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Scientific Literature Review

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Overview:

1. What is a Scientific Literature Review?

2. How to write a Scientific Literature Review

3. Structuring a Coherent Literature Review

4. Literature Review example

What is a Scientific Literature Review?

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Scientific Literature Review:

A scientific literature review is *a CRITICAL account of what has been published on a topic by accredited researchers.*

It may be:

- A stand-alone piece for publication
- An introduction to a thesis
- Part of postdoctoral research/grant proposals

Scientific Literature Review:

A scientific literature review should:

- Provide a **clear statement** of the topical area – *scope?*
- Provide a **range of research** on the topic – and not just the “good” data!
- **Critically analyse** a selected topic using a published body of knowledge – *evidence-based arguments*
- Provide an indication of what **further research** is necessary
- Identify areas of **controversy** in the literature
- Conclude with **new insights and perspectives**

Scientific Literature Review:

A scientific literature review is *not*:

- An English essay… use *scientific writing skills*
- A summary of each research article that you read
- Based on personal opinion or biased towards your research hypotheses
- A chronological history of events in your research area

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Scientific Literature Review:

What is the purpose of a literature review?

Scientific Literature Review:

What is the purpose of a literature review?

To support the advancement of scientific knowledge!

- Scientific knowledge is **not static**: reviews help scientists to understand how knowledge in a particular field is **changing and developing** over time

- There is a **significant output** of scientific publications – literature reviews save time for the scientific community

- Literature reviews can lead to **new scientific insights** and highlight gaps, conflicting results and under-examined areas of research

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How To Write A Scientific Literature Review?

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Scientific Writing!

...is writing about scientific topics aimed at <u>specialists</u> in a particular field

Assume the reader is familiar with the research/topic area but not with the ***specifics*** of your review…

i.e. your Principal Investigator

internal/external examiners

peer-reviewers (journal articles, research papers, book chapters, grant proposals)

Use precision, clarity and objectivity!

Scientific Writing!

1. Be precise!

Ambiguities in writing cause confusion and may prevent a reader from grasping key concepts of your review…

- Use precise concrete language, no ambiguity

  eg 'correlated' ≠ 'related'

- Exclude similes/metaphors (and humour!)

- Be *quantitative* wherever relevant (stats, methodological details etc.)

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Scientific Writing!

2. Be clear!

Concepts in the sciences can often be complex; without clarity the reader may be confused or misled

- Simple language – no unnecessary "frills" (distractions)
- Pay attention to sentence structure, grammar

Your reader will be interested based on the science only… make it easy for them to access!

Scientific Writing!

3. Be objective!

Any claims that you make need to be based on facts, *not intuition or emotion*

- **Passive voice** – focus is on the literature!
- Avoid **assumptions** or premature conclusions
- Be aware of **research limitations** and refer to these in the review

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How to Write a Scientific Literature Review?

Reviewing the literature requires four stages:

1. **Problem formulation** – Defining your scope. Which topic is being examined and why? What aspects will be included/excluded?

2. Literature search - Identifying relevant research

3. Critical analysis – Criticise the experts; identify conflicting evidence, assumptions, errors and misconceptions

4. **Evaluation** – which authors are most convincing and provide the most significant scientific contribution? Have ***I*** conducted a fair and objective literature review?

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1. Problem Formation

Ask yourself questions like these:

- What useful reviews are **missing** or not up to date in my research area?
- What new review topic would be **useful** to scientists?
- Is there a **specific aspect of this topic** that my literature review might help to define?

eg. critically comparing different methodological approaches, contrasting evidence, assessing therapeutic potential, etc.

- What is the **scope** of my literature review? *Be specific*

2. Literature Searching

1. Online Research (basic) – Background Information

- Wikipedia (gasp!)
- Relevant "background" websites (eg. university/company websites, associations eg. American Heart Association)
- YouTube, TED Talks

2. General Literature Search – Literature Overview

- Google Scholar/Books
- PubMed

…find other relevant literature reviews in your chosen format (journal etc) for tips on structure and content

3. Specific Literature Search – The Detail

- Library databases *e.g Web of Science*
- "Advanced search" tool in Google Scholar/PubMed

Keep track of your references as you go!

3. Critical Analysis

In assessing each source, consideration should be given to:

- **Provenance** - Author's credentials? Are the author's arguments supported by evidence?
- **Objectivity** - Is the author's perspective fair? Is contrary data considered? Is information ignored to prove the author's point? (bias)
- **Persuasiveness** – Is the author’s data convincing?
- **Value** - Does the work contribute in a significant way to an understanding of the field?

…this involves CRITICAL THINKING!

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What is critical thinking?

Cottrell (2016):

"The process of looking at ideas and information critically, taking nothing for granted, but questioning accuracy, motivation and inferences, and seeking new understanding, connections and insights."

i.e. weighing up the evidence and arguments for or against something, and coming up with your own informed opinion.

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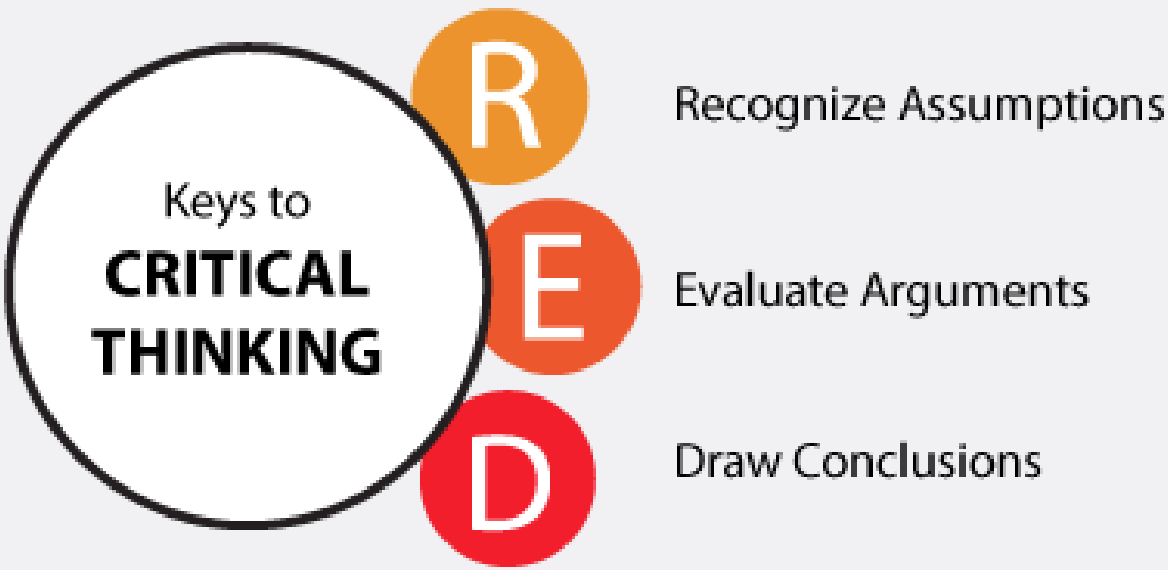
Ask questions!

- "Is that really true?
- How do you know?
- Show me the evidence.
- Is that evidence reliable?"

"There is evidence on both sides"



Red Model based on the Watson-Glaser™ Critical Thinking Appraisal
at www.ThinkWatson.com

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Critical Thinking…

Move from **Description** to **Analysis!**

Description – reproducing information

- Summarising texts - accepting details, results etc.

Analysis – deconstructing information in order to:

- *Challenge* assumptions; perspectives
- Show *limitations* in studies, exceptions to cases
- Highlight *under-examined* aspects of research

Key aspects of critical thinking

- Identify evidence to **back-up AND challenge** key points
- Detecting **inconsistencies and mistakes** in authors' reasoning
- Detecting **bias,** premature conclusions, lacking evidence
- Distinguishing between **fact and opinion**
- Evaluating **conflicting** opinions/research
- Suggesting new or different **solutions**
- Constructing ***your own arguments and opinions***

What should I be asking?

- Why is the author choosing to use the evidence presented?
- Is there a hidden agenda? *(eg. financial gain)*
- Are the sources reliable and objective?
- Is there bias present?
- Have all of the points been cited?
- Is there information missing?
- Are there conflicting opinions/conclusions?

And most importantly….

- ***Do I agree with these opinions/conclusions?***

Critical Thinking…

<u>This is the most important aspect of a good literature review!</u>

Critical thinking is what elevates your writing from a simple summary of the literature to a contributory piece of scientific knowledge…

…your analyses of the literature is valuable!!!

4. Evaluation and Interpretation

- What **conclusions** can I make from the most convincing literature? What are my opinions/arguments?

Also evaluate <u>your own interpretations…</u>

- Have I made a well-informed decision? How good was my **information seeking**? Has my search been <u>wide</u> enough to ensure all relevant material is included? Has it been <u>narrow</u> enough to exclude irrelevant material?

- Have I **critically analysed** the literature I use?
- **Instead of just listing and summarizing research, do I assess them, discussing strengths and weaknesses?**

- Have I cited and discussed studies **contrary** to my perspective to form a well-balanced argument?

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Structuring Coherent Literature Reviews

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Coherent Scientific Literature Reviews

Aim for:

- **Clear and cohesive** communication and analyses
- Tackle **one key point** at a time
- Use **subheadings**, especially in long reviews
- Check the **flow** of your argument for coherence (logical order?)

*…it is all about **STRUCTURE!***

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Scientific Literature Review:

How to structure a scientific literature review?

- **Introduction:** An *overview* of the topic under consideration, along with the *objectives* of the literature review.
- **Main body:** Critical analysis and evaluation of topically relevant research/data
- **Conclusion:** Summarise the **key points and conclusions** from your review

Word count:

Introduction = 10%
Main Body = 80-85%
Conclusion = 5-10%

Before you start writing…

1. Brainstorm your review topics

What aspects of your topic do you want to focus on? *(Problem formulation)*

2. Decide on the number of "topics" you will address based on your remaining word count (80%)

Set aside 15-20% word count for Intro/Conclusion

Of the most interesting/relevant topics… how many can you address in the allocated word count? Prioritise!

3. Choose your topics

Scan the literature, make sure there is enough information out there for you to complete a coherent, critical summary of each chosen topic… *reassess step 2 if necessary*

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1. Introduction

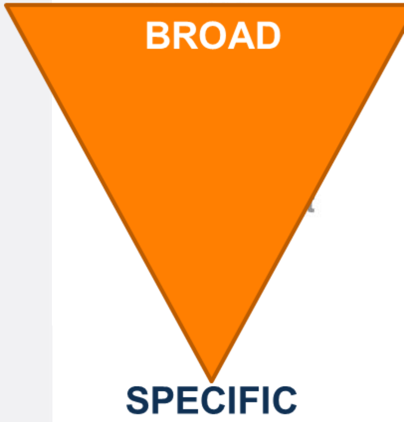
It is usually easier to write this after the main body…

Introduce your topic by highlighting the **core scientific facts** that are well backed up and widely accepted

Highlight the **importance** of the review – are you assessing potential clinical relevance? A new research perspective?

What is the **core aim** of this review? To compare and contrast conflicting evidence? To identify under-examined aspects of the topic?

Tell the reader ***what you are going to talk about… list your topics in order!***



2. Writing the Main Body

- Start with the **most broad** topic and increase **specificity** as you work through

- Focus on **recent** data where possible – scientific fact changes/develops over time!

- Summarize individual studies or articles with as much or as little detail as is relevant – detail denotes significance!

- Tackle **one key point per paragraph** so as not to overwhelm the reader

- Use **sub-headings** to group similar/related topics

- Use diagrams, figures, tables where appropriate

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Tackle 2-3 key points per section…

Sub-headings

INTRO 10% of word count	Go from the broad to the specific. Introduce the general topic, why it is an important area, then state what you will specifically do to investigate it further.
Section 1	Sub-point 1 · Sub-point 2 · Sub-point 3
Section 2	Sub-point 1 · Sub-point 2 · Sub-point 3
Section 3	Sub-point 1 · Sub-point 2 · Sub-point 3
CONCLUSION 10% of word count	Go from the specific to the broad. State the conclusions you can draw from the points you've made in the essay, and connect this learning to the general topic. End by posing a question for future research in the field.

You may need to prioritise topics… you can't cover everything!

…one key point per paragraph!

1. Topic Sentence

- Start with a strong "umbrella" sentence introducing your key point

2. Supporting Sentences

- Provide context, examples or data
- Each point backed up with a source/reference
- Opposing data should also be considered
- Use "linker" words to introduce similar points

3. Concluding Sentence

- Include summary sentence at end of paragraphs… why this information is relevant
- May include link to following paragraph

1. Writing the Main Body

www.smart-words.org

Agreement / Addition / Similarity

The transition words like ***also, in addition, and, likewise***, **add information**, **reinforce ideas**, and **express agreement** with preceding material.

in the first place	again	moreover
not only ... but also	to	as well as
as a matter of fact	and	together with
in like manner	also	of course
in addition	then	likewise
coupled with	equally	comparatively
in the same fashion / way	identically	correspondingly
first, second, third	uniquely	similarly
in the light of	like	furthermore
not to mention	as	additionally
to say nothing of	too	
equally important		
by the same token		

Opposition / Limitation / Contradiction

Transition phrases like ***but***, ***rather*** and ***or***, express that there is evidence to the **contrary** or point out **alternatives**, and thus introduce a change the line of reasoning (**contrast**).

although this may be true	but	although
in contrast	(and) still	instead
different from	unlike	whereas
of course ..., but	or	despite
on the other hand	(and) yet	conversely
on the contrary	while	otherwise
at the same time	albeit	however
in spite of	besides	rather
even so / though	as much as	nevertheless
be that as it may	even though	nonetheless
then again		regardless
above all		notwithstanding
in reality		
after all		

Critical Phrases…

http://www.phrasebank.manchester.ac.uk/

Introducing questions, problems and limitations: theory or argument

The main weakness with this theory is that …
The key problem with this explanation is that …
However, this theory does not fully explain why …
One criticism of much of the literature on X is that …
However, there is an inconsistency with this argument.
A serious weakness with this argument, however, is that …
One question that needs to be asked, however, is whether …
Smith's argument relies too heavily on qualitative analysis of …
Smith's interpretation overlooks much of the historical research …
Many writers have challenged Smith's claim on the grounds that …
Smith's analysis does not take account of X, nor does he examine …
It seems that Jones' understanding of the X framework is questionable.
The existing accounts fail to resolve the contradiction between X and Y.
One of the limitations with this explanation is that it does not explain why…

Identifying a study's weakness

(However,)	Smith fails to fully define what … Jones fails to acknowledge the significance of … the author overlooks the fact that X contributes to Y. what Smith fails to do is to draw a distinction between … the paper would appear to be over-ambitious in its claims. another weakness is that we are given no explanation of how … no attempt was made to quantify the association between X and Y. the main weakness of the study is the failure to address how … the study fails to consider the differing categories of damage that … the research does not take into account pre-existing … such as … the author offers no explanation for the distinction between X and Y. Smith makes no attempt to differentiate between different types of X.

2. Main Body: Figures/Tables

- Aim for one key figure/table per section; this can be to:

  - *illustrate a complex concept*
  - *summarise a large body of relevant data*
  - *describe the order of a process (flow diagrams)*

- Legend *below* image/figure and *above* table

- Always refer to figures/tables in text… direct the reader to them *(as seen in Figure 1; as summarised in Table 1)*

- Provide a detailed legend… each figure + legend should stand in its own right without the review text

- **Figures and tables provide a break for the reader and a chance to understand and reflect on key concepts!**

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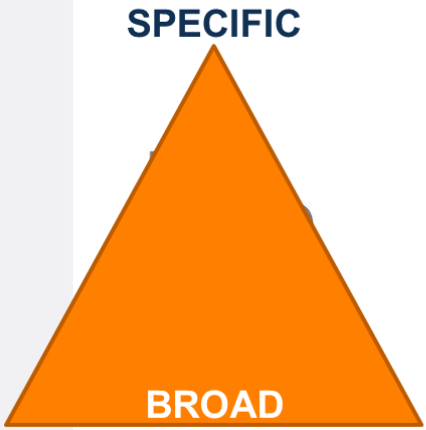
Writing the Conclusion

- Maintain the focus established in the introduction
- Summarise major research contributions to the scientific field (most convincing data) and make your point of view clear
- Point out major flaws/gaps/inconsistencies in research
- Highlight potential future studies
- Provide closure so that the path of the argument ends with a conclusion of some kind

NOTE: A literature review conclusion in a thesis will lead to the research questions that will be addressed.



Additional Sections….

- Usually, a short **ABSTRACT** (approx. 200 words) is required before your literature text to summarise the topics, main findings and conclusions from your review
- *This tells the reader exactly what your review contains so that they can make an informed decision - if it is relevant or not - before reading the full text*

- **TABLE OF CONTENTS –** show the reader where to find the relevant information

- **ACKNOWLEDGEMENTS –** acknowledge any funding bodies/research groups that contributed to the review writing process

- **CONFLICT OF INTEREST –** you must declare if the *primary interest* of your review may be affected by any *secondary interests* (personal benefit)

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Referencing

It is essential to credit published papers for work mentioned in your manuscript…

- In-text
- Reference List/Bibliography – *what is the difference?*

“atherosclerosis has been claimed to be an independent risk factor for cardiovascular death (Detrano *et al.,* 2008)”.

Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008. **358:**pp1336-1345.

Harvard referencing guide….

CiteThemRight….

Zotero referencing manager…

All available from DCU Library website

Mendeley/RefWorks – other options

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Referencing

Figures/Tables:

- In-text citation in the figure legend after description
- May need to ask for permission from the publisher – be careful! *(is the image copyrighted?)*
- If figure is adjusted: "image adapted from [source]"

MAKE SURE YOU REFERENCE THE SOURCE MATERIAL (original research paper) and NOT A REVIEW OF THE RESEARCH !

Except when you are referencing another reviewer's opinion/critique etc.

If submitting for publication, check the requirements of the journal… may have a specific referencing format *(eg. Elsevier merge numbering/Harvard systems)*

Example: Published Review…

Vascular Pharmacology 82 (2016) 30–40

Contents lists available at ScienceDirect

Vascular Pharmacology

Review

Vascular calcification in type-2 diabetes and cardiovascular disease: Integrative roles for OPG, RANKL and TRAIL

Emma Harper[a,*], Hannah Forde[a,b], Colin Davenport[b], Keith D. Rochfort[c], Diarmuid Smith[b], Philip M. Cummins[a]

Concise, informative title

Short abstract – 200 word summary

Table of Contents

Sub-headings

Good paragraph length to clearly analyse key topics

Example: Published Review…

fully delineated, and alongside these reports, additional studies point to the involvement of three specific glycoproteins; OPG, RANKL and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL). The following sections will examine the evidence for involvement of these glycoproteins within the VC process, including proposed cellular mechanisms arising from *in vitro* and animal study models.

4. VC — OPG, RANKL and TRAIL

There are numerous molecular components to the VC signalling cascade, described in detail by Sage and colleagues [40], many of which are related to bone morphogenesis. There is growing evidence that the OPG/RANKL/RANK signalling axis is central to VC manifestation [37]. RANKL actively promotes the calcification process in vascular cells by inducing osteoblastic activity [27]. RANKL, when secreted by endothelial cells (ECs), can bind to the RANK receptor to promote pathological differentiation of healthy VSMCs into calcified VSMCs with an osteoblastic phenotype [27,41,42]. In this respect, RANKL is upregulated in calcified VSMCs [42] and has been shown to exert its pro-calcification actions through activation of the alternative NF-κB pathway [27]. Thus, when serum … entiation process … medial arterial wal… acts as a soluble de… ize RANKL, an eve… anti-calcific effect … RANKL and OPG ap… calcification to thos… ing bone remodelli… has yet to be fully understood.

Interestingly, a third regulatory protein, TRAIL, has been shown to interact with OPG and RANKL during modulation of the VC process [44], although its precise functions in this context are poorly defined. In this regard, an emerging hypothesis within the VC field has proposed a *vasoprotective* role for TRAIL, possibly through pleiotropic effects on vascular gene expression and/or an ability to mediate RANKL signalling; contrastingly, however, some competing theories point to a potential role for TRAIL as an inducer of calcification. As its name suggests, TRAIL is an apoptosis-inducing protein of the TNF ligand superfamily, and is thus far known to be expressed by immune and vascular cells [45,46]. TRAIL is a type-II transmembrane protein with the ability to bind five different receptors found on numerous cell types, as well as a C-terminal domain that can also be cleaved from the cell surface to release a soluble form. Two TRAIL receptors (DR4 and DR5) have a cytoplasmic death domain, whilst two decoy receptors (DcR1 and DcR2) lack a functional death domain; thus TRAIL-induced apoptosis *via* DR4 and DR5 is antagonized by the competitive inhibitory effect of DcR1 and DcR2. OPG acts as an additional decoy receptor for TRAIL (and *vice-versa*); therefore, OPG has a second protective function (*i.e.* in addition to its ability to block RANKL-induced calcification) by virtue of its ability to block TRAIL-dependent apoptotic signalling [47]. TRAIL and its receptors have been identified in vascular endothelial and smooth muscle cells, as well as both healthy and injured arterial wall [38], however its precise roles within the vasculature are as of yet unclear. TRAIL … tro, … ity … oth … es, … in … ive … sed … ion … hin the vascular system, a fact which may be pertinent in explaining the apparent contradictions in TRAIL function. Overall, there is evidence to suggest that TRAIL has substantive yet diverse functional roles within the vasculature, both dependent on and independent of OPG and RANKL.

Informative/relevant image and figure legend

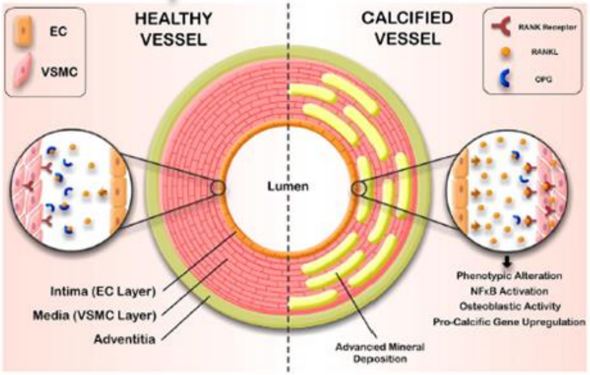

Fig. 2. Vascular calcification. In the vasculature, the EC monolayer releases baseline levels of soluble RANKL. OPG, predominantly secreted by VSMCs, binds and neutralizes RANKL in the extracellular space, preventing RANKL interaction with membrane-bound RANK on the VSMC surface. Thus, phenotypic alteration of the VSMC layer is prevented, resulting in a healthy non-calcified vessel (left). Alternatively, when soluble RANKL levels are high, VSMCs cannot secrete sufficient OPG to neutralize the excess. RANKL interacts with RANK on the VSMC surface, forming a RANK:RANKL complex that initiates VSMC trans-differentiation. NFκB activation, osteoblastic/chondroblastic activity and pro-calcific gene upregulation ensues, finally resulting in advanced mineral deposition and calcification within the VSMC medial layer (right). EC, endothelial cell; VSMC, vascular smooth muscle cell; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand; OPG, osteoprotegerin; NF-κB, nuclear factor kappa-B.

bone degradation and ultimately resulting in low bone mass and fragility [106]. Denosumab, a human monoclonal antibody for RANKL, is one of the latest approved treatment options for osteoporosis [102,107], although its effects on VC have not yet been fully assessed. Mimicking the natural actions of OPG, Denosumab binds and neutralizes RANKL (but not TRAIL), attenuating its osteoclastic effects and allowing osteoblastic build-up of bone to ensue [108]. As RANKL promotes osteochondroblastic activity in VSMCs, anti-RANKL therapy could theoretically function to reduce the extent of calcification in the vasculature. In support of this theory, it has been demonstrated that Denosumab reduced aortic calcium levels by half in a murine model of osteoporosis [109], but contrasti… ing human study completed to date has … therapy on aortic calcification progressio… [110]. It is possible that this disparity is du… cification measurement, as Samelson and … quantitative method (lateral spine X-rays) … tative measurement of aortic calcium dep… and co-workers. Furthermore, this study w… er trial initially completed to assess the eff… on bone mineral density in osteoporotic postmenopausal women (2363 of 7808 patients). The therapeutic potential of anti-RANKL therapy for the treatment of VC therefore awaits further clinical investigation.

8.3. TRAIL administration

Although its potential therapeutic use in cardiovascular protection has been suggested [99], there have been no human clinical investigations conducted to date that address the potential of TRAIL for the treatment of VC. As noted however, recombinant TRAIL administration to $ApoE^{-/-}$ diabetic mice has been shown to significantly reduce atherosclerosis progression [67], whilst TRAIL delivery protects against diabetic vascular in… pathways, it is impossible to ignore the potential therapeutic impact

Clear summary table and table legend

Table 1
Potential therapies for the inhibition/reversal of VC. Key: CAC, coronary artery calcification; GLP-1RA, glucagon-like peptide-1 receptor agonist; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor kappa-beta ligand; T2DM, type-2 diabetes mellitus; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; VC, vascular calcification; VSMC, vascular smooth muscle cell. *Denosumab can be classified as both an OPG/RANKL/TRAIL-related and osteoporosis therapy.

Therapy	Mode of action	Results to date	References
OPG/RANKL/TRAIL-related therapies			
Denosumab*	Neutralizes RANKL; prevents phenotypic transformation of vascular cells.	Decreased aortic VC in a murine study; no effect on calcification in a human sub-analysis of a larger trial.	[109] [110]
Recombinant OPG Therapy	Neutralizes RANKL; prevents phenotypic transformation of vascular cells.	Inhibited VC in a murine study.	[84]
TRAIL Administration	Unclear	Reduced atherosclerosis progression in a murine model; protected against diabetic vascular injury in a rat model.	[67] [111]
Osteoporosis therapies			
Bisphosphonates	Prevents calcium and phosphate release from bone; inhibits crystal nucleation and propagation.	Suppressed calcification in a rat model; conflicting data in human studies.	[113] [114] [115]
Teriparatide	Upregulates circulating concentrations of osteopontin, a calcification inhibitor.	Decreased valve calcification in murine studies.	[116]
Cardiovascular disease therapies			
Statins	Prevent dyslipidemia and inflammation, risk factors for VC.	Protective effects on VC in a rat model; conflicting data in human studies.	[117] [118] [121] [122]
Endothelin receptor agonists	Reduces hypertension, a risk factor for VC.	Significantly reduced VC in a rat model.	[126]
Interleukin-1β	Reduces inflammation, a risk factor for VC.	Attenuated calcification in a murine model.	[127]
T2DM therapies			
Exenatide (GLP-1RA)	Enhances glucose-dependent insulin secretion to reduce T2DM symptoms.	Attenuated VSMC calcification *in vitro*; no *in vivo* studies completed to date.	[124]
Liraglutide (GLP-1RA)	Enhances glucose-dependent insulin secretion to reduce T2DM symptoms.	No decrease in calcification noted in one prospective observational study to date.	[128]
Chronic kidney disease therapies			
Phosphate binders	Decreases circulating concentrations of phosphate.	Conflicting data, but favouring reduced progression of calcification with non-calcium based phosphate binders.	[129]
Calcimimetics	Lower circulating calcium levels.	Reduced mortality in uremic rats; reduced VC in humans in combination with low-dose vitamin D.	[130] [131] [132]
Vitamin D receptor agonists	Mechanism not fully understood, but shown to increase osteopontin expression.	Significantly reduced aortic calcification in a murine model.	[133]
Vitamin K	Upregulates production of MGP, which binds calcium ions.	Prevented arterial calcification in a rat model; slowed the progression of CAC in healthy older adults with pre-existing CAC in one human study.	[134] [135]
Sodium thiosulfate	Chelates calcium, reduces inflammation.	Prevented calcification in a uremic rat model; uncertain if suitable for VC treatment in humans. Recognized treatment for calciphylaxis.	[136] [137] [138]

Example: Published Review…

of other emerging concepts for manipulating VC, some of which are related to current treatments for osteoporosis, CVD, and chronic kidney disease (CKD) [102]. Firstly, like Denosumab, bisphosphonates (pyrophosphate analogs) are a successful osteoporosis treatment that have been considered as a potential VC therapy option due to their inhibitory effect on hydroxyapatite crystal formation [112]. Although animal studies have shown promise [113], human studies involving bisphosphonates and calcification have revealed mixed results [114,115]. Additionally, teriparatide, a shortened recombinant human parathyroid hormone also employed for osteoporosis treatment, has been shown to reduce VC in ldlr$^{-/-}$ mice [116], although to the best of our knowledge, no teriparatide studies in humans have emerged in the literature to date. Due to overlap in the molecular mechanisms involved in osteogenesis and calcification, it is likely that further investigation into these currently existing osteoporosis treatments may aid in the development of an efficacious treatment for VC.

Statins, which have been routinely employed to lower blood cholesterol and prevent vascular complications associated with CVD and T2DM, have also been considered as a potential treatment option for VC in view of their inherent pleiotropic properties [102]. In this respect, studies thus far have demonstrated conflicting results. Statin-treated patients were shown to have reduced aortic stenosis in an early investigation [117], and more recent studies have illustrated a protective influence of statins on VC in rats [118]. Additionally, statins have been shown to reduce levels of pro-calcific serum RANKL [119] and to increase anti-calcific serum OPG [120]. Elsewhere, it has been claimed that statins do not affect aortic stenosis with calcification [121], while a recent study has suggested that statins actually promote coronary atheroma calcification [122]. Further investigation is clearly warranted in order to resolve this ongoing debate and determine if the pleiotropic effects of statins can successfully reduce VC.

Additionally, Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs), a new class of injectable glucose-lowering drugs which function through the incretin system in the gut, are currently employed in T2DM treatment and exhibit simultaneous cardioprotective effects [123]. Recently, Zhan and colleagues examined the effect of exenatide, a GLP-1RA, on VSMC calcification in vitro. Their results illustrated an attenuation of osteoblastic differentiation and calcification of VSMCs in both a time- and dose-dependent manner, alongside a decrease in the expression of RANKL. It was concluded that exenatide can inhibit … RANKL/NFκB signalling pathway [124], … GLP-1RAs as a promising future …

… d to treat hypertension may also … been shown to be effective against … also in rat models of VC [126]. In … served that aortic calcification can … body to interleukin-1β (01BSUR, … ng a new potential therapy for VC … nd inflammation [127]. Owing to the similarity in calcification-driven pathogenesis, the range of existing therapies for CKD including phosphate binders, calcimimetics and vitamin K, may also have promise in the development of a successful VC treatment [102]. The extensive list of potential VC therapies, including their mechanism of action and experimental results to date, are summa… …ed below as arranged into their respective groups (Table 1).

10. Conclusions

There is currently a strong need to fully define the molecular mechanisms underpinning the development and progression of VC, a major risk factor for T2DM and CVD, in order to develop appropriate therapeutic approaches. Research emerging through in vitro, in vivo, and clinical studies now indicates that OPG, RANKL and TRAIL, regulatory glycoproteins typically associated with bone remodelling, are of fundamental relevance to the process of VC. It is likely that some or all of these proteins may prove diagnostically useful as circulating biomarkers that may be employed to stratify patients with respect to VC severity – from newly diagnosed T2DM sufferers to individuals with more well established T2DM and pre-existing CVD complications. In addition, the potential of these glycoproteins as molecular targets for treating VC, alongside currently existing therapies for osteoporosis, CVD and CKD, is attracting considerable attention, as evidenced within the scientific literature.

Conflict of interests

The authors declare that there are no conflicts of interest rega… the publication of this paper.

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Relevant acknowledgements

Lengthy reference list

Concluding with key points and future work

QUESTIONS

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