veterinary medicine (dogs, cats, horses). In these species, hormonal assays are routinely available (Breuhaus 2011; Moreno-Reyes et al. 2013; Peterson et al. 2015; Scott-Moncrieff 2015c; Pramono and Yuwono 2019).

There are 22/206 studies that present standards for hormones and physiological thyroid parameters in domestic ruminants. Only 6/22 studies validated their hormonal or biochemical assay methods for the study of thyroid physiology. The rest of the studies concerning hormonal dosages include intra-study validations which were still considered to report standards, but the method has not been validated for use on a larger scale. Alongside these hormonal dosages, thyroid imaging includes some evidence to date (7/206). For hormonal and biochemical assays, the goat is the least documented species. However, one team has intensively studied thyroid gland imaging in goats, with 3/7 for thyroid gland imaging.

4.11.1. Assessment of the thyroidal function in ruminants

Among the analysis methods validated in the literature, CLIA and ECLIA have therefore been recognized as alternative methods to RIA for measuring total T4 and T3 in sheep, with ECLIA corresponding better to the results obtained with RIA (Hopkins et al. 1975; Eshratkhah et al. 2011a, 2011b;

Eshratkhah 2012). The immunofluorimetric method (DELFIA) was validated and applied to the determination of FT3 and FT4 in buffalo (Ambrosio et al. 2009). Interestingly, a method for measuring the T3 metabolite in European mouflon feces has been established using an ELISA kit for measuring T3 (Pasciu et al. 2022). Although the study used an ELISA kit focused for human medicine, the results were promising and more studies are needed to establish standards and eventually be able to use this assay in other species (Pasciu et al. 2022). Finally, a RIA method has been validated for measuring bovine TSH (Guyot and Rollin 2007) but is unfortunately no longer available. In Belgian rural veterinary practice, total T4 analysis is routinely available, but other methods of analysis, although described in scientific studies, are not available to clients in the field. Table 4 lists the reference standards found in the literature for ruminants. Care must be taken to interpret these standards according to the analytical method and the units used.

Iodine can be tested, although it must be kept in mind that it is a nutritional marker and not a functional one. As far as iodine concentration is concerned, PII is the most reliable parameter for assessing dietary iodine intake in the 3 days prior to sampling (McCoy et al. 1997). Total iodine, on the other hand, includes both PII and iodine contained in the various thyroid hormones. It is an imprecise parameter that should not be measured on its own (Kincaid 2000). However, urinary iodine and milk iodine are correlated with blood iodine concentration and therefore with iodine in diet and can be used to interpret dietary iodine intake (Hillman and Curtis 1980; Aumont and Tressol 1987). A single measurement of PII or T4 is insufficient to diagnose hypothyroidism. T4 and PII should be measured together repeatedly in the event of iodine deficiency, so that kinetics can be observed, and the result correctly interpreted (Guyot et al. 2007b; Colston 2018). To diagnose hypothyroidism in a calf, bovine TSH alone appears to be a good marker to distinguish goitrous from healthy calves (Guyot et al. 2007a). In addition, in calves, the T4/T3 index can be used to diagnose endemic goiter (Takahashi et al. 2001).

Table 4 shows that few different assay techniques are scientifically validated, and that there is a real inequity in the validation of these tests between species. While cattle and sheep have several validated hormone tests, goats have none.

Tables 5–7 show the additional tests used to assess thyroid function, which have been scientifically validated for different species: cattle, sheep and goats.

4.11.2. Assessment of thyroidal morphology in ruminants

In addition to blood tests, the thyroid gland can also be imaged in ruminants. Using ultrasonography (US), the thyroid gland appears homogeneous, in the shape of a spindle. The gland is examined under sagittal and transversal views, with a convex 3.5 MHz US probe and/or a linear US probe ranging from 3.5 to 5 MHz (Braun et al. 1994). A subsequent study scanned the thyroid of calves using a 6.5 MHz linear probe and found a strong correlation between US and *post-mortem* measurements (measurements taken on the thyroid gland at necropsy) (Metzner et al. 2015). Recently, a study technically validated thyroid US in calves and cows with a convex US probe of 5 MHz for cows and a linear US probe of 10 MHz for calves (Eppe et al. 2023). The inter-observer variability was 10.4% and 11.8% for calves and cows, respectively (Eppe et al. 2023). Thyroid US is a rapid method of exploring the thyroid gland that does not require the animal to be sedated (Metzner et al. 2015; Eppe et al. 2023). It was also possible to identify thyroid cysts on ultrasound scans of adult cows, with this lesion being confirmed post-mortem and on histological examination (Eppe et al. 2024). This lesion has not yet been linked to any disease or metabolic disorder. Thyroid US with *post-mortem* measurements were also documented in goats. However, the measurements *in vivo* and *post-mortem* were not correlated (Pankowski et al. 2020). The reasons for these differences discussed in the study were the difficulty of finding the true length of the thyroid lobe due to differences in shape, and the difficulty of performing the measurement on a single view, since the length exceeds the length of the probe. Finally, there is a study in which the thyroid gland was measured by CT-scan (Pankowski et al. 2021). This CT-scan examination was carried out for the first time in goats and this study serves as a reference for future studies. Thyroid gland attenuation by CT-scan in goats is 80.9 HU, which is less than in dogs (123.2 HU) and cats (107.5 HU). Thyroid gland densities on CT-scan may vary depending on the species, the imaging techniques used to measure density, in the case of thyroid disease as in humans, or depending on certain breeds, as has been noted in brachycephalic breeds of dog (lower thyroid gland density in these breeds, without associated thyroid disease).

Table 5. Diagnostic tools and reference ranges in cattle.

Functional assessment								
Marker	Matrix	Sample tube	Analysis method	Validation of the method	Deficiency or hypothyroidism	Excessive	Normal range	Unit
Total T3	Serum Plasma Serum Serum Serum Plasma	Dry Heparin Dry Dry Dry Heparin	RIA RIA RIA RIA RIA RIA	Intra-study Validated by laboratory Intra-study Not validated for cattle[7] Intra-study Validated by laboratory	- - - - - - - - – 0.62–12.37[9] (NB) - -	- - - - - - - - - - - -	1–2 [1] (buffalo bulls) 2.02–16.12[2] (NB) 1.34 ± 0.04[4] (DC early lactation) 1.24 ± 0.04[4] (DC mid lactation) 1.34 ± 0.04[4] (DC late lactation) 4.18 ± 0.38[5] (extreme DM) 2.16 ± 0.45[5] (moderate DM) 1.48 ± 0.67[5] (normal DM) Between 0.65 ± 0.07 and 2.49 ± 0.13[8] (DC) 6.49–9.28[9] (NB) 0.93–1.7[9] (DC) 4.95–6.93[11] (NB)	ng/mL nmol/L ng/mL nmol/L
Free T3	Serum	Dry	RIA	Intra-study	- -	- -	2.98–6.23[8] (DC) 3.45–5.37[8] (DC in lactation)	pg/mL
rT3	Serum	Dry	RIA	Intra-study	- - -	- - -	333 ± 17[4] (DC early lactation) 314 ± 17[4] (DC mid lactation) 340 ± 16[4] (DC late lactation)	pg/mL
Total T4	Serum Plasma Serum Serum Serum Serum	Dry Heparin Dry Dry Dry Dry	RIA RIA RIA RIA RIA CLIA	Intra-study Validated by laboratory Intra-study Validated[7] Intra-study Validated by laboratory	- - - - - - - - – 6–142[9] (NB) - - - <40[12]	- - - - - - - - - - - - - -	20–40[1] (bulls) 25–95[2] (DC) 50 ± 1.9[4] (DC early lactation) 55.2 ± 2.3[4] (DC mid lactation) 61.5 ± 1.6[4] (DC late lactation) 67.7 ± 5.8[5] (extreme DM) 47.2 ± 6.8[5] (moderate DM) 58.6 ± 5.9[5] (normal DM) Between 39.16 ± 3.13 and 88.5 ± 4.41[8] (DC) 232–373[9] (NB) 64–116[9] (DC) Between 58 ± 0.08 and 119 ± 4[10] (independent of iodine supply) 50.8–105[12]	ng/mL mmol/L ng/mL nmol/L
Free T4	Serum	Dry	RIA	Intra-study	- -	- -	1.47–1.86[8] (DC) 1.37–1.85[8] (DC in lactation)	ng/dL
TSH	Serum PlasmaPlasma	Dry Heparin Heparin	RIA RIA RIA	Validated [2] Intra-study Validated by laboratory	- > 35[6] (NB) - -	- - - -	1.3–13[2] (DC) 1.3–19.7[2] (NB) 2–5[3] (DC) 2–5[11] (NB)	µU/mL ng/mL µU/mL
PII	Plasma	Heparin	Sandell-Kolthoff ICP-MS	Validated[14]	<80[10] (pregnant DC)	>1000[16]	105–287[10] (pregnant DC)	ng/mL

(*Continued*)

Table 5. Continued.

Functional assessment								
Marker	Matrix	Sample tube	Analysis method	Validation of the method	Deficiency or hypothyroidism	Excessive	Normal range	Unit
IT	Serum	Dry	ICP-MS	Validated	1–5[16]	70–300[16] 100–2500[16] (toxic chronic) >1000[16] (toxic acute)	10–40[16]	μg/dL
	Milk	–	Sandell-Kolthoff ICP-MS	Validated[13]	8–25[16]	500–3500[16]	370 ± 3[15] (DC) 30–300[16]	μg/L
	Urine	–	Sandell-Kolthoff ICP-MS	Validated[13]	–	>50[16]	18.7 ± 19[15] (DC) 10–25[16]	μg/dL
	Allantoid	–	Ion-exchange chromatography	Validated[14]	66 ± 27[18]	–	818 ± 980[18]	μg/L
	Amnios				157 ± 75[18]	–	1605 ± 1142[18]	μg/L
	Colostrum				87 ± 21[18]	–	333 ± 192[18]	μg/L
Morphological assessment								
Parameter	Matrix	Sample	Method	Validation of the method	Deficiency or hypothyroidism	Excessive	Normal range	Unit
Weight	Thyroid	Fresh Thyroid	Scale	–	>30[17] (NB)	–	5–12[18] (NB)	g
Technique	Technical information			Validation of the method	Deficiency or hypothyroidism	Excessive	Normal range	Unit
Ultrasound	Convex probe, 3.5–5mHz (DC) [19,20]			Intra-/inter-observers[19]	-	-	No normal range available	
	Linear probe, 6.5–10mHz (calves) [19,21]			Intra-/inter-observers[19]	-	-	No normal range available	
CT-scan	The are not CT-scan method described for cattle.							

[1]Agarwal et al. (1983); [2]Guyot et al. (2007a); [3]Hopkins et al. (1975); [4]Akasha et al. (1987); [5]Strath (1982); [6]Guyot et al. (2007b); [7]Chopra et al. (1972); [8]Nixon et al. (1988); [9]Takahashi et al. (2001); [10]Hemingway et al. (2001); [11]Cabello (1980); [12]Livesey et al. (2014); [13]Aumont and Tressol (1986); [14]Aumont and Tressol (1987); [15]Hillman and Curtis (1980); [16]Puls (1994); [17]Smyth et al. (1996); [18]Guyot et al. (2011); [19]Eppe et al. (2023); [20]Braun et al. 1994; [21]Metzner et al. (2015).
DC, dairy cows; lact, lactation; DM, double muscled; PII, plasma inorganic iodine; IT, iodine total; ELISA, enzyme-linked immunosorbent assay; RIA: Radio-immuno assay; MEIA, Microparticle Enzyme Immunoassay; FPIA, Fluorescence Polarization Immunoassay

The thyroid of goats is nevertheless clearly visible, as described in precited animal species (Pankowski et al. 2021).

Very recently, US, X-ray and CT-scan were tested on thyroid of goitrous goat kids (Davoodi et al. 2022; Pankowski and Bartyzel 2023). The thyroid US of a goitrous goat kid was normal in echogenicity, but with a heterogeneous pattern of the gland, and more voluminous, since the size of the gland exceeded the surface of the ultrasound probe (Davoodi et al. 2022; Pankowski and Bartyzel 2023). This unfortunately does not correspond to what is described in dogs where a thyroid gland with low echogenicity suggests hypothyroidism (Reese et al. 2005). The measurements of the glands, carried out either during ultrasound or during radiography, were unrealizable without obtaining a systematic error, on the one hand because the size of the gland exceeded the width of the probe, but also because on radiography it is impossible to distinguish the thyroid gland from the rest of the soft tissues (Pankowski and Bartyzel 2023). X-rays alone do not allow a goiter to be diagnosed but allow soft tissue enlargement to be suspected (Pankowski and Bartyzel 2023). On CT scan, the thyroid density (dependent of the iodine content) was reduced in goitrous goat's kids, what is consistent with what is described in humans (Pankowski and Bartyzel 2023).

Thyroid imaging methods are well documented in goats, and partially in cattle. However, there are no validated imaging methods for sheep. Although imaging methods have been described, there is still too little evidence of the use of these imaging examinations for the diagnosis of thyroid disease.

4.12. Thyroid disorders identified in domestic ruminants

Among thyroid diseases, a distinction should be made between those reported in case studies that cause symptoms and those that are aleatory discoveries (tumors, lesions following a nuclear explosion) or experimentally induced diseases (hyperthyroidism). Studies that induced conditions in animals and then subjected them to treatment were rejected in this scoping review. Few exceptions for studies

Table 6. Diagnostic tools and reference ranges in sheep.

Functional assessment								
Marker	Matrix	Sample tube	Analysis method	Validation of the method	Deficiency or hypothyroidism	Excessive	Normal range	Unit
Total T3	Serum	Dry	ELISA	Intra-study	-	-	1.56–4.76[1] (non-productive)	nmol/L
	Serum	Dry	MEIA	Intra-study	-	-	1.56 ± 0.35[2] (non-productive)	
	Plasma	Heparin	CLIA	Validated[3]	-	-	1.81 ± 0.6[3] (non-productive)	
	Plasma	Heparin	ECLIA	Validated[3]	-	-	2.33 ± 0.8[3] (non-productive)	
	Plasma	Heparin	RIA	Validated[3]	-	-	1.4 ± 0.4[3] (non-productive)	
	Serum	Dry	MEIA	Intra-study	-	-	1.58 ± 0.27[2] (pregnant ewe)	
	Serum	Dry	MEIA	Intra-study	-	-	1.26 ± 0.20[2] (lactating ewe)	
Free T3	Serum	Dry	ELISA	Intra-study	–	–	5.15–8.63[1]	pmol/L
Total T4	Serum	Dry	ELISA	Intra-study	-	-	102.51–120.78[4] (non-productive)	nmol/L
	Serum	Dry	FPIA	Intra-study	-	-	40.88 ± 18.05[2] (non-productive)	
	Plasma	Heparin	CLIA	Validated[3]	-	-	53.1 ± 10.7[3] (non-productive)	
	Plasma	Heparin	ECLIA	Validated[3]	-	-	86.1 ± 15.7[3] (non-productive)	
	Serum	Dry	RIA	Validated[3]	-	-	95.3 ± 23.3[3] (non-productive)	
			CLIA	Validated by laboratory	<40[4]	-	42.66 ± 17.04[2] (pregnant ewe)	
							43.48 ± 18.18[2] (lactating ewe)	
							61.7–108[4]	
Free T4	Serum	Dry	ELISA	Intra-study	–	–	17.95–49.18[1]	pmol/L
TSH	Plasma	Heparin	RIA	Intra-study	–	–	2–6[5]	ng/mL
PII	Plasma	Heparin	Sandell-Kolthoff ICP-MS	Validated[6]	<30[7]	100–950[7]	30–40[7]	ng/mL
IT	Serum	Dry	ICP-MS	Validated	2.5[7]	800–2600[7] 4000–30000[7] (toxic)	3–12.3[7]	µg/dL
	Milk	–	Sandell-Kolthoff ICP-MS	Validated[8]	12–80[7]	1000–2000[7]	80–400[7]	µg/dL
Morphological assessment								
Parameter	Matrix	Sample	Method	Validation of the method	Deficiency or hypothyroidism	Excessive	Normal range	Unit
Weight	Thyroid	Fresh Thyroid	Scale	–	–	–	<0.4[9] (NB; thyroid/ birth weight ratio)	g/kg
Ultrasound	There are not ultrasound method described for sheep.							
CT scan	The are not CT-scan method described for sheep.							

[1]Fazio et al. (2017); [2]Novoselec et al. (2009); [3]Eshratkhah et al. (2011); [4]Livesey et al. (2014); [5]Hopkins et al. (1975); [6]Aumont and Tressol (1987); [7]Puls (1994); [8]Aumont and Tressol (1986); [9]Colston (2018).
PII, plasma inorganic iodine; IT, iodine total; ELISA, enzyme-linked immunosorbent assay; RIA, Radio-immuno assay; ECLIA: electrochemiluminescence immunoassay; MEIA, Microparticle Enzyme Immunoassay; FPIA, Fluorescence Polarization Immunoassay

describing the clinical expression of hyperthyroidism, hypothyroidism, and iodine poisoning were nevertheless preserved.

4.12.1. Hypothyroidism

By far, the most common thyroid disease described in the literature in domestic ruminants is hypothyroidism (47/206), with or without goiter. Goiter is an enlarged thyroid gland that gives animals a swollen neck appearance and may be a symptom of hypothyroidism in ruminants (Watson and Scholes 2010; Campbell et al. 2012; Joshi et al. 2017; Davoodi et al. 2022; Kujur et al. 2022). Hypothyroidism may have a dietary (iodine deficiency/excess, selenium deficiency, ingestion of goitrogenic plants) or genetic origin (Falconer 1966; Rac et al. 1968; Sipos et al. 2004; Philippe et al. 2009; Micheloud et al. 2019; Sampaio et al. 2021). An autosomal recessive genetic defect in thyroglobulin synthesis has been identified in

Table 7. Diagnostic tools and reference ranges in goats.

Functional assessement								
Marker	Matrix	Sample tube	Analysis method	Validation of the method	Deficiency Or hypothyroidism	Excessive	Normal range	Unit
Total T3	Serum	Dry	ELISA	Intra-study	–	–	2.20–3.60[1]	nmol/L
Free T3	Serum	Dry	ELISA	Intra-study	–	–	3.85–12.14[1]	pmol/L
Total T4	Serum	Dry	ELISA	Intra-study	–	–	101.50–110.87 (non-productive)	nmol/L
Free T4	Serum	Dry	ELISA	Intra-study	–	–	12.77–33.39[1]	pmol/L
IT	Serum	Dry	ICP-MS	Validated	<519	>5019 1200–500019 (toxic)	7–10[2]	µg/dL
	Milk	–	Sandell-Kolthoff ICP-MS	Validated[3]	<2519	>50019 35000–4750019 (toxic)	25–400[2]	µg/dL

Morphological assessment						
Technique	Technical information	Validation of the method	Deficiency or hypothyroidism	Excessive	Normal range	Unit
Ultrasound	Linear probe, 5–13mHz[4]	Post-mortem comparisons[4]	Reduced or normal echogenicity [5]. Higher values in measurements but no range, higher margin of error[5].	–	Lobes are perfectible visibles. Homogeneous echostructure and echogenicity. Mean ± SD lobe measurement[4]: Length – 30.2 ± 3.73 Width – 10.5 ± 1.66 Height – 6.3 ± 1.15	mm mm mm
CT-scan	16-row scanner with parameters 120 kV, 150 mA, slice thickness 0.75 to 2 mm and reconstructed in a soft tissue algorithm[6].	Ultrasound comparison[6]	Reduced density[5]. No range for measurement or density[5].		Hyperdense (mean 80.9 HU) Mean ± SD lobe measurement[6]: Length – 30.25 ± 5.67 Width – 12.71 ± 1.94 Height – 6.68 ± 1.05 Volume – 1.32 ± 0.54	mm mm mm mm^3

[1]Fazio et al. (2017); [2]Puls (1994); [3]Aumont and Tressol (1986); [4]Pankowski et al. (2020); [5]Pankowski et al. (2023); [6]Pankowski and Bartyzel (2021).
IT, iodine total; ELISA, enzyme-linked immunosorbent assay.

goats (de Vijlder et al. 1978; Kok et al. 1987), cattle (Ricketts et al. 1985; Philippe et al. 2009; Watson and Scholes 2010) and sheep (Jones et al. 1986). In the case of fetuses with a thyroglobulin formation defect, it is possible that the problem does not impair fetus development because of the transplacental transfer of T4 by the mother, even though the thyroid relay was expected in the fetus (Poisik et al. 1997). Hypothyroidism is often described as an outbreak in a herd (King 1976; Bath et al. 1979; Campbell et al. 2012; Micheloud et al. 2019), but could also be endemic (Statham and Bray 1975; Morinaga et al. 1990). If the animals survive, the thyroid gland regresses to normal size within 6 weeks (King 1976). Hypothyroidism in a herd often results in abortions and peri-natal mortality (George et al. 1966; Domínguez-Vara et al. 2017). Aborted fetuses often have a goiter, with an enlarged thyroid gland that is firm and stained red (Domínguez-Vara et al. 2017). Young animals are born weak, with respiratory difficulties and sometimes an enlarged thyroid gland (Micheloud et al. 2019). The gland may have a short anterior-posterior face, widened at the sides (Bath et al. 1979). Animals are fatter, dull, and inactive (Bath et al. 1979; Joshi et al. 2017). Brain development can also be impaired (Potter et al. 1982). Animals may present facial edema, different degrees of alopecia, emaciation, hydrothorax, hydropericardium, hydroceles, lethargy, higher BCS, diminution of rectal temperature, and poor wool or hair covering (Thrift et al. 1999; Sokkar et al. 2000; Watson and Scholes 2010; Campbell et al. 2012; Buiuc et al. 2022). Hypothyroidism reduces testosterone production, which lowers the quality of semen and could make males less fertile (Reddy et al. 1998). In females, hypothyroidism increases ovarian response to superovulation treatment, but fertility is nevertheless compromised (Bernal et al. 1999). Growth retardation is observed, with a reduction in the mineralization of bone epiphyses (Campbell et al. 2012). Hypothyroidism is implicated in acute respiratory distress syndrome in neonates. Without thyroid hormones, angiotensin is lower at the end of gestation (Forhead and Fowden 2002). Thyroid hormones play an important role in controlling lung and kidney development (Liggins et al. 1988; Schellenberg et al. 1988; Forhead and Fowden 2002), especially T4 in lung maturation and surfactant production, together with cortisol (Jones et al. 1986). In fact, the lecithin/sphingomyelin ratio of lung surfactant is reduced in cases of thyroid deficiency (Jones et al. 1986). Prolonged iodine deficiency induces compensatory changes in the activity of selenodependent DIOs (Zagrodzki et al. 1998). Thyroid hormones are also important in the structural and functional development of the gastrointestinal tract in the near-term fetal sheep, implying that near-term hypothyroidism may cause gastrointestinal disturbances (Young et al. 2023).

Thyroid metabolism is involved in the functioning of the immune system. Depression of the immune mediator cell response and of the humoral response has been reported in goitrous goats (Singh et al. 2006). This condition is reversible after treatment of hypothyroidism with oral iodine and thyroxine (Singh et al. 2006). At the herd level, iodine deficiency should be suspected whenever there is poor reproductive performance and perinatal mortality (Sargison et al. 1998). Hypothyroid animals show hyperlipidemia and hypercholesterolemia (Mostaghni et al. 2008). A decline in HDL and an increase in LDL are also observed (Mostaghni et al. 2008). Some goitrous sheep show no decrease in serum iodine concentration, nor any defect in the transport or peripheral metabolism of T4 or T3. The compensatory enlargement of the gland must be the result of decrease in T3/T4 concentration and increase in TSH, and a genetic defect must therefore be suspected in these cases (Falconer 1966). Soil ingestion could represent a source of iodine for ewes and explain the absence of goiter in certain flocks (Healy et al. 1972). Hypothyroid calves have lower PII (if hypothyroidism is induced by iodine deficiency), lower T3 and T4 thyroid hormones and higher TSH (Guyot and Rollin 2007; Philippe et al. 2009). One study in lamb suggests using T4 blood concentration for assessing iodine deficiency (Andrewartha et al. 1980). The size of the thyroid gland in lambs is linked to the percentage of mortality; the larger it is, the higher the mortality percentage (King 1976). Lambs with a thyroid/BW ratio equal to or greater than 0.40 g/kg have higher neonatal mortality than lambs whose dams are supplemented with iodine (Clark et al. 1998; Knowles and Grace 2007). In newborn calves, a thyroid gland weighing more than 30 g is most likely abnormal (Hernandez et al. 1972; Szuba et al. 1992; Smyth et al. 1996). A recent study reports a case of hypothyroidism caused by a selenium and zinc deficiency (Sampaio et al. 2021).

Histological examination is an innovative way of diagnosing hypothyroidism in a herd (Clark 1998; Menaka et al. 2022). The lesion observed microscopically in hypothyroidism is follicular hyperplasia (Micheloud et al. 2019), colloid goiter (Cheema et al. 2010; Nourani and Sadr 2023) or hyperplastic goiter (Herenda and Dukes 1989; Ong et al. 2014; Ankita et al. 2023). The mechanism of these histological changes is as follows: a prolonged stimulation of the thyroid gland with TSH that induces follicular hyperplasia which, if it lasts for a long time, can lead to colloid goiter (Ozmen and Haligur 2005). A recent study proposes a gradation of goiter in calves: grade 0 or normal gland (G0), grade 1 or mild goiter (G1), grade 2 or moderate goiter (G2) and grade 3 or severe goiter (G3) (Colque-Caro et al. 2023). This study grades the degree of severity of goiter according to the size of follicles, follicular epithelium, colloid, and perifollicular interstitium (Colque-Caro et al. 2023).

4.12.2. Iodine poisoning in ruminants

Other diseases documented in the literature (4/206) include iodine poisoning. Iodine daily requirements for cows should be between minimum 0.1 mg/kg DM and 1 mg/kg DM iodine in the diet (Colston 2018) or 0.02 mg/kg BW for maintenance animals (NRC 2000). Iodine poisoning can occur at doses ranging from 20 times the requirements of calves to 7.5 times the requirements of adult cows. Symptoms of intoxication appear at doses higher than 5 ppm in DM iodine in calves (Fish and Swanson 1982). Severe or fatal symptoms occur at a dose from 10 mg iodine per kg DM iodine for calves, or 70 to 600 mg iodine per adult cow per day (Paulíková et al. 2002). Fetal damage can occur at maternal doses of between 5 and 7.5 mg iodine per kg BW, with calves born hypothyroid (Fish and Swanson 1982). Sheep seem to be the least sensitive ruminants to iodine intoxication (Paulíková et al. 2002) but the most susceptible to iodine deficiency (Colston 2018). The sources of intoxication are long-term consumption of a feed containing several iodine supplements, incorrect management of mineralization over a long period of time, and the use of iodine-containing compounds in the treatment and prevention of infections such as pododermatitis, actinomycosis, actinobacillosis, mastitis, infertility, or the complex of respiratory diseases

(Paulíková et al. 2002; Żarczyńska et al. 2022). The clinical signs of iodine intoxication initially include signs associated with transient hyperthyroidism: persistent cough, tachycardia, nervousness, hyperthermia, exophthalmia, nasal and ocular discharge, dermatitis, alopecia, weight loss, high metabolism rate. When this intoxication occurs, a Wolff-Chaikoff effect can occur, leading the thyroid gland to block access to iodine. Therefore, symptoms of hypothyroidism appear, with depression, reduced milk production, reduced growth in calves, and high susceptibility to respiratory diseases (Paulíková et al. 2002). There is no specific treatment; simply removing the source of intoxication will bring about remission (Paulíková et al. 2002; Żarczyńska et al. 2022).

4.12.3. Hyperthyroidism

A few studies (6/206) have reported hyperthyroidism induced experimentally with T3 or T4 in cows or sheep (Lorijn et al. 1980; Goldman et al. 1982; Gay et al. 1987; Weekes 1992; De Moraes et al. 1998; Thrift et al. 1999). Hyperthyroid heifers were nervous and irritable. They showed poor weight gain and lost BCS during treatment. These losses were accompanied by compensatory growth after treatment. Skeletal traits and reproductive performance were not dramatically affected in this trial (Thrift et al. 1999). Hyperthyroidism results in a higher number of cows in anestrus and abnormally long estrous cycles in cows (De Moraes et al. 1998). A study has shown that moderate hyperthyroidism in growing sheep increases the sensitivity of glucose metabolism to insulin (Weekes 1992). Induction of hyperthyroidism in fetal lambs resulted in an increase in lung maturation and cardiac output 22% better than in control animals (Lorijn et al. 1980). In calves, intramuscular injection of T4 improves left ventricular contractibility, enlarges the left ventricular circumference, increases blood volume, reducing venous compliance and has a positive inotropic effect (Goldman et al. 1982; Gay et al. 1987). The mechanism by which T4 causes tachycardia is called the Frank-Starling Mechanism (Goldman et al. 1982).

4.12.4. Post-slaughter lesions

Several studies (8/206) looked at the lesions found on thyroid glands at slaughter in ruminants: buffaloes, goats, sheep, and cattle (Salunke et al. 2008; Shelke et al. 2009; Alipourzamani et al. 2011; Mohajeri et al. 2012). A summary of the prevalence of lesions observed at the abattoir is available in Table 3. The prevalence of lesions on thyroids was between 23 and 65.9%. Prevalences were calculated based on the number of lesions found out of the number of thyroids observed at the abattoir. This number varied from 100 to 386. The lesions were colloid goiter, parenchymatous or hyperplastic goiter, lymphocytic thyroiditis, fibrosis, cysts, or congestion and hemorrhages (Salunke et al. 2008; Shelke et al. 2009; Alipourzamani et al. 2011; Darakhshesh et al. 2011; Mohajeri et al. 2012; Sasaki et al. 2019). Primary tumors of the thyroid gland have been described in cows (Vitovec 1976). Benign tumors include trabecular adenomas, tubular adenomas, and microfollicular adenomas, while malignant tumors include cystopapillary adenocarcinomas and small solid cell carcinomas (Vitovec 1976; Bundza and Stead 1986). Although few studies are included in Table 3, it can be noted that the prevalence of lesions is not the same between different species, with hyperplastic goiter appearing to be more prevalent in sheep and goats than in buffalo. This trend is reversed for colloidal goiter, which seems to be more prevalent in buffaloes than in sheep and goats. There are too few studies to comment on these results, and none of them included blood tests to assess thyroid function or iodine intake in these animals.

4.12.5. Thyroid dysfunctions and health in ruminants

Thyroid metabolism is known to be involved in two syndromes in cattle: (poly)cystic ovaries syndrome and acute respiratory distress syndrome.

In cows with ovarian cysts, lower levels of serum TSH and serum fT4 were observed alongside higher levels of serum estrogen. Estrogens (sex steroids) are known to also have a negative feedback effect on the hypothalamus (Figure 3A). However, although ovarian disease can be associated with alterations in the thyroid gland in women, it is difficult to implicate thyroid dysfunction as a cause or consequence of cystic ovary. A screening of the thyroid gland in treatment-refractory cows suffering of (poly)cystic ovaries syndrome could lead to the therapeutic approach of administering L-thyroxine (Mutinati et al. 2013).

Finally, as previously stated, thyroxine treatment could also be considered for calves suffering from acute respiratory distress syndrome (Jones et al. 1986; Danlois et al. 2000; Forhead and Fowden 2002).

4.13. Outcomes used to assess thyroid function in ruminants

Dark areas of knowledge remain in bovine thyroid metabolism and the complete understanding of the involvement of this metabolism in the production of foodstuffs (Huszenicza et al. 2002; Todini 2007). Besides this, few thyroid diseases are documented in ruminants, while diseases like humans are found in dogs, cats, and even horses (Breuhaus 2011; Scott-Moncrieff 2015a, 2015b, 2015c; Chaker et al. 2024).

In human medicine, it is well described that it is the systematization of thyroid ultrasound as a routine examination of the thyroid gland which has made it possible to detect 65% of people with cysts in the population (Durante et al. 2018).

It should also be noted that the distribution of knowledge and diagnostic tools available for ruminants is uneven across species. In goats, for example, there were no validated hormone assay. In sheep, thyroid imaging has never been documented. Even if validated tools are available in other species, there is little evidence of their use and the conclusions could be drawn from them, particularly in the diagnosis of thyroid disease. Developing these tools would be a good way to better understand the physiology of the thyroid gland in these ruminants. It therefore seems quite clear that without diagnostic means, it is possible to miss certain disorders.

In a current situation where society is committed to ecology, resource optimization, and animal welfare, and where veterinary medicine is constantly evolving, better understanding the metabolism of cattle could help us to optimize the production of livestock. The development of more effective diagnostic tools, enabling the establishment of reference standards, seems to be an essential step in improving the care of livestock.

4.14. Limitation of this scoping review

This scoping review aimed to identify all studies addressing the function of the thyroid gland within the hypothalamic-pituitary-thyroid axis in ruminants. However, several limitations should be noted.

Firstly, studies varied widely in terms of methodology and number of experimental animals. This prevented more in-depth statistical work, and there remain contradictions that cannot be explained. The authors have tried to use the results in a cautious way to avoid hasty conclusions. All studies have been cited in this work, even those with contradictory results.

Then, studies that did not directly focus on understanding this axis in ruminants were excluded. Many studies measured thyroid hormones for other purposes, such as assessing the effect of treatments on thyroid function rather than exploring thyroid metabolism itself. Including these studies would have required significantly more time and effort, especially since they provided information in the opposite direction (i.e. treatments influencing thyroid metabolism rather than metabolism's effect on the body).

Additionally, *in vitro* studies or those involving artificial inductions (e.g. thyroidectomies, treatments to induce specific conditions) were also excluded. Only studies that described natural phenomena, disease symptoms, or the physiological thyroid metabolism in ruminants were retained. This narrowed the focus but may have excluded valuable experimental insights.

Another limitation stems from the review process itself: data extraction was conducted by a single individual, contrary to standard scoping review methodology, which recommends blind extraction by two reviewers to ensure consistency and reduce bias. The absence of a second reviewer for comparison represents a methodological limitation.

Lastly, 41% of the studies identified could not be retrieved in full text. This was due to many oral or poster abstracts, as well as older references that had not been digitized. The inability to access the full content of these documents hindered their integration into the review. Nevertheless, many of the references included in this review incorporated elements of these unavailable studies as secondary sources.

5. Conclusions

The results of this scoping review enable us to sketch out the landscape of what is known about thyroid function and dysfunction in ruminants and to shed light on the grey areas. This can be summarized as follows:

1. **State of knowledge**: Although most of the studies found in the literature described the physiology or anatomy of the ruminant thyroid gland, few verified the euthyroid status of their subjects. For this reason, all these results must be assessed with caution. However, processes related to reproduction, heat stress, nutrition and animal production are widely studied.
2. **Clinical veterinary involvement**: The most well-documented thyroid disease found in ruminants is hypothyroidism, mainly caused by iodine deficiency. The other diseases described are experimentally induced and have not been reported in practical veterinary medicine. This is different in humans and other animal species, which have other types of thyroid diseases (thyroiditis, cancer, etc.). However, upon observation of lesions at the slaughterhouse, it appears that thyroiditis and cancer can be found in the thyroid glands of animals presumed to be healthy.
3. **Lack of diagnostic tools**: Although numerous studies document the physiology and thyroid diseases with hormonal, histological and even supporting imaging analyses, the only tools developed to date to evaluate the thyroid metabolism in ruminants are the assays of the hormones total T4, total T3, TSH, total serum iodine, milk iodine, urine iodine and PII. In addition, pioneering studies focusing on thyroid gland imaging (ultrasound, CT-can) exist in cattle and goats. All of these tools are partially available in veterinary practice in the field. The authors suspect that the lack of analysis of this metabolism in farm monitoring and health issues prevents us from discovering other thyroid diseases of interest in domestic ruminants, such as thyroiditis.

Thyroid physiology is vast and complex, and a great deal of work is still needed to understand it better. Future work, particularly on new diagnostic methods validated in ruminants, could lead to significant advances.

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Ethical approval

The authors confirm that the ethical policies of the journal, as stated in the author guidelines, have been adhered to. No ethical approval was required for this study as it is a review article with no original research data.

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ORCID

Justine Eppe http://orcid.org/0000-0003-1011-6894
Frédéric Rollin http://orcid.org/0000-0001-8387-3672
Sandrina Vandenput http://orcid.org/0000-0001-6534-3707
Hugues Guyot http://orcid.org/0000-0002-3573-0586

Data availability statement

The authors declare that all data necessary for understanding the manuscript are available.

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