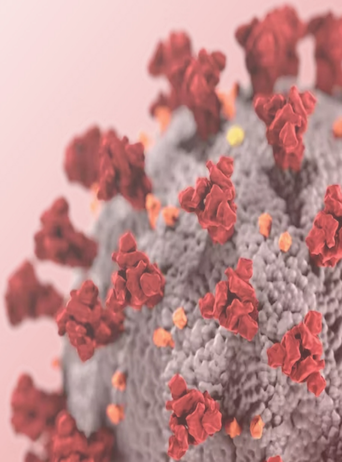
FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

UNDERSTANDING & TREATING
SPIKE PROTEIN-INDUCED DISEASES

October 14-16, 2022 • Orlando, Florida

Diagnosis and Management of Endocrinological Indications



Presented By:

Flávio A. Cadegiani, MD, MSc, PhD
Board certified endocrinologist

Diagnosis and Management of Endocrinological Indications

Conflicts of interest

Classical definition: **NONE**

‘Amplified’ definition:

1. Author of the book “New Perspectives on Overtraining Syndrome in the Athlete” – Spring Nature – 1st edition – November/2021
2. Current or previous consultant or part of the advisory board, *pro bono* or not, related or unrelated to the content of the present lecture: Novo Nordisk, Lilly, Anvisa (Brazilian Health Agency), Applied Biology Inc, TJDFT (Department of Justice – state of Distrito Federal), TJBA, (Department of Justice – state of Bahia), Câmara dos Deputados (Lower House of the Brazilian Parliament), Vitamedic (Ivermectin manufacturer
3. Senior Editor (Scientific Chief) of BMC Endocrine Disorders (Nature), Guest Editor of BMC Sports Science, Medicine, and Rehabilitation (Nature), Frontiers in Endocrinology, and Frontiers in Medicine
4. Reviewer for more than 30 medical journals and 150 scientific articles
5. Hypothesis defended in previous articles: a. Markers, predictors and triggers of chronic fatigue; b. Vitamin D as an immune modulator; c. Aggressive combined repurposed pharmacotherapy with other modalities for obesity – to prevent bariatric surgery; d. Overtraining as not being the cause of overtraining syndrome, but a combination of factors instead, and proposal of a renaming for the syndrome, to Paradoxical Deconditioning Syndrome (PDS); e. Inexistence of a disease called ‘Adrenal Fatigue’ since the root cause is not in the adrenals; f. Changes in the hormonal reference ranges for athletes; among other hypotheses.
6. Regular prescriber (when medically indicated) of GLP-1 analogues, SGLT-2 inhibitor, biguanide (metformin), male and female hormonal replacement therapy, low-dose stimulants, anti-depressants and anxiolytics, phytotherapies, LDN, vitamin D, optimized supplementation, whey protein, resisted physical activity (weight lifting), etc
7. Founder and CEO of Corpometria Institute

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

Diagnosis and Management of Endocrinological Indications

Objectives

1 - The effects of SARS-CoV-2 spike protein *reservoirs* on hormones and metabolism: impacts in the pituitary, adrenals, thyroid, pancreas, liver, testicles, ovaries, parathyroids, hypothalamus, intestine, muscles, fat tissue, and in the nucleotide, glucose, lipids and amino acid metabolism.

2 - What should we predict from future epidemics caused by persistent exposure to SARS-CoV-2 spike protein: endocrine conditions are not developed right after the exposure, but in the long term instead.

3 - Endocrine and metabolic diseases related to COVID-19 infection and SARS-CoV-2 vaccines, those exclusively related to the vaccines, and those related to the combination between COVID-19 infection and vaccines that were never supposed to happen because vaccines should have never allowed COVID-19 infections and COVID-19 infections should have never been followed by SARS-CoV-2 vaccines.

4 - From the best to the worst: different scenarios in 5, 10, and 20 years from now.

5 - A practical approach to the person with suspected SARS-CoV-2 spike protein-related diseases in the world of hormones and metabolism: from diagnosis to management.

Diagnosis and Management of Endocrinological Indications

Agenda

1. Challenges to demonstrate causality with SARS-CoV-2 vaccines – what really matters?
2. Literature on endocrine-related SARS-CoV-2 spike protein-induced diseases – methods of search and reflections
3. Documented, confirmed, evidenced, likely, anecdotal, expected, predicted, possible – beyond speculation for diseases of the future in the endocrinology field
4. Fundamental endocrinologic aspects of SARS-CoV-2 spike protein-induced diseases
5. Male gonadal axis
6. Female gonadal axis
7. Endocrine pancreas
8. Thyroid axis
9. Adrenal glands
10. Hypothalamic-pituitary axes
11. Parathyroid, vitamin D, calcium, and bone
12. Fat tissue
13. Incretin system
14. Muscles
15. Practical approach
16. Take-home messages

SARS-CoV-2 spike-related injuries
Introduction – challenges to determine causality

Types of detection to determine that
injuries are related to SARS-CoV-2 spike protein:

1. In an individual basis →

→ Chronological correlation with vaccines

→ New onset, worsening, relapse

→ a. Not justified by other causes or

b. Re-incidence after further re-exposure (additional shots)

\+ (slow) improvement with time(+treatment)

2. In a populational level →

a. Increase in the incidence of new-onset endocrinological and metabolic-related diseases

b. Atypical reports of endocrine disease presentation (severity, types of manifestations, disease course, complications)

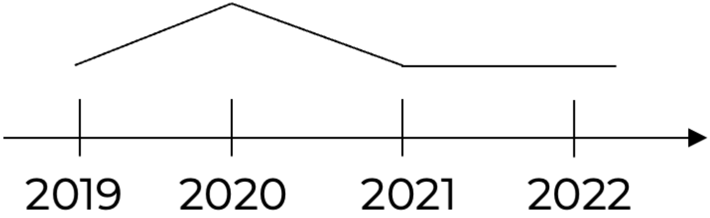
SARS-CoV-2 spike-related injuries
Introduction – challenges to determine causality

→ The 'alibi' against the confirmation of injuries caused by the vaccines will be that it will not be (theoretically) feasible to differentiate post-COVID from post-SARS-CoV-2 vaccine injuries.

→ A more thorough analysis of the prevalence of diseases and mortality:

Scenario 1. Increase from 2019 to 2020, with further reduction from 2021 on → COVID-19 infection-related diseases only.

- COVID-19 infection



FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

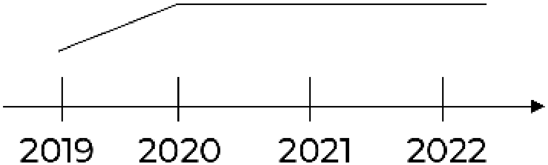
SARS-CoV-2 spike-related injuries
Introduction – challenges to determine causality

Scenario 2. Increase from 2019 to 2020 that persisted in 2021 and 2022 →

a. Diseases related to COVID-19 infection and also related to SARS-CoV-2 vaccine and/or booster

b. Diseases triggered to COVID-19 infection that persisted throughout time

- Post-COVID
- SARS-CoV-2 vaccines

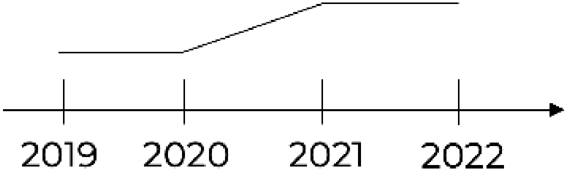


Scenario 3. Increase from 2020 to 2021 that persisted in 2022, with lack of increase from 2019 to 2020 →

a. SARS-CoV-2 vaccine-triggered diseases (2021) that persisted (2022)

b. Diseases triggered by the exposure to SARS-CoV-2 vaccine after COVID-19 infection

- SARS-CoV-2 vaccines
- Vaccines+COVID



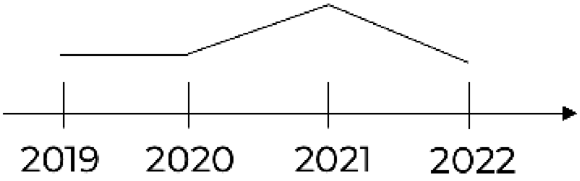
SARS-CoV-2 spike-related injuries
Introduction – challenges to determine causality

Scenario 4. Increase from 2020 to 2021, with further reduction in 2022 and lack of increase from 2019 to 2020 →

a. SARS-CoV-2 vaccine-triggered diseases (2021) that were transitory (2022)

b. Temporary diseases triggered by the exposure to SARS-CoV-2 vaccine after COVID-19 infection

- Transitory SARS-CoV-2 vaccines
  - Transitory vaccines+COVID



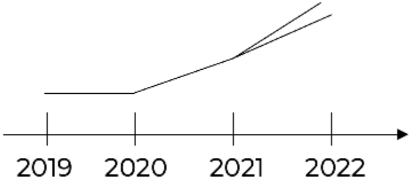
Scenario 5. Increase from 2020 to 2021 , with further incre 0 →

a. SARS-CoV-2 vaccine-triggered diseases (2021) that was enhanced with boosters (2022)

b. Progressive diseases and late-onset triggered diseases by the exposure to SARS-CoV-2 vaccine after COVID-19 infection

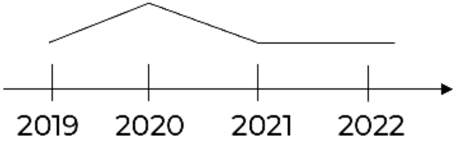
c. Diseases triggered by COVID-19 infection after SARS-CoV-2 vaccine and booster

- Progressive SARS-CoV-2 vaccines
  - Synergic vaccines+COVID
- Late-onset SARS-CoV-2 vaccines

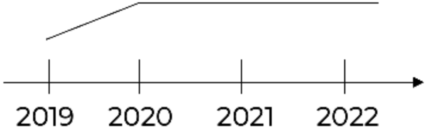


SARS-CoV-2 spike-related injuries
Introduction – challenges to determine causality

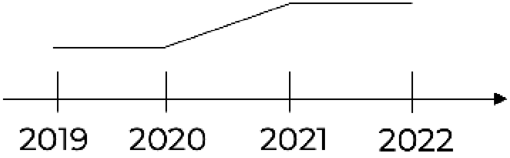
#1 - COVID-19 infection



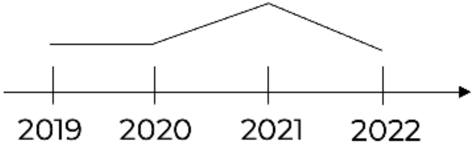
#2 - Post-COVID
- SARS-CoV-2 vaccines



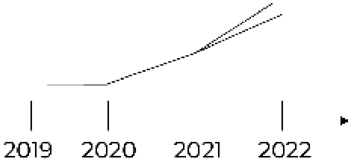
#3 - SARS-CoV-2 vaccines
- Vaccines+COVID



#4 - Transitory SARS-CoV-2 vaccines
- Transitory vaccines+COVID



#5 - Progressive SARS-CoV-2 vaccines
- Synergic vaccines+COVID
- Late-onset SARS-CoV-2 vaccines



FLCCC ALLIANCE
EDUCATIONAL CONFERENCE 2022

SARS-CoV-2 spike-related injuries
Introduction – challenges to determine causality

All diseases that did not increase from 2019 to 2020, but from 2020 to 2021 on must be blamed on the vaccines:

a. Vaccines alone

b. Vaccines+COVID-19

The ‘confounding’ factors will always take off the responsibilities from vaccines.

SARS-CoV-2 spike-related diseases
Introduction – challenges to determine causality

However, if…the biggest issue are not vaccines alone, but the combination between vaccines+COVID (pre- or post-COVID vaccination)?

1. COVID-19 vaccines do not prevent COVID-19 infection (widely accepted)

2. Misleading trials:

a. Vaccination only (lack of vaccine trials among subjects who had COVID-19)
b. Short-term effects only
c. No active biochemical monitoring
d. Lack of monitoring of the 'unexpected' COVID-19 after vaccine and its effects
d. Loss of placebo groups for comparison purposes (it was 'ethical' to give vaccines to the placebo group – pretending no further safety surveillance was needed);
e. Vaccines were not given to the population studied

SARS-CoV-2 spike-related diseases
Introduction – challenges to determine causality

The complexity of SARS-CoV-2 allows us to conclude that:

1. Safety of vaccines after COVID-19 is unclear

→ Specific post-COVID vaccination trials focused on safety profile should've been conducted

→ It is unusual to vaccinate to a virus short after its infection

→ Safety profile of immunological reactions of the 'combination' is unknown

2. COVID-19 infection after being vaccinated in unexpected

→ COVID-19 after getting vaccinated should've led to a massive 'recall'

→ It was alleged an almost 100% efficacy to prevent infection (remember?)

→ POST-VACCINATION INFECTION IS RARE IN MEDICAL HISTORY

→ This should've been considered as A SEVERE ADVERSE EVENT OF VACCINES

3. The unsubstantiated 'guarantees' on the effects the 'novel phenomena'

→ Who has ever guaranteed that there are no negative synergistic effects between the disease and vaccines when they're basically overlapped?

→ There is strong plausibility to believe that immunological responses should be not only 'over-maximized', but also to become dysfunctional.

4. The unvaccinated population should be the 'group' to be followed.

→ COVID-19+vaccine x COVID-19 alone

SARS-CoV-2 spike-related diseases
Methods of search – and reflections

Search in Pubmed + preprints + GoogleScholar

→ Suppression of publications against SARS-CoV-2 vaccines: a political goal

→ Multiple expressions and combinations

- Which type of vaccine?

1. Intersection of complications – vaccines mixed or not specified
2. Reactions to each type of vaccine

- We are still observing short-term effects:

→ The current lack of adverse effects now in a certain tissue does not mean that it is safe in the long term

→ The concept of 'reserve' in the Endocrinology field

→ In the short term, several aspects may not be affected, but a reserve decreased by SARS-CoV-2 spike protein may become an issue in the future

→ Potential examples yet to be observed 'early' somatopause, adrenopause, thyropause, andropause, accelerated aging

SARS-CoV-2 spike-related diseases
Methods of search – and reflections

- We must know where we are now.

→ For each disease and its correlation with SARS-CoV-2 spike protein, it can be:

1. Confirmed
2. Probable/likely
3. Possible
4. Expected
5. Underdiagnosed
6. Long-term, yet to be captured
7. None of the above, but that deserves monitoring (basically everything)

SARS-CoV-2 spike-related diseases
Methods of search – and reflections

- Aspects we must consider when it comes to Endocrinology:

→ Level of surveillence according to the likelihood of developing the disease and the specificity of its manifestations (↑ likelihood + ↓ specificity of symptoms = more active surveillence)

→ Slow progression of endocrine diseases → Example: GHD after athletes' retirement in impact sports.

→ Sub-clinical

→ Clinical but undetectable through basal tests

→ Root cause versus consequences

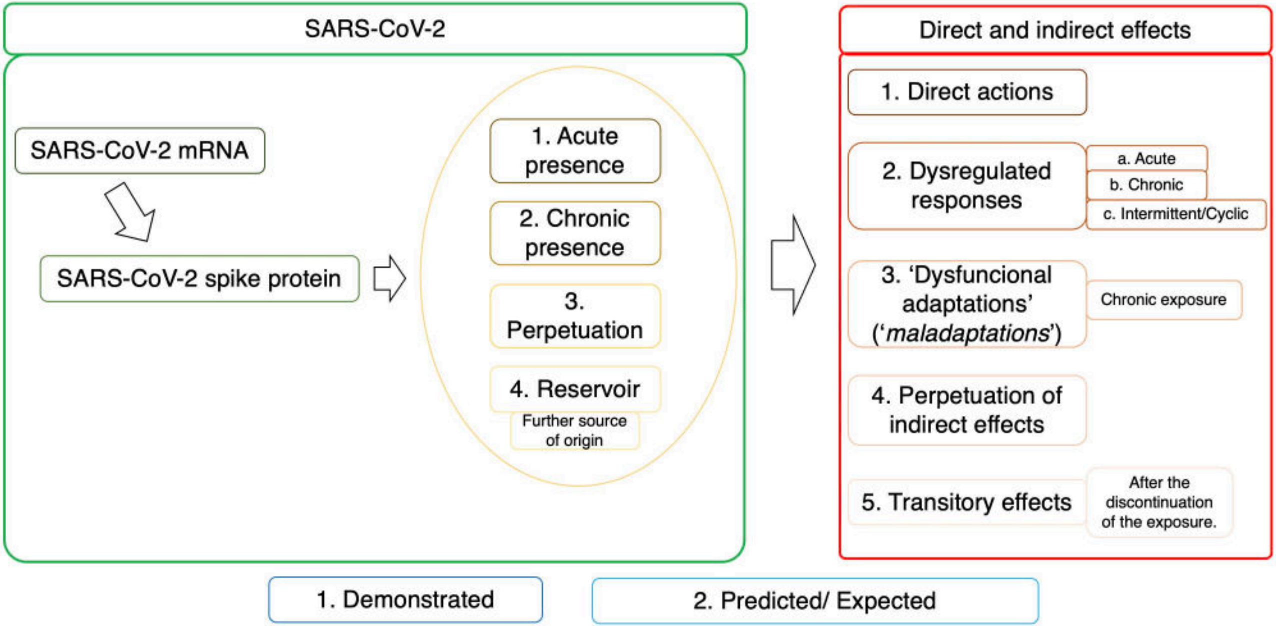
→ Combination of mild abnormalities – and none of the abnormalities are clinically or biochemically detected – challenges on the diagnosis

Predicting future diseases....

speculative or careful?

SARS-CoV-2 spike-related diseases

Methods of search – and reflections



SARS-CoV-2

SARS-CoV-2 mRNA

SARS-CoV-2 spike protein

1. Acute presence
2. Chronic presence
3. Perpetuation
4. Reservoir

Further source of origin

Direct and indirect effects

1. Direct actions
2. Dysregulated responses
   - a. Acute
   - b. Chronic
   - c. Intermittent/Cyclic
3. 'Dysfuncional adaptations' ('*maladaptations*')
   - Chronic exposure
4. Perpetuation of indirect effects
5. Transitory effects
   - After the discontinuation of the exposure.

1. Demonstrated

2. Predicted/ Expected

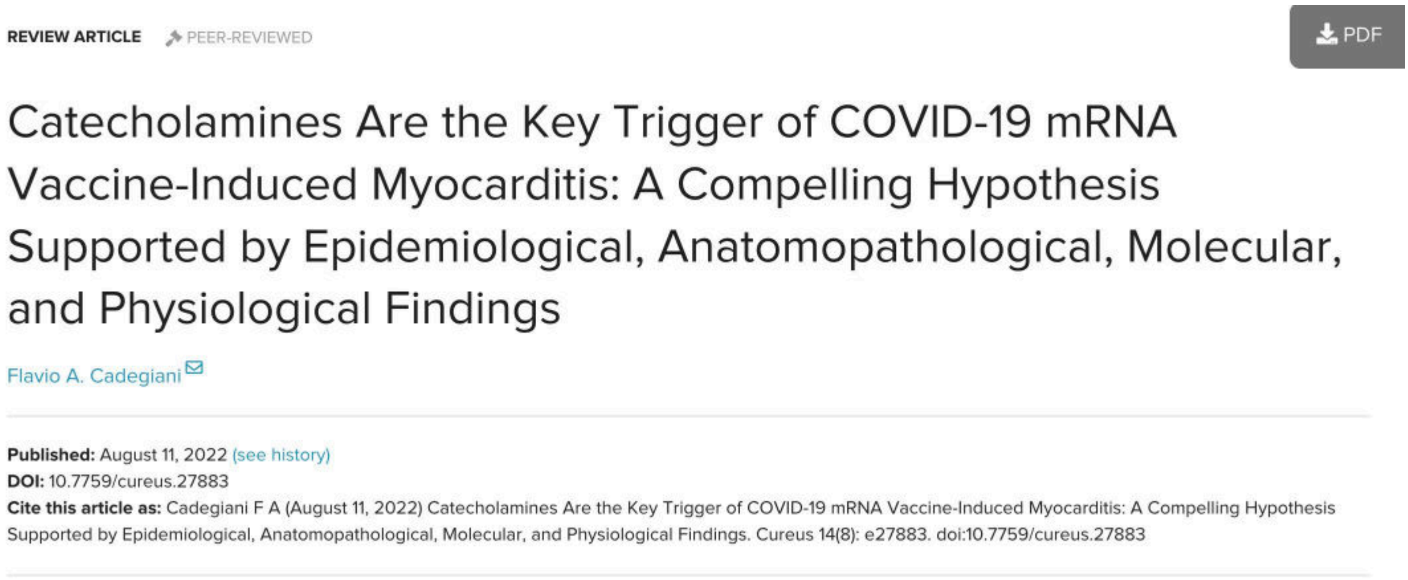
FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

SARS-CoV-2 spike-related diseases

A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation



REVIEW ARTICLE PEER-REVIEWED

Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings

Flavio A. Cadegiani

Published: August 11, 2022 (see history)
DOI: 10.7759/cureus.27883
Cite this article as: Cadegiani F A (August 11, 2022) Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus 14(8): e27883. doi:10.7759/cureus.27883

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE 2022

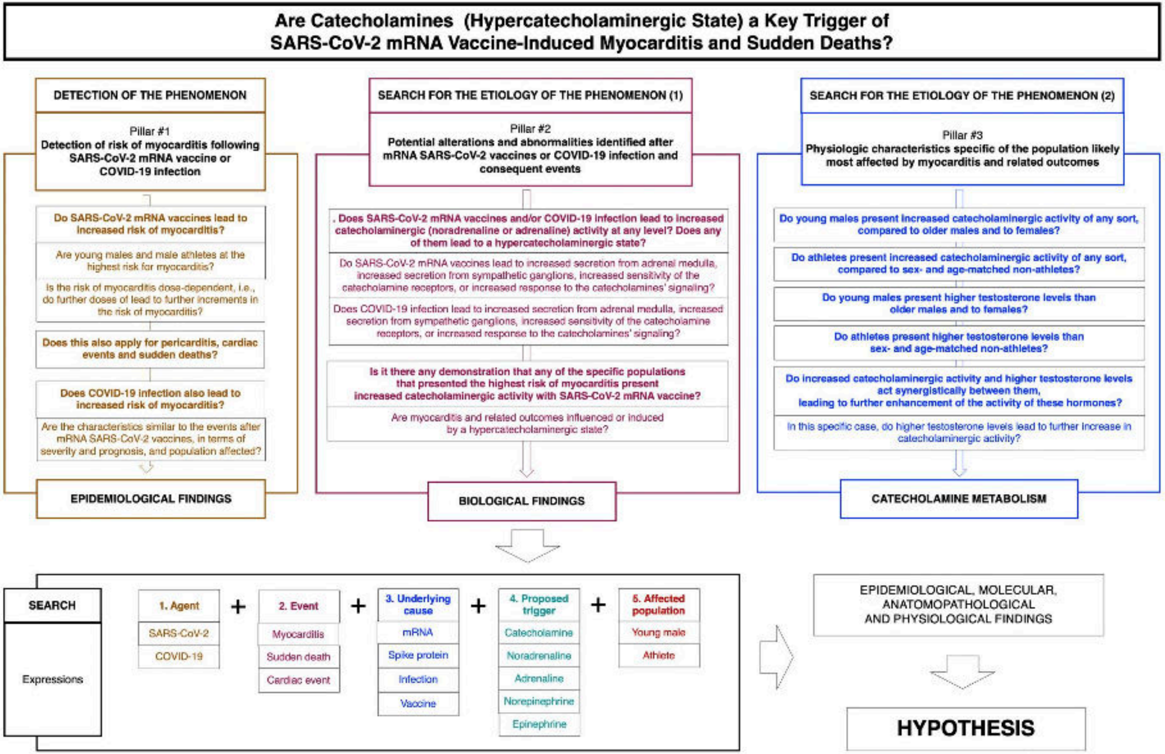
Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

SARS-CoV-2 spike-related diseases

A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation



Are Catecholamines (Hypercatecholaminergic State) a Key Trigger of SARS-CoV-2 mRNA Vaccine-Induced Myocarditis and Sudden Deaths?

DETECTION OF THE PHENOMENON

Pillar #1
Detection of risk of myocarditis following SARS-CoV-2 mRNA vaccine or COVID-19 infection

Do SARS-CoV-2 mRNA vaccines lead to increased risk of myocarditis?

Are young males and male athletes at the highest risk for myocarditis?

Is the risk of myocarditis dose-dependent, i.e., do further doses of lead to further increments in the risk of myocarditis?

Does this also apply for pericarditis, cardiac events and sudden deaths?

Does COVID-19 infection also lead to increased risk of myocarditis?

Are the characteristics similar to the events after mRNA SARS-CoV-2 vaccines, in terms of severity and prognosis, and population affected?

EPIDEMIOLOGICAL FINDINGS

SEARCH FOR THE ETIOLOGY OF THE PHENOMENON (1)

Pillar #2
Potential alterations and abnormalities identified after mRNA SARS-CoV-2 vaccines or COVID-19 infection and consequent events

. Does SARS-CoV-2 mRNA vaccines and/or COVID-19 infection lead to increased catecholaminergic (noradrenaline or adrenaline) activity at any level? Does any of them lead to a hypercatecholaminergic state?

Do SARS-CoV-2 mRNA vaccines lead to increased secretion from adrenal medulla, increased secretion from sympathetic ganglions, increased sensitivity of the catecholamine receptors, or increased response to the catecholamines' signaling?

Does COVID-19 infection lead to increased secretion from adrenal medulla, increased secretion from sympathetic ganglions, increased sensitivity of the catecholamine receptors, or increased response to the catecholamines' signaling?

Is it there any demonstration that any of the specific populations that presented the highest risk of myocarditis present increased catecholaminergic activity with SARS-CoV-2 mRNA vaccine?

Are myocarditis and related outcomes influenced or induced by a hypercatecholaminergic state?

BIOLOGICAL FINDINGS

SEARCH FOR THE ETIOLOGY OF THE PHENOMENON (2)

Pillar #3
Physiologic characteristics specific of the population likely most affected by myocarditis and related outcomes

Do young males present increased catecholaminergic activity of any sort, compared to older males and to females?

Do athletes present increased catecholaminergic activity of any sort, compared to sex- and age-matched non-athletes?

Do young males present higher testosterone levels than older males and to females?

Do athletes present higher testosterone levels than sex- and age-matched non-athletes?

Do increased catecholaminergic activity and higher testosterone levels act synergistically between them, leading to further enhancement of the activity of these hormones?

In this specific case, do higher testosterone levels lead to further increase in catecholaminergic activity?

CATECHOLAMINE METABOLISM

SEARCH	1. Agent	+	2. Event	+	3. Underlying cause	+	4. Proposed trigger	+	5. Affected population
Expressions	SARS-CoV-2 COVID-19		Myocarditis Sudden death Cardiac event		mRNA Spike protein Infection Vaccine		Catecholamine Noradrenaline Adrenaline Norepinephrine Epinephrine		Young male Athlete

EPIDEMIOLOGICAL, MOLECULAR, ANATOMOPATHOLOGICAL AND PHYSIOLOGICAL FINDINGS

HYPOTHESIS

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

SARS-CoV-2 spike-related diseases

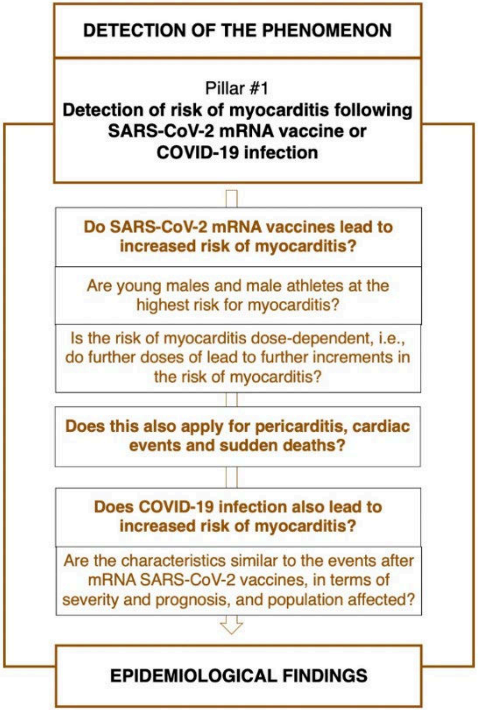
A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation

1. Is the proposed hypothesis supported by epidemiological data?

1. Phenomenon
2. Specific to the hypothesis
3. Population affected



DETECTION OF THE PHENOMENON

Pillar #1
Detection of risk of myocarditis following SARS-CoV-2 mRNA vaccine or COVID-19 infection

Do SARS-CoV-2 mRNA vaccines lead to increased risk of myocarditis?

Are young males and male athletes at the highest risk for myocarditis?

Is the risk of myocarditis dose-dependent, i.e., do further doses of lead to further increments in the risk of myocarditis?

Does this also apply for pericarditis, cardiac events and sudden deaths?

Does COVID-19 infection also lead to increased risk of myocarditis?

Are the characteristics similar to the events after mRNA SARS-CoV-2 vaccines, in terms of severity and prognosis, and population affected?

EPIDEMIOLOGICAL FINDINGS

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

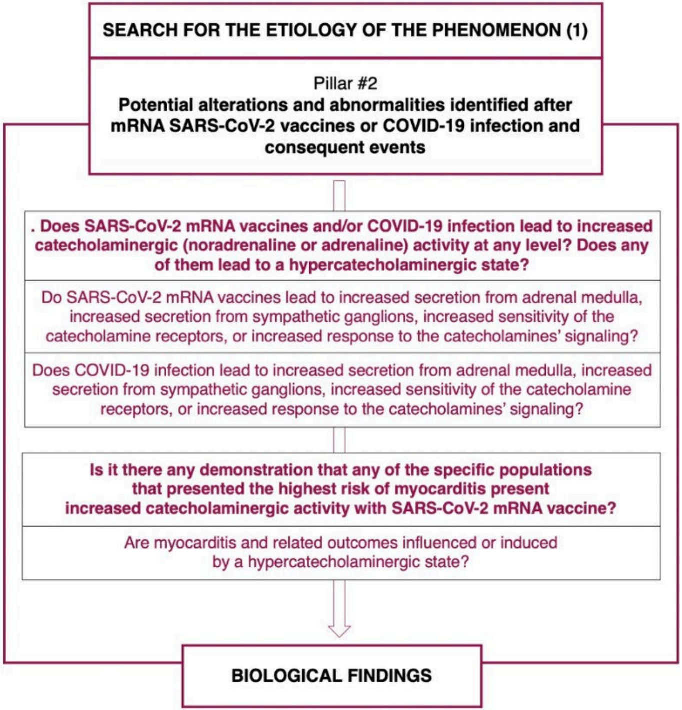
SARS-CoV-2 spike-related diseases

A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation

2. Is the epidemiologically detected phenomenon supported by the hypothesized reason?



SEARCH FOR THE ETIOLOGY OF THE PHENOMENON (1)

Pillar #2
Potential alterations and abnormalities identified after mRNA SARS-CoV-2 vaccines or COVID-19 infection and consequent events

. Does SARS-CoV-2 mRNA vaccines and/or COVID-19 infection lead to increased catecholaminergic (noradrenaline or adrenaline) activity at any level? Does any of them lead to a hypercatecholaminergic state?

Do SARS-CoV-2 mRNA vaccines lead to increased secretion from adrenal medulla, increased secretion from sympathetic ganglions, increased sensitivity of the catecholamine receptors, or increased response to the catecholamines' signaling?

Does COVID-19 infection lead to increased secretion from adrenal medulla, increased secretion from sympathetic ganglions, increased sensitivity of the catecholamine receptors, or increased response to the catecholamines' signaling?

Is it there any demonstration that any of the specific populations that presented the highest risk of myocarditis present increased catecholaminergic activity with SARS-CoV-2 mRNA vaccine?

Are myocarditis and related outcomes influenced or induced by a hypercatecholaminergic state?

BIOLOGICAL FINDINGS

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

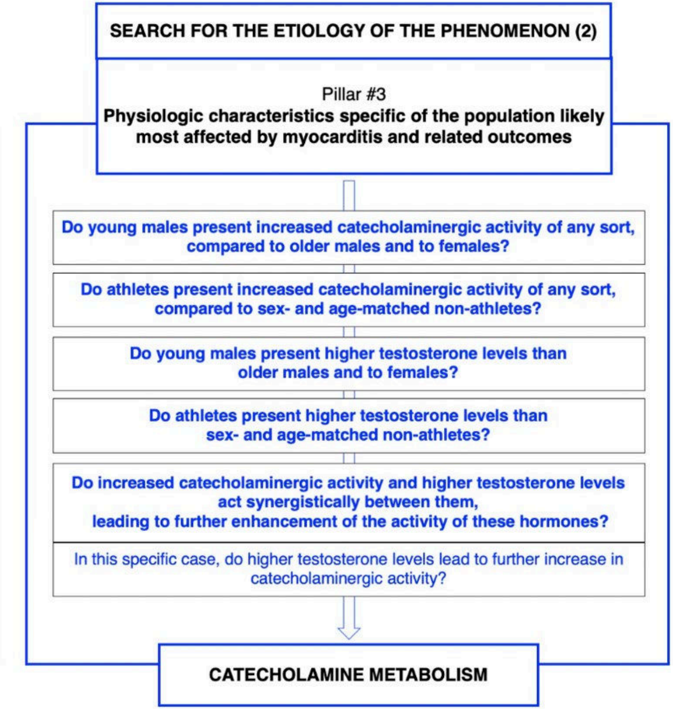
SARS-CoV-2 spike-related diseases

A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation

3. Is the population more susceptible to the phenomenon more exposed to the proposed cause?



SEARCH FOR THE ETIOLOGY OF THE PHENOMENON (2)

Pillar #3
Physiologic characteristics specific of the population likely most affected by myocarditis and related outcomes

Do young males present increased catecholaminergic activity of any sort, compared to older males and to females?

Do athletes present increased catecholaminergic activity of any sort, compared to sex- and age-matched non-athletes?

Do young males present higher testosterone levels than older males and to females?

Do athletes present higher testosterone levels than sex- and age-matched non-athletes?

Do increased catecholaminergic activity and higher testosterone levels act synergistically between them, leading to further enhancement of the activity of these hormones?

In this specific case, do higher testosterone levels lead to further increase in catecholaminergic activity?

CATECHOLAMINE METABOLISM

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

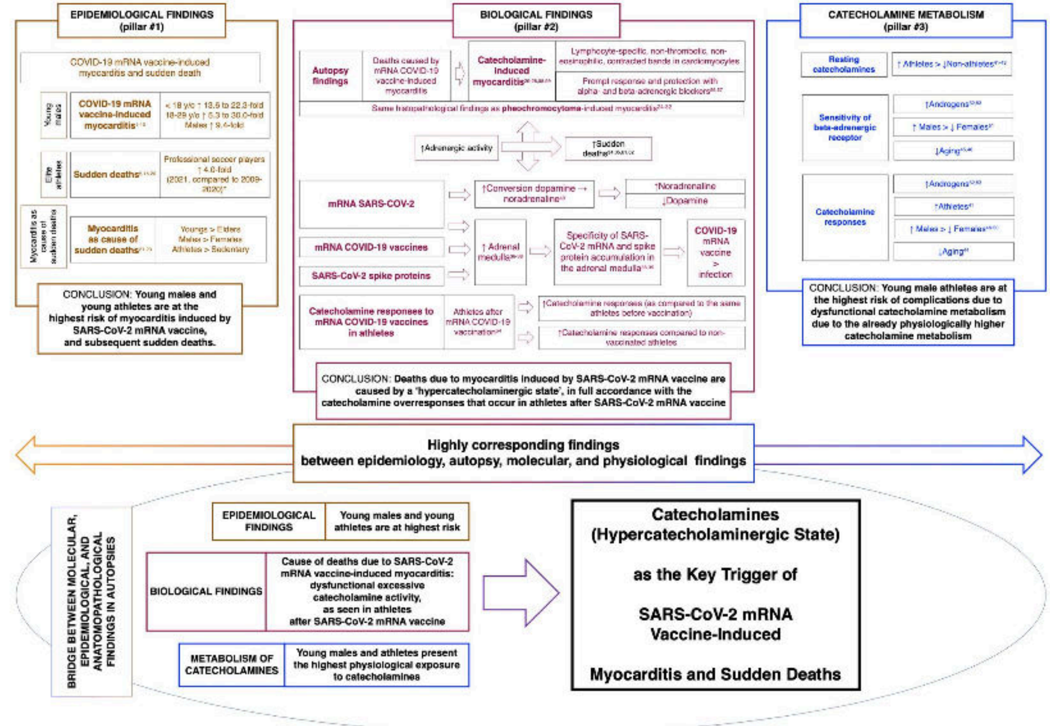
Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

SARS-CoV-2 spike-related diseases

A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation



All data contained is in this figure is supported by the literature and can be found in the corresponding references

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

SARS-CoV-2 spike-related diseases

A representative example of :

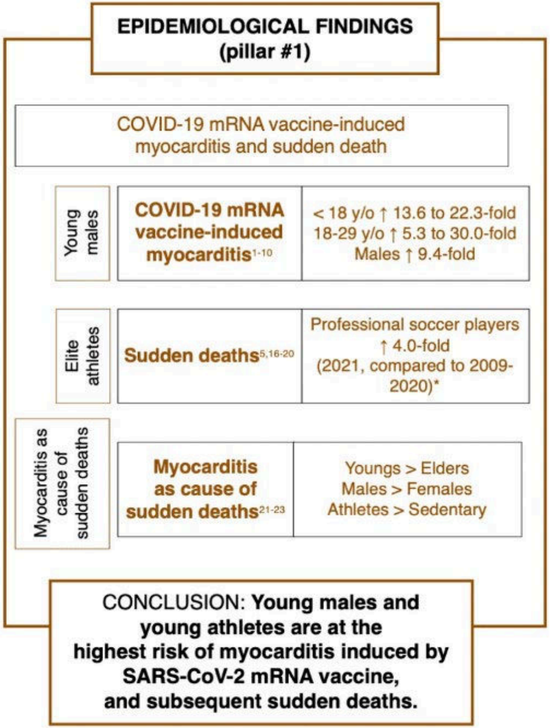
1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation

1. Is the proposed hypothesis supported by epidemiological data?

1. Phenomenon
2. Specific to the hypothesis
3. Population affected

1. The phenomenon is strongly supported by epidemiological data, is specific to the hypothesis and its affected population.



EPIDEMIOLOGICAL FINDINGS (pillar #1)

COVID-19 mRNA vaccine-induced myocarditis and sudden death

Young males	**COVID-19 mRNA vaccine-induced myocarditis**[1-10]	< 18 y/o ↑ 13.6 to 22.3-fold 18-29 y/o ↑ 5.3 to 30.0-fold Males ↑ 9.4-fold
Elite athletes	**Sudden deaths**[5,16-20]	Professional soccer players ↑ 4.0-fold (2021, compared to 2009-2020)*
Myocarditis as cause of sudden deaths	**Myocarditis as cause of sudden deaths**[21-23]	Youngs > Elders Males > Females Athletes > Sedentary

CONCLUSION: **Young males and young athletes are at the highest risk of myocarditis induced by SARS-CoV-2 mRNA vaccine, and subsequent sudden deaths.**

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

SARS-CoV-2 spike-related diseases

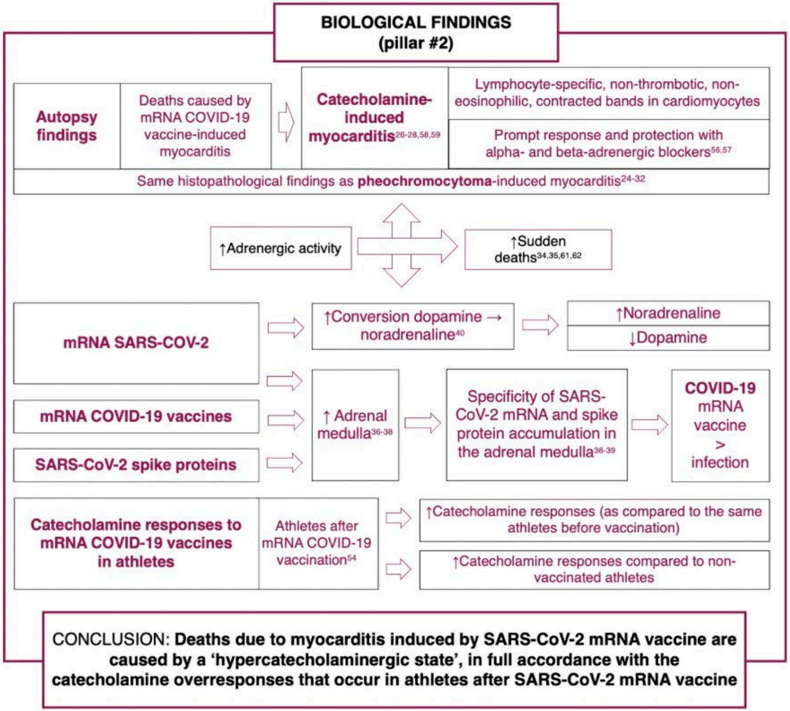
A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation

2. Is the epidemiologically detected phenomenon supported by the hypothesized reason?

2. The phenomenon has strong data from different sources and aspects that supports the hypothesized reason as the cause for the phenomenon



BIOLOGICAL FINDINGS (pillar #2)

Autopsy findings – Deaths caused by mRNA COVID-19 vaccine-induced myocarditis ⇒ **Catecholamine-induced myocarditis**[26-28,58,59]

- Lymphocyte-specific, non-thrombotic, non-eosinophilic, contracted bands in cardiomyocytes
- Prompt response and protection with alpha- and beta-adrenergic blockers[56,57]

Same histopathological findings as **pheochromocytoma**-induced myocarditis[24-32]

↑Adrenergic activity ⇒ ↑Sudden deaths[34,35,61,62]

mRNA SARS-COV-2 ⇒ ↑Conversion dopamine → noradrenaline[40] ⇒ ↑Noradrenaline / ↓Dopamine

mRNA SARS-COV-2, **mRNA COVID-19 vaccines**, **SARS-CoV-2 spike proteins** ⇒ ↑ Adrenal medulla[36-38] ⇒ Specificity of SARS-CoV-2 mRNA and spike protein accumulation in the adrenal medulla[36-39] ⇒ **COVID-19** mRNA vaccine > infection

Catecholamine responses to mRNA COVID-19 vaccines in athletes – Athletes after mRNA COVID-19 vaccination[54]

- ↑Catecholamine responses (as compared to the same athletes before vaccination)
- ↑Catecholamine responses compared to non-vaccinated athletes

CONCLUSION: **Deaths due to myocarditis induced by SARS-CoV-2 mRNA vaccine are caused by a 'hypercatecholaminergic state', in full accordance with the catecholamine overresponses that occur in athletes after SARS-CoV-2 mRNA vaccine**

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

SARS-CoV-2 spike-related diseases

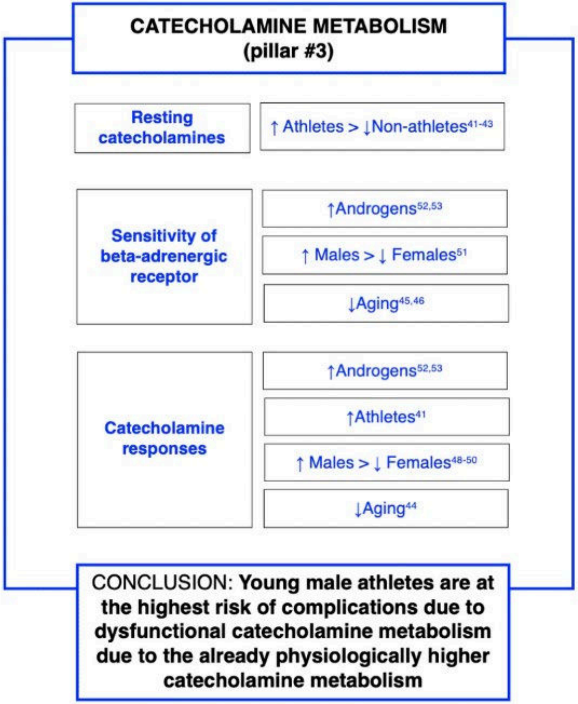
A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation

3. Is the population more susceptible to the phenomenon more exposed to the proposed cause?

3. The population more susceptible to the phenomenon is undoubtedly the most exposed population to the cause of the phenomenon.



CATECHOLAMINE METABOLISM (pillar #3)

Resting catecholamines
- ↑ Athletes > ↓Non-athletes[41-43]

Sensitivity of beta-adrenergic receptor
- ↑Androgens[52,53]
- ↑ Males > ↓ Females[51]
- ↓Aging[45,46]

Catecholamine responses
- ↑Androgens[52,53]
- ↑Athletes[41]
- ↑ Males > ↓ Females[48-50]
- ↓Aging[44]

CONCLUSION: **Young male athletes are at the highest risk of complications due to dysfunctional catecholamine metabolism due to the already physiologically higher catecholamine metabolism**

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

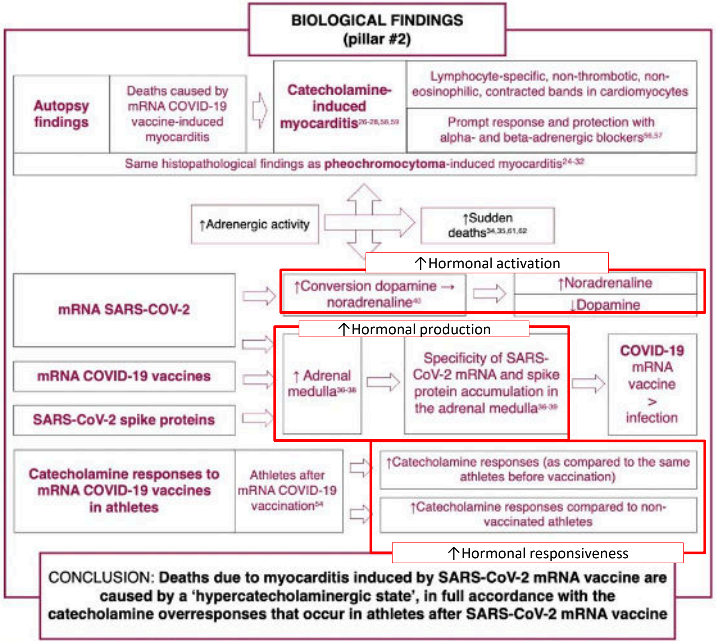
Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

SARS-CoV-2 spike-related diseases

A representative example of :

1. Methods to explore a hypothesis

2. Multiple levels of hormonal dysregulation



BIOLOGICAL FINDINGS (pillar #2)

Autopsy findings | Deaths caused by mRNA COVID-19 vaccine-induced myocarditis ⇨ **Catecholamine-induced myocarditis**[26-28,58,59]
- Lymphocyte-specific, non-thrombotic, non-eosinophilic, contracted bands in cardiomyocytes
- Prompt response and protection with alpha- and beta-adrenergic blockers[56,57]

Same histopathological findings as **pheochromocytoma**-induced myocarditis[24-32]

↑Adrenergic activity ⇨ ↑Sudden deaths[34,35,61,62]

↑Hormonal activation

mRNA SARS-COV-2 ⇨ ↑Conversion dopamine → noradrenaline[40] ⇨ ↑Noradrenaline / ↓Dopamine

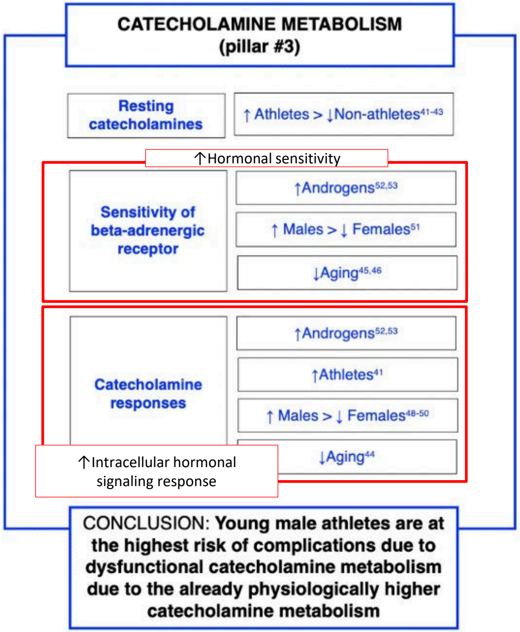
↑Hormonal production

mRNA COVID-19 vaccines / **SARS-CoV-2 spike proteins** ⇨ ↑ Adrenal medulla[36-38] ⇨ Specificity of SARS-CoV-2 mRNA and spike protein accumulation in the adrenal medulla[36-39] ⇨ **COVID-19 mRNA vaccine > infection**

Catecholamine responses to mRNA COVID-19 vaccines in athletes | Athletes after mRNA COVID-19 vaccination[54]
- ↑Catecholamine responses (as compared to the same athletes before vaccination)
- ↑Catecholamine responses compared to non-vaccinated athletes

↑Hormonal responsiveness

CONCLUSION: **Deaths due to myocarditis induced by SARS-CoV-2 mRNA vaccine are caused by a 'hypercatecholaminergic state', in full accordance with the catecholamine overresponses that occur in athletes after SARS-CoV-2 mRNA vaccine**



CATECHOLAMINE METABOLISM (pillar #3)

Resting catecholamines | ↑ Athletes > ↓Non-athletes[41-43]

↑Hormonal sensitivity

Sensitivity of beta-adrenergic receptor
- ↑Androgens[52,53]
- ↑ Males > ↓ Females[51]
- ↓Aging[45,46]

Catecholamine responses
- ↑Androgens[52,53]
- ↑Athletes[41]
- ↑ Males > ↓ Females[48-50]
- ↓Aging[44]

↑Intracellular hormonal signaling response

CONCLUSION: **Young male athletes are at the highest risk of complications due to dysfunctional catecholamine metabolism due to the already physiologically higher catecholamine metabolism**

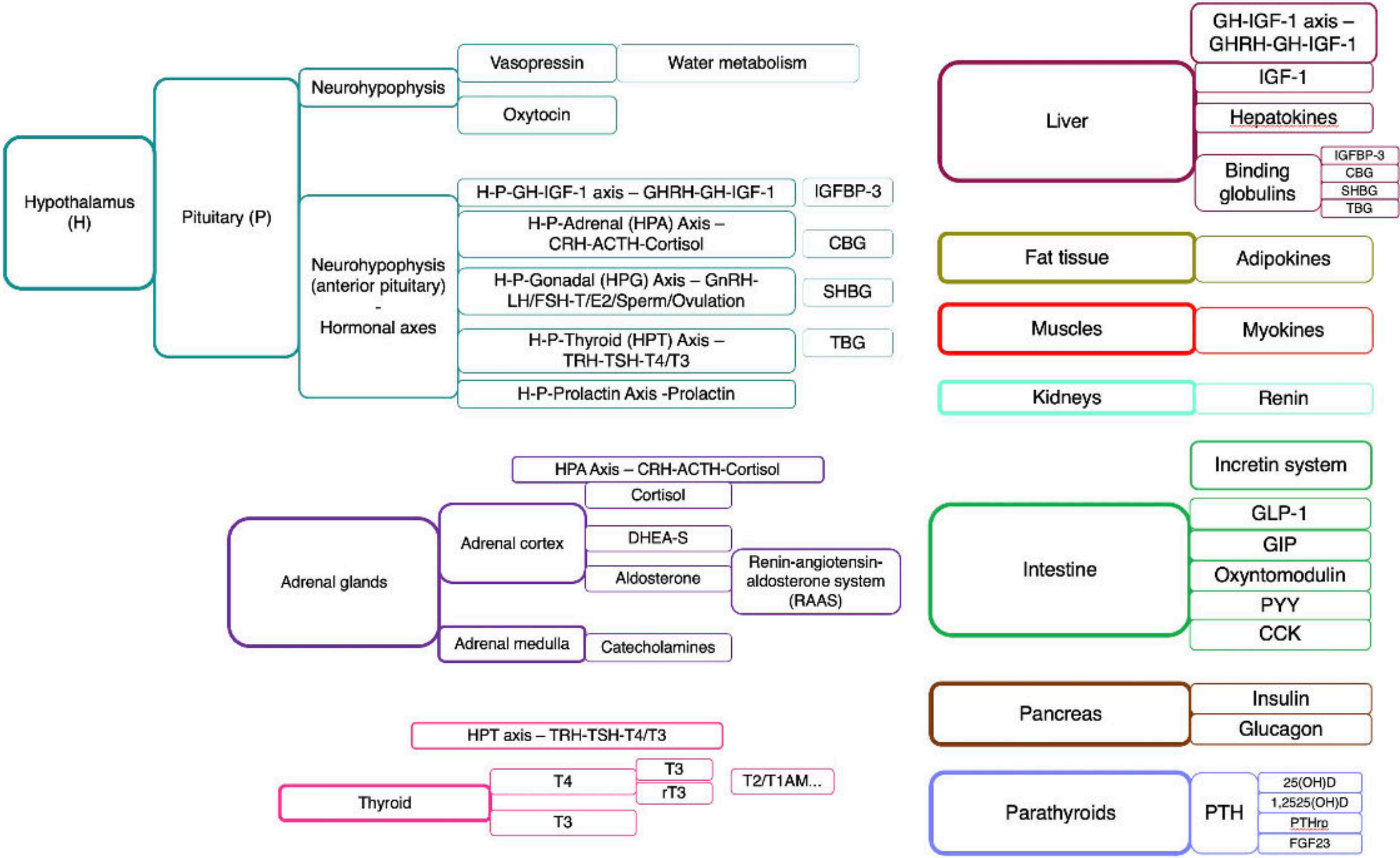
Hypercatecholaminergic state ⇨

↑Hormonal production
↑Hormonal activation
↑Hormonal sensitivity
↑Intracellular hormonal signaling response
↑Hormonal responsiveness

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesi↑s Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

SARS-CoV-2 spike-related diseases
Main endocrine axis



Hypothalamus (H)

Pituitary (P)

Neurohypophysis

Vasopressin

Water metabolism

Oxytocin

Neurohypophysis (anterior pituitary) - Hormonal axes

H-P-GH-IGF-1 axis – GHRH-GH-IGF-1

IGFBP-3

H-P-Adrenal (HPA) Axis – CRH-ACTH-Cortisol

CBG

H-P-Gonadal (HPG) Axis – GnRH-LH/FSH-T/E2/Sperm/Ovulation

SHBG

H-P-Thyroid (HPT) Axis – TRH-TSH-T4/T3

TBG

H-P-Prolactin Axis -Prolactin

HPA Axis – CRH-ACTH-Cortisol

Adrenal glands

Adrenal cortex

Cortisol

DHEA-S

Aldosterone

Renin-angiotensin-aldosterone system (RAAS)

Adrenal medulla

Catecholamines

HPT axis – TRH-TSH-T4/T3

Thyroid

T4

T3

rT3

T2/T1AM...

T3

GH-IGF-1 axis – GHRH-GH-IGF-1

Liver

IGF-1

Hepatokines

Binding globulins

IGFBP-3

CBG

SHBG

TBG

Fat tissue

Adipokines

Muscles

Myokines

Kidneys

Renin

Incretin system

Intestine

GLP-1

GIP

Oxyntomodulin

PYY

CCK

Pancreas

Insulin

Glucagon

Parathyroids

PTH

25(OH)D

1,2525(OH)D

PTHrp

FGF23

Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. BMC Endocr Disord. 2020 Sep 29;20(1):149. doi: 10.1186/s12902-020-00626-0.

SARS-CoV-2 spike-related diseases
Endocrinology, metabolism, and omics

Genomics

Transcriptomics

Proteomics

Metabolomics

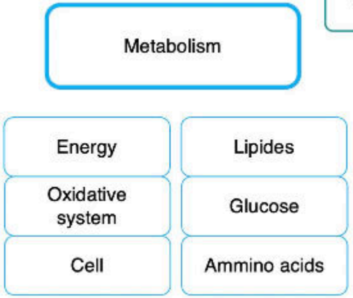
Lipidomics

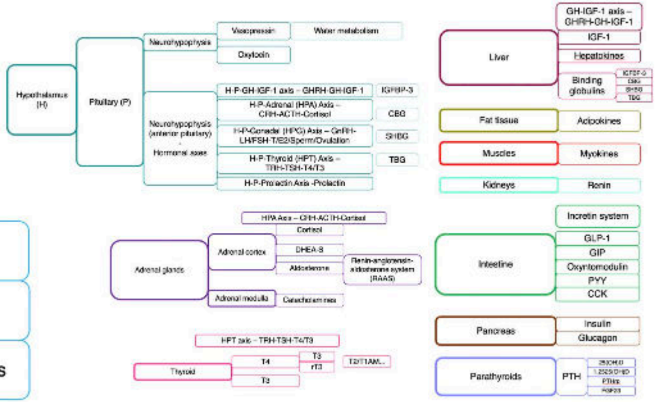
Glycomics

Secretomics

'Steroidomics'

Secretomics

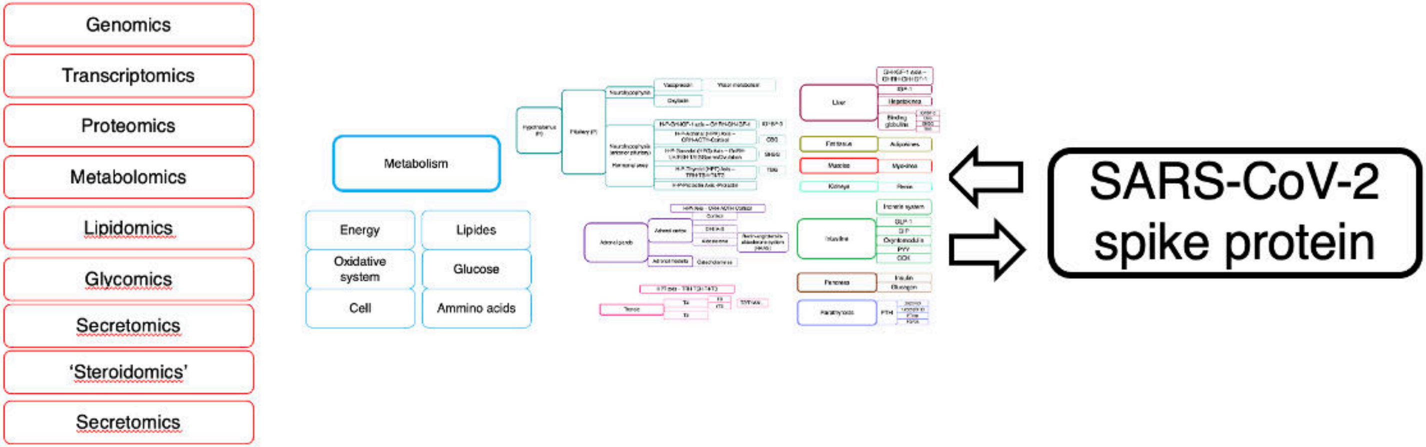




FLCCC
ALLIANCE
EDUCATIONAL CONFERENCE
2022

Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. BMC Endocr Disord. 2020 Sep 29;20(1):149. doi: 10.1186/s12902-020-00626-0.

SARS-CoV-2 spike-related diseases
Endocrinology, metabolism, and omics



Genomics

Transcriptomics

Proteomics

Metabolomics

Lipidomics

Glycomics

Secretomics

'Steroidomics'

Secretomics

Metabolism

Energy

Lipides

Oxidative system

Glucose

Cell

Ammino acids

SARS-CoV-2 spike protein

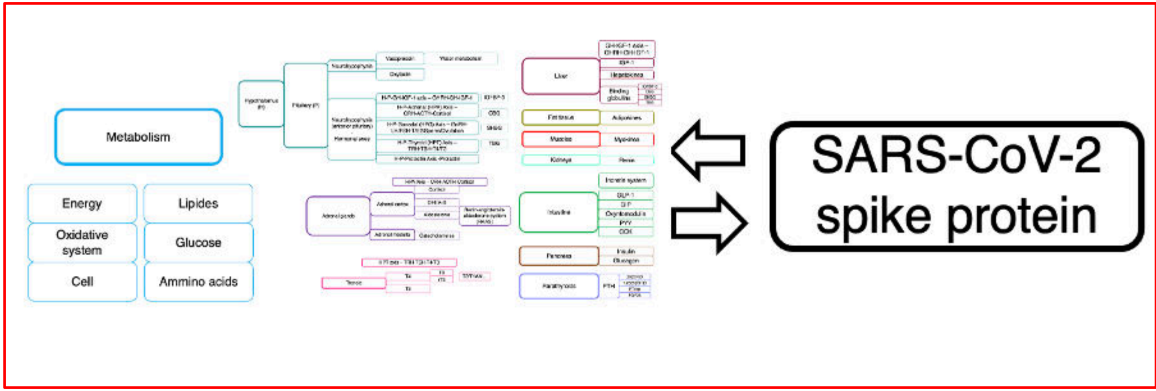
"SARS-CoV-2 vaccines could represent new external triggers for autoimmune endocrine diseases (AIED) in patients with individual predisposition."

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. BMC Endocr Disord. 2020 Sep 29;20(1):149. doi: 10.1186/s12902-020-00626-0.

SARS-CoV-2 spike-related diseases
Endocrinology, metabolism, and omics

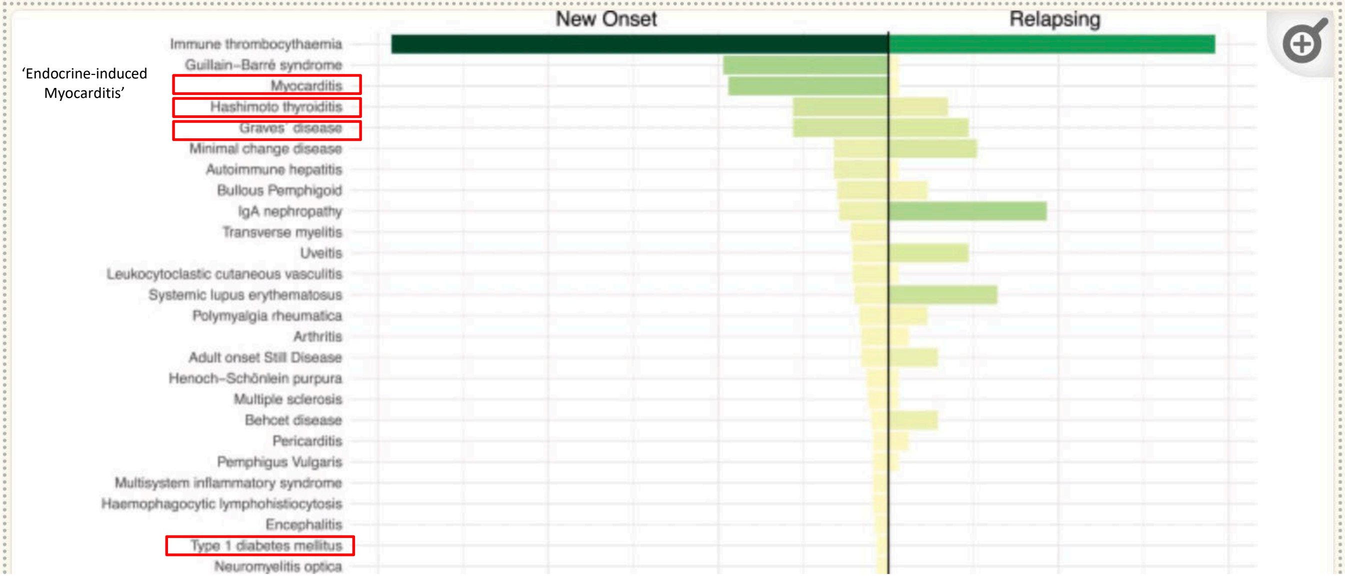
- Genomics
- Transcriptomics
- Proteomics
- Metabolomics
- Lipidomics
- Glycomics
- Secretomics
- 'Steroidomics'
- Secretomics



"SARS-CoV-2 vaccines could represent new external triggers for autoimmune endocrine diseases (AIED) in patients with individual predisposition."

Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. BMC Endocr Disord. 2020 Sep 29;20(1):149. doi: 10.1186/s12902-020-00626-0.

SARS-CoV-2 vaccines-induced diseases – Most documented endocrinopathies



‘Endocrine-induced Myocarditis’

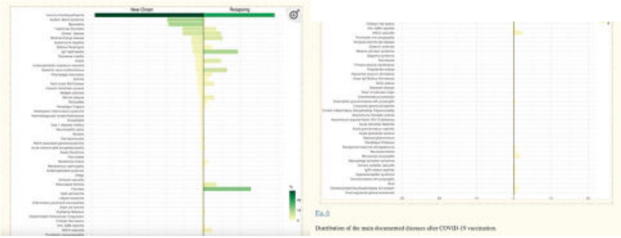


Fig. 6

Distribution of the main documented diseases after COVID-19 vaccination.

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

Rodríguez Y, Rojas M, Beltrán S, Polo F, Camacho-Domínguez L, Morales SD, Gershwin ME, Anaya JM. Autoimmune and autoinflammatory conditions after COVID-19 vaccination. New case reports and updated literature review. J Autoimmun. 2022 Aug 24;132:102898. doi: 10.1016/j.jaut.2022.102898.

HPG axis in males with SARS-CoV-2 spike protein

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-T/Sperm | SHBG

→ The male genitalia potentially is vulnerable to SARS-CoV-2 infection

→ SARS-CoV-2 mRNA → ↓ GnRH (at all ages) → Multiple consequences

→ Presence of SARS-CoV-2 within semen samples:
1. Direct viral damage
2. Secondary inflammatory response → orchitis
3. Immunologic activation
4. The amount (and persistance) of viral load predicts testicular damage
5. Possible formation of anti-sperm antibodies (ASA) → immunological infertility
6. ↑ Sperm DNA fragmentation

→ ↑ ACE2 signalling in macrophages and mast cells + oxidative stress + inflammation → Spermatogenesis failure =
1. Abnormal sperm motility
2. DNA fragmentation
3. Male infertility

Sheikhzadeh Hesari F, Hosseinzadeh SS, Asl Monadi Sardroud MA. Review of COVID-19 and male genital tract. Andrologia. 2021 Feb;53(1):e13914. doi: 10.1111/and.13914.
Haghpanah A, Masjedi F, Alborzi S, Hosseinpour A, Dehghani A, Malekmakan L, Roozbeh J. Potential mechanisms of SARS-CoV-2 action on male gonadal function and fertility: Current status and future prospects. Andrologia. 2021 Feb;53(1):e13883. doi: 10.1111/and.13883.
Sabetian S, Castiglioni I, Jahromi BN, Mousavi P, Cava C. In Silico Identification of miRNA-lncRNA Interactions in Male Reproductive Disorder Associated with COVID-19 Infection. Cells. 2021 Jun 12;10(6):1480. doi: 10.3390/cells10061480.
Yang M., Chen S., Huang B., Zhong J.-M., Su H., Chen Y.-J., Cao Q., Ma L., He J., Li X.-F., et al. Pathological findings in the testes of COVID-19 patients: Clinical implications. Eur. Urol. Focus. 2020;6:1124–1129. doi: 10.1016/j.euf.2020.05.009.
Achua J.K., Chu K.Y., Ibrahim E., Khodamoradi K., Delma K.S., Iakymenko O.A., Kryvenko O.N., Arora H., Ramasamy R. Histopathology and ultrastructural findings of fatal COVID-19 infections on testis. World J. Mens Health. 2021;39:65. doi: 10.5534/wjmh.200170.
Kresch E., Achua J., Saltzman R., Khodamoradi K., Arora H., Ibrahim E., Kryvenko O.N., Almeida V.W., Firdaus F., Hare J.M., et al. COVID-19 endothelial dysfunction can cause erectile dysfunction: Histopathological, immunohistochemical, and ultrastructural study of the human penis. World J. Mens Health. 2021;39:466. doi: 10.5534/wjmh.210055.
https://www.medrxiv.org/content/10.1101/2022.02.05.22270327v1

HPG axis in males with SARS-CoV-2 spike protein

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-T/Sperm | SHBG

→ Invasion of SARS-CoV-2 spike protein to
1. The spermatogonia → Extensive germ cell destruction, Hyalinization and thickening of the basement membrane of the seminiferous tubules, with lymphocyte infiltration, germ cell apoptosis, thickening of the tunica propria
2. Leydig cells → Scattering, inhibition, inflammation, and fibrosis
3. Sertoli cells → Defoliation, edema, vacuolation, cytoplasmic rarefaction, barrier loss, evident hemorrhage, angiogenesis
→ Sex hormonal alteration + Impaired gonadal function

"Coronavirus-like particles are presente in the cytoplasm of the interstitial cells of the testes"
"Macrophages and spermatogonial cells → The main SARS-CoV-2 lodging sites"
"SARS-CoV-2 maintains its replicative and infective abilities long after the patient's infection in the testes → Viral sanctuary"

03 months after infection: subfertility resolved (one study) +
< 60 days after infection = ↓16% | > 60 days after COVID-19 ↑ 16% →
Any long-term male infertility issue should be attributed to vaccine

Penis and SARS-CoV-2 spike protein →
1. COVID-19 endothelial dysfunction → erectile dysfunction
2. Extracellular viral particles in the peri-vascular erectile tissue.

Sheikhzadeh Hesari F, Hosseinzadeh SS, Asl Monadi Sardroud MA. Review of COVID-19 and male genital tract. Andrologia. 2021 Feb;53(1):e13914. doi: 10.1111/and.13914.
Haghpanah A, Masjedi F, Alborzi S, Hosseinpour A, Dehghani A, Malekmakan L, Roozbeh J. Potential mechanisms of SARS-CoV-2 action on male gonadal function and fertility: Current status and future prospects. Andrologia. 2021 Feb;53(1):e13883. doi: 10.1111/and.13883.
Sabetian S, Castiglioni I, Jahromi BN, Mousavi P, Cava C. In Silico Identification of miRNA-lncRNA Interactions in Male Reproductive Disorder Associated with COVID-19 Infection. Cells. 2021 Jun 12;10(6):1480. doi: 10.3390/cells10061480.
Yang M., Chen S., Huang B., Zhong J.-M., Su H., Chen Y.-J., Cao Q., Ma L., He J., Li X.-F., et al. Pathological findings in the testes of COVID-19 patients: Clinical implications. Eur. Urol. Focus. 2020;6:1124–1129. doi: 10.1016/j.euf.2020.05.009.
Achua J.K., Chu K.Y., Ibrahim E., Khodamoradi K., Delma K.S., Iakymenko O.A., Kryvenko O.N., Arora H., Ramasamy R. Histopathology and ultrastructural findings of fatal COVID-19 infections on testis. World J. Mens Health. 2021;39:65. doi: 10.5534/wjmh.200170.
Kresch E., Achua J., Saltzman R., Khodamoradi K., Arora H., Ibrahim E., Kryvenko O.N., Almeida V.W., Firdaus F., Hare J.M., et al. COVID-19 endothelial dysfunction can cause erectile dysfunction: Histopathological, immunohistochemical, and ultrastructural study of the human penis. World J. Mens Health. 2021;39:466. doi: 10.5534/wjmh.210055.
https://www.medrxiv.org/content/10.1101/2022.02.05.22270327v1

HPG axis in males with SARS-CoV-2 spike protein

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-T/Sperm | SHBG

‘Forcing evidence of safety of SARS-CoV-2 vaccines’
+
‘Forcing evidence of harm with COVID-19 infections’

Review Article | Open Access | Published: 27 October 2021

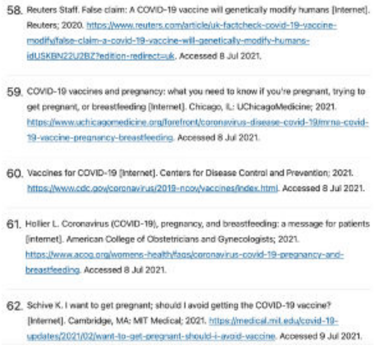
Effects of SARS CoV-2, COVID-19, and its vaccines on male sexual health and reproduction: where do we stand?

Sharon P. Lo, Tung-Chin Hsieh, Alexander W. Pastuszak, James M. Hotaling & Darshan P. Patel

International Journal of Impotence Research **34**, 138–144 (2022) | Cite this article

48k Accesses | **7** Citations | **206** Altmetric | Metrics

There is currently no evidence that the vaccine can cause infertility in men or women, damage to the placenta, or lead to miscarriages [58,59,60,61,62,63]. The ASRM states in their COVID-



58. Reuters Staff. False claim: A COVID-19 vaccine will genetically modify humans [Internet]. Reuters; 2020. https://www.reuters.com/article/uk-factcheck-covid-19-vaccine-modify/false-claim-a-covid-19-vaccine-will-genetically-modify-humans-idUSKBN22U2BZ?edition-redirect=uk. Accessed 8 Jul 2021.
59. COVID-19 vaccines and pregnancy: what you need to know if you're pregnant, trying to get pregnant, or breastfeeding [Internet]. Chicago, IL: UChicagoMedicine; 2021. https://www.uchicagomedicine.org/forefront/coronavirus-disease-covid-19/mrna-covid-19-vaccine-pregnancy-breastfeeding. Accessed 8 Jul 2021.
60. Vaccines for COVID-19 [Internet]. Centers for Disease Control and Prevention; 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html. Accessed 8 Jul 2021.
61. Hollier L. Coronavirus (COVID-19), pregnancy, and breastfeeding: a message for patients [internet]. American College of Obstetricians and Gynecologists; 2021. https://www.acog.org/womens-health/faqs/coronavirus-covid-19-pregnancy-and-breastfeeding. Accessed 8 Jul 2021.
62. Schive K. I want to get pregnant; should I avoid getting the COVID-19 vaccine? [Internet]. Cambridge, MA: MIT Medical; 2021. https://medical.mit.edu/covid-19-updates/2021/02/want-to-get-pregnant-should-i-avoid-vaccine. Accessed 9 Jul 2021.

These are the ‘references’ for the ‘lack of evidence’ that vaccines can affect fertility in the ‘gold-standard review’

Eric Topol
@EricTopol

There is zero evidence that vaccines cause infertility in men (or women) but a new report about Covid and live virus found in testicles: "SARS-CoV-2 infects, replicates, elevates angiotensin II and activates immune cells in human testes"
medrxiv.org/content/10.110...

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE 2022

HPG axis in males with SARS-CoV-2 spike protein

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-T/Sperm | SHBG

‘Forcing evidence of safety of SARS-CoV-2 vaccines’
+
‘forcing evidence of harm with COVID-19 infections’

Review Article | Open Access | Published: 27 October 2021

Effects of SARS CoV-2, COVID-19, and its vaccines on male sexual health and reproduction: where do we stand?

Sharon P. Lo, Tung-Chin Hsieh, Alexander W. Pastuszak, James M. Hotaling & Darshan P. Patel

International Journal of Impotence Research **34**, 138–144 (2022) | Cite this article

48k Accesses | **7** Citations | **206** Altmetric | Metrics

There is currently no evidence that the vaccine can cause infertility in men or women, damage to the placenta, or lead to miscarriage [58,59,60,61,62,63]. The ASRM states in their COVID-

58. Reuters Staff. False claim: A COVID-19 vaccine will genetically modify humans [Internet]. Reuters; 2020. https://www.reuters.com/artic[illegible]eck-covid-19-vaccine-modify/false-claim-a-covid-19-vaccine-will-[illegible]etically-modify-humans-idUSKBN22U2BZ?edition-redirect=uk. Accessed 8 Jul 2[illegible]
59. COVID-19 vaccines and pregnancy: what you need to know if you're pregnant, trying to get pregnant, or breastfeeding [Internet]. Chicago, IL: UChicagoMedicine; 2021. https://www.uchicagomedicine.org/forefront/coronavirus-disease-covid-19/mrna-covid-19-vaccine-pregnancy-breastfeeding. Accessed 8 Jul 2021.
60. Vaccines for COVID-19 [Internet]. Centers for Disease Control and Prevention; 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html. Accessed 8 Jul 2021.
61. Hollier L. Coronavirus (COVID-19), pregnancy, and breastfeeding: a message for patients [internet]. American College of Obstetricians and Gynecologists; 2021. https://www.acog.org/womens-health/faqs/coronavirus-covid-19-pregnancy-and-breastfeeding. Accessed 8 Jul 2021.
62. Schive K. I want to get pregnant; should I avoid getting the COVID-19 vaccine? [Internet]. Cambridge, MA: MIT Medical; 2021. https://medical.mit.edu/covid-19-updates/2021/02/want-to-get-pregnant-should-i-avoid-vaccine. Accessed 9 Jul 2021.

These are the ‘references’ for the ‘lack of evidence’ that vaccines can affect fertility in the ‘gold-standard review’

Eric Topol @EricTopol

There is zero evidence that vaccines cause infertility in men (or women) but a new report about Covid and live virus found in testicles: "SARS-CoV-2 infects, replicates, elevates angiotensin II and activates immune cells in human testes"
medrxiv.org/content/10.110...

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE 2022

HPG axis in males with SARS-CoV-2 spike protein - Summary

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-T/Sperm | SHBG

Early

1. Semen virus detection

Late

1. Impaired spermatogenesis

Proposed mechanisms

1. Direct virus effect
2. Seminiferous injuries
3. Reduction in Leydig cells number
4. Inflammation

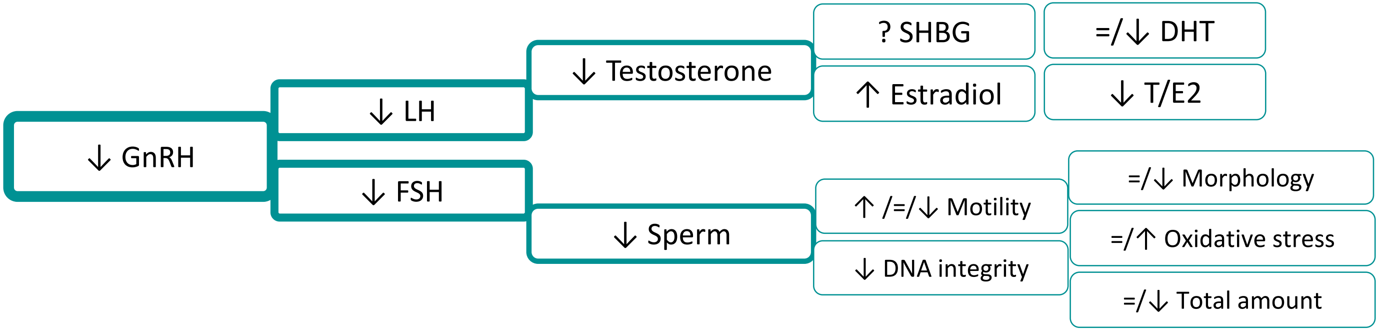
Expected

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Gonzalez D.C., Nassau D.E., Khodamoradi K., Ibrahim E., Blachman-Braun R., Ory J., Ramasamy R. Sperm Parameters Before and After COVID-19 mRNA Vaccination. JAMA. 2021;326:273–274. doi: 10.1001/jama.2021.9976.
Lifshitz D., Haas J., Lebovitz O., Raviv G., Orvieto R., Aizer A. Does mRNA SARS-CoV-2 vaccine detrimentally affect male fertility, as reflected by semen analysis? Reprod. Biomed. Online. 2022

HPG axis in males with SARS-CoV-2 spike protein - expected

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-T/Sperm | SHBG

Predicted (not based on current evidence)


↓ GnRH

↓ LH

↓ FSH

↓ Testosterone

↓ Sperm

? SHBG

↑ Estradiol

=/↓ DHT

↓ T/E2

↑ /=/↓ Motility

↓ DNA integrity

=/↓ Morphology

=/↑ Oxidative stress

=/↓ Total amount

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Gonzalez D.C., Nassau D.E., Khodamoradi K., Ibrahim E., Blachman-Braun R., Ory J., Ramasamy R. Sperm Parameters Before and After COVID-19 mRNA Vaccination. JAMA. 2021;326:273–274. doi: 10.1001/jama.2021.9976.
Lifshitz D., Haas J., Lebovitz O., Raviv G., Orvieto R., Aizer A. Does mRNA SARS-CoV-2 vaccine detrimentally affect male fertility, as reflected by semen analysis? Reprod. Biomed. Online. 2022

HPG axis in females with SARS-CoV-2 spike protein

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-Egg/E2/P | SHBG

- COVID-19 infection

→ No influence →

“IVF treatment outcomes and the rate of early pregnancy loss appears to be unaffected by SARS-CoV-2 disease”

“No inflammatory lesions of the endometrium were identified histologically.”

“Fertilization rate, embryo development, and clinical outcomes after embryo transfer were reassuring.”

- Inactivated COVID-19 vaccines →

→ No negative effects were found on female fertility in IUI cycles following exposure to the inactivated COVID-19 vaccine

→ 8.8% menstruation disturbances | 4.6% metrorragia | 1.6% hirsutism → Significant linear correlation with number of doses

→ → Endometrial samples did not express SARS-CoV-2 RNA → And spike protein?

Xu Z, Wu Y, Lin Y, Cao M, Liang Z, Li L, Lin J, Chen Q, Liu J, Liu H. Effect of inactivated COVID-19 vaccination on intrauterine insemination cycle success: A retrospective cohort study. Front Public Health. 2022 Sep 12;10:966826. doi: 10.3389/fpubh.2022.96682
Y Bentov, O Beharier, A Moav-Zafrir, M Kabessa, M Godin, C S Greenfield, M Ketzinel-Gilad, E Ash Broder, H E G Holzer, D Wolf, E Oiknine-Djian, I Barghouti, D Goldman-Wohl, S Yagel, A Walfisch, A Hersko Klement, Ovarian follicular function is not altered by SARS–CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination, Human Reproduction, Volume 36, Issue 9, September 2021, Pages 2506–2513, https://doi.org/10.1093/humrep/deab182
https://www.medrxiv.org/content/10.1101/2022.07.07.22277371v1
https://www.medrxiv.org/content/10.1101/2022.03.30.22273165v1
https://www.medrxiv.org/content/10.1101/2021.11.23.21266709v3
https://www.medrxiv.org/content/10.1101/2022.07.30.22278213v2
Kabalkin Y, Bentov Y, Gil M, Beharier O, Jaber S, Moav-Zafrir A, Khwies D, Ben-Meir A, Esh Broder E, Walfisch A, Holzer HEG, Hershko Klement A. Mild COVID-19 Was Not Associated with Impaired IVF Outcomes or Early Pregnancy Loss in IVF Patients. J Clin Med. 2022 Sep 6;11(18):5265. doi: 10.3390/jcm11185265.
Abdollahi A, Naseh I, Kalroozi F, Kazemi-Galougahi MH, Nezamzadeh M, Sabeti Billandi S, Yousefi Zoshk M. Comparison of Side Effects of COVID-19 Vaccines: Sinopharm, AstraZeneca, Sputnik V, and Covaxin in Women in Terms of Menstruation Disturbances, Hirsutism, and Metrorrhagia: A Descriptive-Analytical Cross-Sectional Study. Int J Fertil Steril. 2022 Aug 21;16(3):237-243. doi: 10.22074/ijfs.2022.544706.1236.
Horowitz E, Mizrachi Y, Ganer Herman H, Oz Marcuschamer E, Shalev A, Farhi J, Barber E, Orna SH, Raziel A, Weissman A. The effect of SARS-CoV-2 mRNA vaccination on AMH concentrations in infertile women. Reprod Biomed Online. 2022 Jun 22;45(4):779–84. doi: 10.1016/j.rbmo.2022.06.015.
Karavani G, Chill HH, Dick A, Meirman C, Gutman-Ido E, Herzberg S, Ben-Meir A, Imbar T. Pfizer SARS-CoV-2 BNT162b2 mRNA vaccination SARS-CoV-2 mRNA vaccination (BNT162b2) has no adverse effect on elective oocyte cryopreservation outcomes. Reprod Biomed Online. 2022 Jun 8:S1472-6483(22)00410-2. doi: 10.1016/j.rbmo.2022.06.001.
Dong M, Wu S, Zhang X, Zhao N, Qi J, Zhao D, Sang Y, Tan J. Effects of COVID-19 vaccination status, vaccine type, and vaccination interval on IVF pregnancy outcomes in infertile couples. J Assist Reprod Genet. 2022 Aug;39(8):1849-1859. doi: 10.1007/s10815-022-02543-8.
Lu-Culligan A, Tabachnikova A, Pérez-Then E, Tokuyama M, Lee HJ, Lucas C, Silva Monteiro V, Miric M, Brache V, Cochon L, Muenker MC, Mohanty S, Huang J, Kang I, Dela Cruz C, Farhadian S, Campbell M, Yildirim I, Shaw AC, Ma S, Vermund SH, Ko AI, Omer SB, Iwasaki A. No evidence of fetal defects or anti-syncytin-1 antibody induction following COVID-19 mRNA vaccination. PLoS Biol. 2022 May 24;20(5):e3001506. doi: 10.1371/journal.pbio.3001506.
Castiglione Morelli MA, Iuliano A, Schettini SCA, Ferri A, Colucci P, Viggiani L, Matera I, Ostuni A. Are the Follicular Fluid Characteristics of Recovered Coronavirus Disease 2019 Patients Different From Those of Vaccinated Women Approaching in vitro Fertilization? Front Physiol. 2022 Feb 22;13:840109. doi: 10.3389/fphys.2022.840109.
Carp-Veliscu A, Mehedintu C, Frincu F, Bratila E, Rasu S, Iordache I, Bordea A, Braga M. The Effects of SARS-CoV-2 Infection on Female Fertility: A Review of the Literature. Int J Environ Res Public Health. 2022 Jan 16;19(2):984. doi: 10.3390/ijerph19020984.
Boudry L, Essahib W, Mateizel I, Van de Velde H, De Geyter D, Piérard D, Waelput W, Uvin V, Tournaye H, De Vos M, De Brucker M. Undetectable viral RNA in follicular fluid, cumulus cells, and endometrial tissue samples in SARS-CoV-2-positive women. Fertil Steril. 2022 Apr;117(4):771-780. doi: 10.1016/j.fertnstert.2021.12.032.

HPG axis in females with SARS-CoV-2 spike protein

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-Egg/E2/P | SHBG

- COVID-19 mRNA vaccies →

↑Cycle length (Pfizer → 1st dose - 0.50 days and 2nd dose - 0.39 days; Moderna → 1.26 days)

→ If vaccinated with COVID-19 mRNA in the follicular phase →

↑ ↑ Cycle length (Pfizer → 1st dose - 0.97 days and 2nd dose - 1.43 days; Moderna → 2.27 days)

→ Unrelated to symptoms after vaccinations

→ ↓ 7% AMH levels compared to prior to vaccines (ovarian reserve)

→ ↑ FSH (early sign of menopause)

↑ Ala and Pro together + ↓ lipids + ↓ trimethylamine N-oxide (TMAO) in follicular fluids (FFs)

↓ TNF-α recovered COVID-19 patients and SARS-CoV-2 vaccinated women

- Overall SARS-CoV-2 vaccines →

→ 4x higher reported changes in menstrual cycle and menopause in 2021 compared to 2020 → clear influence of the vaccines

Vaccination for COVID-19, menstrual disturbance occurred in 20% of individuals in a UK sample

→ COVID-19 before vaccines was an aggravating factor

→ Oestrogen was a protective factor

Xu Z, Wu Y, Lin Y, Cao M, Liang Z, Li L, Lin J, Chen Q, Liu J, Liu H. Effect of inactivated COVID-19 vaccination on intrauterine insemination cycle success: A retrospective cohort study. Front Public Health. 2022 Sep 12;10:966826. doi: 10.3389/fpubh.2022.96682
Y Bentov, O Beharier, A Moav-Zafrir, M Kabessa, M Godin, C S Greenfield, M Ketzinel-Gilad, E Ash Broder, H E G Holzer, D Wolf, E Oiknine-Djian, I Barghouti, D Goldman-Wohl, S Yagel, A Walfisch, A Hersko Klement, Ovarian follicular function is not altered by SARS–CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination, Human Reproduction, Volume 36, Issue 9, September 2021, Pages 2506–2513, https://doi.org/10.1093/humrep/deab182
https://www.medrxiv.org/content/10.1101/2022.07.07.22277371v1
https://www.medrxiv.org/content/10.1101/2022.03.30.22273165v1
https://www.medrxiv.org/content/10.1101/2021.11.23.21266709v3
https://www.medrxiv.org/content/10.1101/2022.07.30.22278213v2
Kabalkin Y, Bentov Y, Gil M, Beharier O, Jaber S, Moav-Zafrir A, Khwies D, Ben-Meir A, Esh Broder E, Walfisch A, Holzer HEG, Hershko Klement A. Mild COVID-19 Was Not Associated with Impaired IVF Outcomes or Early Pregnancy Loss in IVF Patients. J Clin Med. 2022 Sep 6;11(18):5265. doi: 10.3390/jcm11185265.
Abdollahi A, Naseh I, Kalroozi F, Kazemi-Galougahi MH, Nezamzadeh M, Sabeti Billandi S, Yousefi Zoshk M. Comparison of Side Effects of COVID-19 Vaccines: Sinopharm, AstraZeneca, Sputnik V, and Covaxin in Women in Terms of Menstruation Disturbances, Hirsutism, and Metrorrhagia: A Descriptive-Analytical Cross-Sectional Study. Int J Fertil Steril. 2022 Aug 21;16(3):237-243. doi: 10.22074/ijfs.2022.544706.1236.
Horowitz E, Mizrachi Y, Ganer Herman H, Oz Marcuschamer E, Shalev A, Farhi J, Barber E, Orna SH, Raziel A, Weissman A. The effect of SARS-CoV-2 mRNA vaccination on AMH concentrations in infertile women. Reprod Biomed Online. 2022 Jun 22;45(4):779–84. doi: 10.1016/j.rbmo.2022.06.015.
Karavani G, Chill HH, Dick A, Meirman C, Gutman-Ido E, Herzberg S, Ben-Meir A, Imbar T. Pfizer SARS-CoV-2 BNT162b2 mRNA vaccination SARS-CoV-2 mRNA vaccination (BNT162b2) has no adverse effect on elective oocyte cryopreservation outcomes. Reprod Biomed Online. 2022 Jun 8:S1472-6483(22)00410-2. doi: 10.1016/j.rbmo.2022.06.001.
Dong M, Wu S, Zhang X, Zhao N, Qi J, Zhao D, Sang Y, Tan J. Effects of COVID-19 vaccination status, vaccine type, and vaccination interval on IVF pregnancy outcomes in infertile couples. J Assist Reprod Genet. 2022 Aug;39(8):1849-1859. doi: 10.1007/s10815-022-02543-8.
Lu-Culligan A, Tabachnikova A, Pérez-Then E, Tokuyama M, Lee HJ, Lucas C, Silva Monteiro V, Miric M, Brache V, Cochon L, Muenker MC, Mohanty S, Huang J, Kang I, Dela Cruz C, Farhadian S, Campbell M, Yildirim I, Shaw AC, Ma S, Vermund SH, Ko AI, Omer SB, Iwasaki A. No evidence of fetal defects or anti-syncytin-1 antibody induction following COVID-19 mRNA vaccination. PLoS Biol. 2022 May 24;20(5):e3001506. doi: 10.1371/journal.pbio.3001506.
Castiglione Morelli MA, Iuliano A, Schettini SCA, Ferri A, Colucci P, Viggiani L, Matera I, Ostuni A. Are the Follicular Fluid Characteristics of Recovered Coronavirus Disease 2019 Patients Different From Those of Vaccinated Women Approaching in vitro Fertilization? Front Physiol. 2022 Feb 22;13:840109. doi: 10.3389/fphys.2022.840109.
Carp-Veliscu A, Mehedintu C, Frincu F, Bratila E, Rasu S, Iordache I, Bordea A, Braga M. The Effects of SARS-CoV-2 Infection on Female Fertility: A Review of the Literature. Int J Environ Res Public Health. 2022 Jan 16;19(2):984. doi: 10.3390/ijerph19020984.
Boudry L, Essahib W, Mateizel I, Van de Velde H, De Geyter D, Piérard D, Waelput W, Uvin V, Tournaye H, De Vos M, De Brucker M. Undetectable viral RNA in follicular fluid, cumulus cells, and endometrial tissue samples in SARS-CoV-2-positive women. Fertil Steril. 2022 Apr;117(4):771-780. doi: 10.1016/j.fertnstert.2021.12.032.

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

HPG axis in females with SARS-CoV-2 spike protein

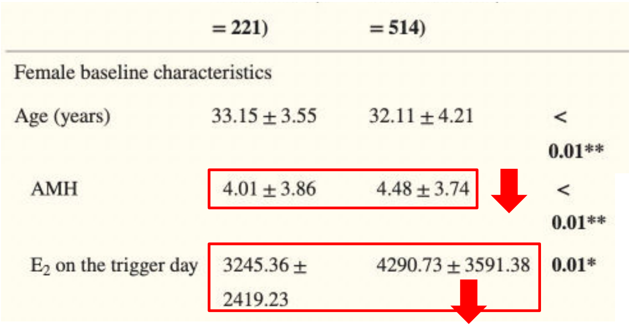
Hypothalamus

Pituitary

Anterior Pituitary

HPG axis – GnRH-LH/FSH-Egg/E2/P

SHBG



	= 221)	= 514)	
Female baseline characteristics			
Age (years)	33.15 ± 3.55	32.11 ± 4.21	< 0.01**
AMH	4.01 ± 3.86	4.48 ± 3.74	< 0.01**
E_2 on the trigger day	3245.36 ± 2419.23	4290.73 ± 3591.38	0.01*

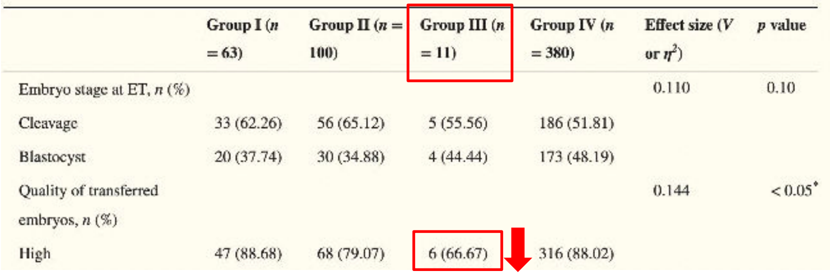
SARS-CoV-2 mRNA vaccine

↓ 10% AMH levels

↓ 20% estradiol peak

↓ Quality of transferred embryos

mRNA vaccine



	Group I (n = 63)	Group II (n = 100)	Group III (n = 11)	Group IV (n = 380)	Effect size (V or η^2)	p value
Embryo stage at ET, n (%)					0.110	0.10
Cleavage	33 (62.26)	56 (65.12)	5 (55.56)	186 (51.81)		
Blastocyst	20 (37.74)	30 (34.88)	4 (44.44)	173 (48.19)		
Quality of transferred embryos, n (%)					0.144	$< 0.05^*$
High	47 (88.68)	68 (79.07)	6 (66.67)	316 (88.02)		

Groups I/II – Innactivated virus

Group III – mRNA vaccine

Group IV – Unvaccinated

Xu Z, Wu Y, Lin Y, Cao M, Liang Z, Li L, Lin J, Chen Q, Liu J, Liu H. Effect of inactivated COVID-19 vaccination on intrauterine insemination cycle success: A retrospective cohort study. Front Public Health. 2022 Sep 12;10:966826. doi: 10.3389/fpubh.2022.96682
Y Bentov, O Beharier, A Moav-Zafrir, M Kabessa, M Godin, C S Greenfield, M Ketzinel-Gilad, E Ash Broder, H E G Holzer, D Wolf, E Oiknine-Djian, I Barghouti, D Goldman-Wohl, S Yagel, A Walfisch, A Hersko Klement, Ovarian follicular function is not altered by SARS–CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination, Human Reproduction, Volume 36, Issue 9, September 2021, Pages 2506–2513, https://doi.org/10.1093/humrep/deab182
https://www.medrxiv.org/content/10.1101/2022.07.07.22277371v1
https://www.medrxiv.org/content/10.1101/2022.03.30.22273165v1
https://www.medrxiv.org/content/10.1101/2021.11.23.21266709v3
https://www.medrxiv.org/content/10.1101/2022.07.30.22278213v2
Kabalkin Y, Bentov Y, Gil M, Beharier O, Jaber S, Moav-Zafrir A, Khwies D, Ben-Meir A, Esh Broder E, Walfisch A, Holzer HEG, Hershko Klement A. Mild COVID-19 Was Not Associated with Impaired IVF Outcomes or Early Pregnancy Loss in IVF Patients. J Clin Med. 2022 Sep 6;11(18):5265. doi: 10.3390/jcm11185265.
Abdollahi A, Naseh I, Kalroozi F, Kazemi-Galougahi MH, Nezamzadeh M, Sabeti Billandi S, Yousefi Zoshk M. Comparison of Side Effects of COVID-19 Vaccines: Sinopharm, AstraZeneca, Sputnik V, and Covaxin in Women in Terms of Menstruation Disturbances, Hirsutism, and Metrorrhagia: A Descriptive-Analytical Cross-Sectional Study. Int J Fertil Steril. 2022 Aug 21;16(3):237-243. doi: 10.22074/ijfs.2022.544706.1236.
Horowitz E, Mizrachi Y, Ganer Herman H, Oz Marcuschamer E, Shalev A, Farhi J, Barber E, Orna SH, Raziel A, Weissman A. The effect of SARS-CoV-2 mRNA vaccination on AMH concentrations in infertile women. Reprod Biomed Online. 2022 Jun 22;45(4):779–84. doi: 10.1016/j.rbmo.2022.06.015.
Karavani G, Chill HH, Dick A, Meirman C, Gutman-Ido E, Herzberg S, Ben-Meir A, Imbar T. Pfizer SARS-CoV-2 BNT162b2 mRNA vaccination SARS-CoV-2 mRNA vaccination (BNT162b2) has no adverse effect on elective oocyte cryopreservation outcomes. Reprod Biomed Online. 2022 Jun 8:S1472-6483(22)00410-2. doi: 10.1016/j.rbmo.2022.06.001.
Dong M, Wu S, Zhang X, Zhao N, Qi J, Zhao D, Sang Y, Tan J. Effects of COVID-19 vaccination status, vaccine type, and vaccination interval on IVF pregnancy outcomes in infertile couples. J Assist Reprod Genet. 2022 Aug;39(8):1849-1859. doi: 10.1007/s10815-022-02543-8.
Lu-Culligan A, Tabachnikova A, Pérez-Then E, Tokuyama M, Lee HJ, Lucas C, Silva Monteiro V, Miric M, Brache V, Cochon L, Muenker MC, Mohanty S, Huang J, Kang I, Dela Cruz C, Farhadian S, Campbell M, Yildirim I, Shaw AC, Ma S, Vermund SH, Ko AI, Omer SB, Iwasaki A. No evidence of fetal defects or anti-syncytin-1 antibody induction following COVID-19 mRNA vaccination. PLoS Biol. 2022 May 24;20(5):e3001506. doi: 10.1371/journal.pbio.3001506.
Castiglione Morelli MA, Iuliano A, Schettini SCA, Ferri A, Colucci P, Viggiani L, Matera I, Ostuni A. Are the Follicular Fluid Characteristics of Recovered Coronavirus Disease 2019 Patients Different From Those of Vaccinated Women Approaching in vitro Fertilization? Front Physiol. 2022 Feb 22;13:840109. doi: 10.3389/fphys.2022.840109.
Carp-Veliscu A, Mehedintu C, Frincu F, Bratila E, Rasu S, Iordache I, Bordea A, Braga M. The Effects of SARS-CoV-2 Infection on Female Fertility: A Review of the Literature. Int J Environ Res Public Health. 2022 Jan 16;19(2):984. doi: 10.3390/ijerph19020984.
Boudry L, Essahib W, Mateizel I, Van de Velde H, De Geyter D, Piérard D, Waelput W, Uvin V, Tournaye H, De Vos M, De Brucker M. Undetectable viral RNA in follicular fluid, cumulus cells, and endometrial tissue samples in SARS-CoV-2-positive women. Fertil Steril. 2022 Apr;117(4):771-780. doi: 10.1016/j.fertnstert.2021.12.032.

HPG axis in females with SARS-CoV-2 spike protein

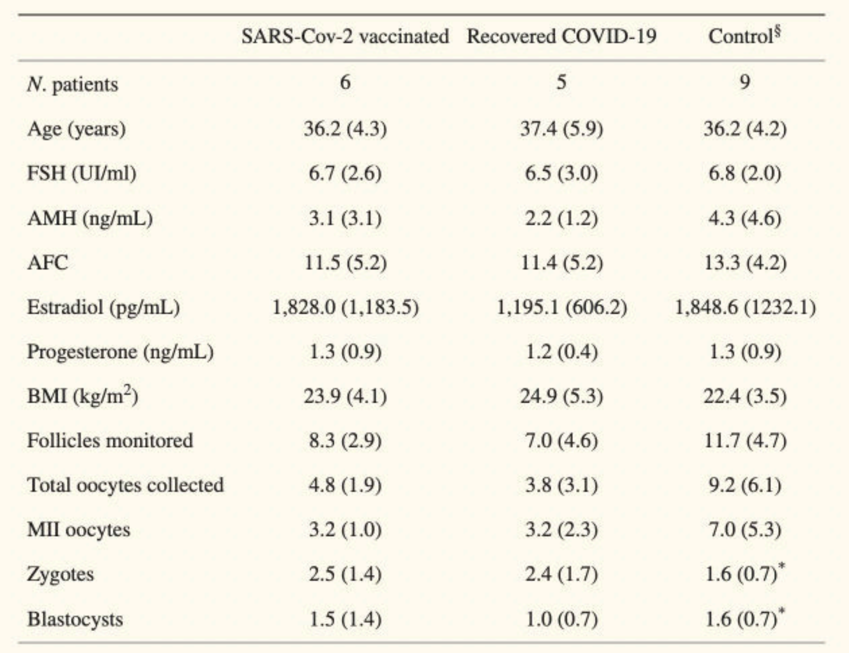
Hypothalamus

Pituitary

Anterior Pituitary

HPG axis – GnRH-LH/FSH-Egg/E2/P

SHBG



	SARS-Cov-2 vaccinated	Recovered COVID-19	Control§
N. patients	6	5	9
Age (years)	36.2 (4.3)	37.4 (5.9)	36.2 (4.2)
FSH (UI/ml)	6.7 (2.6)	6.5 (3.0)	6.8 (2.0)
AMH (ng/mL)	3.1 (3.1)	2.2 (1.2)	4.3 (4.6)
AFC	11.5 (5.2)	11.4 (5.2)	13.3 (4.2)
Estradiol (pg/mL)	1,828.0 (1,183.5)	1,195.1 (606.2)	1,848.6 (1232.1)
Progesterone (ng/mL)	1.3 (0.9)	1.2 (0.4)	1.3 (0.9)
BMI (kg/m^2)	23.9 (4.1)	24.9 (5.3)	22.4 (3.5)
Follicles monitored	8.3 (2.9)	7.0 (4.6)	11.7 (4.7)
Total oocytes collected	4.8 (1.9)	3.8 (3.1)	9.2 (6.1)
MII oocytes	3.2 (1.0)	3.2 (2.3)	7.0 (5.3)
Zygotes	2.5 (1.4)	2.4 (1.7)	1.6 (0.7)*
Blastocysts	1.5 (1.4)	1.0 (0.7)	1.6 (0.7)*

Xu Z, Wu Y, Lin Y, Cao M, Liang Z, Li L, Lin J, Chen Q, Liu J, Liu H. Effect of inactivated COVID-19 vaccination on intrauterine insemination cycle success: A retrospective cohort study. Front Public Health. 2022 Sep 12;10:966826. doi: 10.3389/fpubh.2022.96682
Y Bentov, O Beharier, A Moav-Zafrir, M Kabessa, M Godin, C S Greenfield, M Ketzinel-Gilad, E Ash Broder, H E G Holzer, D Wolf, E Oiknine-Djian, I Barghouti, D Goldman-Wohl, S Yagel, A Walfisch, A Hersko Klement, Ovarian follicular function is not altered by SARS–CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination, Human Reproduction, Volume 36, Issue 9, September 2021, Pages 2506–2513, https://doi.org/10.1093/humrep/deab182
https://www.medrxiv.org/content/10.1101/2022.07.07.22277371v1
https://www.medrxiv.org/content/10.1101/2022.03.30.22273165v1
https://www.medrxiv.org/content/10.1101/2021.11.23.21266709v3
https://www.medrxiv.org/content/10.1101/2022.07.30.22278213v2
Kabalkin Y, Bentov Y, Gil M, Beharier O, Jaber S, Moav-Zafrir A, Khwies D, Ben-Meir A, Esh Broder E, Walfisch A, Holzer HEG, Hershko Klement A. Mild COVID-19 Was Not Associated with Impaired IVF Outcomes or Early Pregnancy Loss in IVF Patients. J Clin Med. 2022 Sep 6;11(18):5265. doi: 10.3390/jcm11185265.
Abdollahi A, Naseh I, Kalroozi F, Kazemi-Galougahi MH, Nezamzadeh M, Sabeti Billandi S, Yousefi Zoshk M. Comparison of Side Effects of COVID-19 Vaccines: Sinopharm, AstraZeneca, Sputnik V, and Covaxin in Women in Terms of Menstruation Disturbances, Hirsutism, and Metrorrhagia: A Descriptive-Analytical Cross-Sectional Study. Int J Fertil Steril. 2022 Aug 21;16(3):237-243. doi: 10.22074/ijfs.2022.544706.1236.
Horowitz E, Mizrachi Y, Ganer Herman H, Oz Marcuschamer E, Shalev A, Farhi J, Barber E, Orna SH, Raziel A, Weissman A. The effect of SARS-CoV-2 mRNA vaccination on AMH concentrations in infertile women. Reprod Biomed Online. 2022 Jun 22;45(4):779–84. doi: 10.1016/j.rbmo.2022.06.015.
Karavani G, Chill HH, Dick A, Meirman C, Gutman-Ido E, Herzberg S, Ben-Meir A, Imbar T. Pfizer SARS-CoV-2 BNT162b2 mRNA vaccination SARS-CoV-2 mRNA vaccination (BNT162b2) has no adverse effect on elective oocyte cryopreservation outcomes. Reprod Biomed Online. 2022 Jun 8:S1472-6483(22)00410-2. doi: 10.1016/j.rbmo.2022.06.001.
Dong M, Wu S, Zhang X, Zhao N, Qi J, Zhao D, Sang Y, Tan J. Effects of COVID-19 vaccination status, vaccine type, and vaccination interval on IVF pregnancy outcomes in infertile couples. J Assist Reprod Genet. 2022 Aug;39(8):1849-1859. doi: 10.1007/s10815-022-02543-8.
Lu-Culligan A, Tabachnikova A, Pérez-Then E, Tokuyama M, Lee HJ, Lucas C, Silva Monteiro V, Miric M, Brache V, Cochon L, Muenker MC, Mohanty S, Huang J, Kang I, Dela Cruz C, Farhadian S, Campbell M, Yildirim I, Shaw AC, Ma S, Vermund SH, Ko AI, Omer SB, Iwasaki A. No evidence of fetal defects or anti-syncytin-1 antibody induction following COVID-19 mRNA vaccination. PLoS Biol. 2022 May 24;20(5):e3001506. doi: 10.1371/journal.pbio.3001506.
Castiglione Morelli MA, Iuliano A, Schettini SCA, Ferri A, Colucci P, Viggiani L, Matera I, Ostuni A. Are the Follicular Fluid Characteristics of Recovered Coronavirus Disease 2019 Patients Different From Those of Vaccinated Women Approaching in vitro Fertilization? Front Physiol. 2022 Feb 22;13:840109. doi: 10.3389/fphys.2022.840109.
Carp-Veliscu A, Mehedintu C, Frincu F, Bratila E, Rasu S, Iordache I, Bordea A, Braga M. The Effects of SARS-CoV-2 Infection on Female Fertility: A Review of the Literature. Int J Environ Res Public Health. 2022 Jan 16;19(2):984. doi: 10.3390/ijerph19020984.
Boudry L, Essahib W, Mateizel I, Van de Velde H, De Geyter D, Piérard D, Waelput W, Uvin V, Tournaye H, De Vos M, De Brucker M. Undetectable viral RNA in follicular fluid, cumulus cells, and endometrial tissue samples in SARS-CoV-2-positive women. Fertil Steril. 2022 Apr;117(4):771-780. doi: 10.1016/j.fertnstert.2021.12.032.

HPG axis in females with SARS-CoV-2 spike protein

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-Egg/E2/P | SHBG

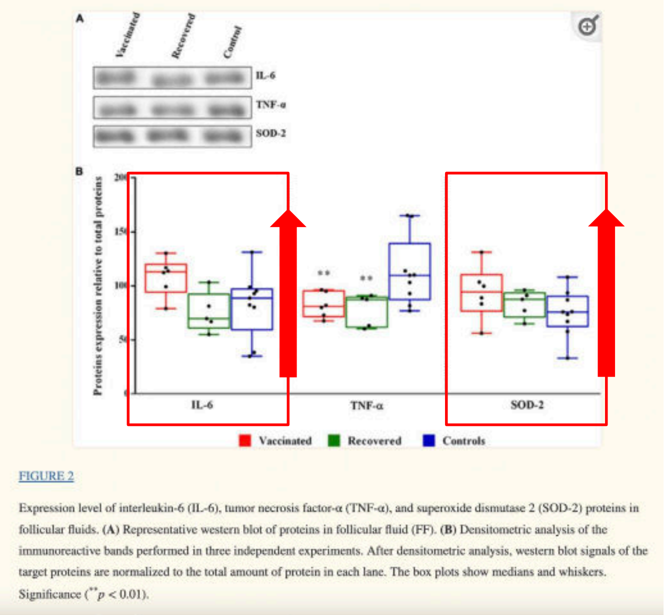


FIGURE 2

Expression level of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and superoxide dismutase 2 (SOD-2) proteins in follicular fluids. **(A)** Representative western blot of proteins in follicular fluid (FF). **(B)** Densitometric analysis of the immunoreactive bands performed in three independent experiments. After densitometric analysis, western blot signals of the target proteins are normalized to the total amount of protein in each lane. The box plots show medians and whiskers. Significance ($^{**}p < 0.01$).

SARS-CoV-2 mRNA vaccine

↑ IL-6 (bad for fertility)
↑ SOD-2 (good for fertility)

Xu Z, Wu Y, Lin Y, Cao M, Liang Z, Li L, Lin J, Chen Q, Liu J, Liu H. Effect of inactivated COVID-19 vaccination on intrauterine insemination cycle success: A retrospective cohort study. Front Public Health. 2022 Sep 12;10:966826. doi: 10.3389/fpubh.2022.96682
Y Bentov, O Beharier, A Moav-Zafrir, M Kabessa, M Godin, C S Greenfield, M Ketzinel-Gilad, E Ash Broder, H E G Holzer, D Wolf, E Oiknine-Djian, I Barghouti, D Goldman-Wohl, S Yagel, A Walfisch, A Hersko Klement, Ovarian follicular function is not altered by SARS–CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination, Human Reproduction, Volume 36, Issue 9, September 2021, Pages 2506–2513, https://doi.org/10.1093/humrep/deab182
https://www.medrxiv.org/content/10.1101/2022.07.07.22277371v1
https://www.medrxiv.org/content/10.1101/2022.03.30.22273165v1
https://www.medrxiv.org/content/10.1101/2021.11.23.21266709v3
https://www.medrxiv.org/content/10.1101/2022.07.30.22278213v2
Kabalkin Y, Bentov Y, Gil M, Beharier O, Jaber S, Moav-Zafrir A, Khwies D, Ben-Meir A, Esh Broder E, Walfisch A, Holzer HEG, Hershko Klement A. Mild COVID-19 Was Not Associated with Impaired IVF Outcomes or Early Pregnancy Loss in IVF Patients. J Clin Med. 2022 Sep 6;11(18):5265. doi: 10.3390/jcm11185265.
Abdollahi A, Naseh I, Kalroozi F, Kazemi-Galougahi MH, Nezamzadeh M, Sabeti Billandi S, Yousefi Zoshk M. Comparison of Side Effects of COVID-19 Vaccines: Sinopharm, AstraZeneca, Sputnik V, and Covaxin in Women in Terms of Menstruation Disturbances, Hirsutism, and Metrorrhagia: A Descriptive-Analytical Cross-Sectional Study. Int J Fertil Steril. 2022 Aug 21;16(3):237-243. doi: 10.22074/ijfs.2022.544706.1236.
Horowitz E, Mizrachi Y, Ganer Herman H, Oz Marcuschamer E, Shalev A, Farhi J, Barber E, Orna SH, Raziel A, Weissman A. The effect of SARS-CoV-2 mRNA vaccination on AMH concentrations in infertile women. Reprod Biomed Online. 2022 Jun 22;45(4):779–84. doi: 10.1016/j.rbmo.2022.06.015.
Karavani G, Chill HH, Dick A, Meirman C, Gutman-Ido E, Herzberg S, Ben-Meir A, Imbar T. Pfizer SARS-CoV-2 BNT162b2 mRNA vaccination SARS-CoV-2 mRNA vaccination (BNT162b2) has no adverse effect on elective oocyte cryopreservation outcomes. Reprod Biomed Online. 2022 Jun 8:S1472-6483(22)00410-2. doi: 10.1016/j.rbmo.2022.06.001.
Dong M, Wu S, Zhang X, Zhao N, Qi J, Zhao D, Sang Y, Tan J. Effects of COVID-19 vaccination status, vaccine type, and vaccination interval on IVF pregnancy outcomes in infertile couples. J Assist Reprod Genet. 2022 Aug;39(8):1849-1859. doi: 10.1007/s10815-022-02543-8.
Lu-Culligan A, Tabachnikova A, Pérez-Then E, Tokuyama M, Lee HJ, Lucas C, Silva Monteiro V, Miric M, Brache V, Cochon L, Muenker MC, Mohanty S, Huang J, Kang I, Dela Cruz C, Farhadian S, Campbell M, Yildirim I, Shaw AC, Ma S, Vermund SH, Ko AI, Omer SB, Iwasaki A. No evidence of fetal defects or anti-syncytin-1 antibody induction following COVID-19 mRNA vaccination. PLoS Biol. 2022 May 24;20(5):e3001506. doi: 10.1371/journal.pbio.3001506.
Castiglione Morelli MA, Iuliano A, Schettini SCA, Ferri A, Colucci P, Viggiani L, Matera I, Ostuni A. Are the Follicular Fluid Characteristics of Recovered Coronavirus Disease 2019 Patients Different From Those of Vaccinated Women Approaching in vitro Fertilization? Front Physiol. 2022 Feb 22;13:840109. doi: 10.3389/fphys.2022.840109.
Carp-Veliscu A, Mehedintu C, Frincu F, Bratila E, Rasu S, Iordache I, Bordea A, Braga M. The Effects of SARS-CoV-2 Infection on Female Fertility: A Review of the Literature. Int J Environ Res Public Health. 2022 Jan 16;19(2):984. doi: 10.3390/ijerph19020984.
Boudry L, Essahib W, Mateizel I, Van de Velde H, De Geyter D, Piérard D, Waelput W, Uvin V, Tournaye H, De Vos M, De Brucker M. Undetectable viral RNA in follicular fluid, cumulus cells, and endometrial tissue samples in SARS-CoV-2-positive women. Fertil Steril. 2022 Apr;117(4):771-780. doi: 10.1016/j.fertnstert.2021.12.032.

HPG axis in females with SARS-CoV-2 spike protein - Summary

Hypothalamus
Pituitary
Anterior Pituitary
HPG axis – GnRH-LH/FSH-Egg/E2/P
SHBG

Early

1. Vaginal fluid positive
2. Increased risk for premature delivery
3. Vertical transmission not confirmed

Late

1. Adverse pregnancy outcomes
2. Adverse perinatal outcomes

Proposed mechanisms

1. Inflammation

Mirza SA, Sheikh AAE, Barbera M, Ijaz Z, Javaid MA, Shekhar R, Pal S, Sheikh AB. COVID-19 and the Endocrine System: A Review of the Current Information and Misinformation. Infect Dis Rep. 2022 Mar 11;14(2):184-197. doi: 10.3390/idr14020023.

Lipkind H.S., Vazquez-Benitez G., DeSilva M., Vesco K.K., Ackerman-Banks C., Zhu J., Boyce T.G., Daley M.F., Fuller C.C., Getahun D., et al. Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth—Eight Integrated Health Care Organizations, United States, December 15, 2020–July 22, 2021. Morb. Mortal. Wkly. Rep. 2022;71:26–30.

Blakeway H., Prasad S., Kalafat E., Heath P.T., Ladhani S.N., Le Doare K., Magee L.A., O'Brien P., Rezvani A., von Dadelszen P., et al. COVID-19 vaccination during pregnancy: Coverage and safety. Am. J. Obstet. Gynecol. 2022;226:236.e1–236.e14. doi: 10.1016/j.ajog.2021.08.007.

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

HPG axis in females with SARS-CoV-2 spike protein - expected

Hypothalamus

Pituitary

Anterior Pituitary

HPG axis – GnRH-LH/FSH-Egg/E2/P

SHBG

Predicted (not based on current evidence)

↑/=/↓ SHBG

↑/↓ Estradiol

↑/↓ LH

↑/↓ GnRH

↑/↓ Progesterone

↑/↓ FSH

↓ Ovulation

↓ AMH

? DHT

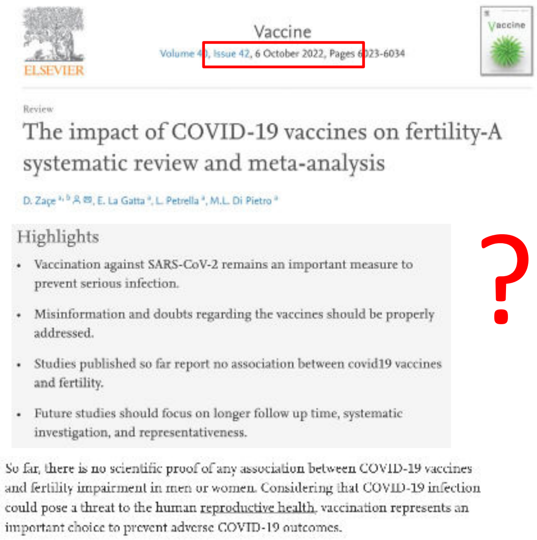
? Testosterone

↑ Estrone

Mirza SA, Sheikh AAE, Barbera M, Ijaz Z, Javaid MA, Shekhar R, Pal S, Sheikh AB. COVID-19 and the Endocrine System: A Review of the Current Information and Misinformation. Infect Dis Rep. 2022 Mar 11;14(2):184-197. doi: 10.3390/idr14020023.
Lipkind H.S., Vazquez-Benitez G., DeSilva M., Vesco K.K., Ackerman-Banks C., Zhu J., Boyce T.G., Daley M.F., Fuller C.C., Getahun D., et al. Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth—Eight Integrated Health Care Organizations, United States, December 15, 2020–July 22, 2021. Morb. Mortal. Wkly. Rep. 2022;71:26–30.
Blakeway H., Prasad S., Kalafat E., Heath P.T., Ladhani S.N., Le Doare K., Magee L.A., O'Brien P., Rezvani A., von Dadelszen P., et al. COVID-19 vaccination during pregnancy: Coverage and safety. Am. J. Obstet. Gynecol. 2022;226:236.e1–236.e14. doi: 10.1016/j.ajog.2021.08.007.

HPG axis in females with SARS-CoV-2 spike protein

Hypothalamus | Pituitary | Anterior Pituitary | HPG axis – GnRH-LH/FSH-Egg/E2/P | SHBG



ELSEVIER

Vaccine

Volume 40, Issue 42, 6 October 2022, Pages 6023-6034

Review

The impact of COVID-19 vaccines on fertility-A systematic review and meta-analysis

D. Zaçe [a, b], E. La Gatta [a], L. Petrella [a], M.L. Di Pietro [a]

Highlights

- Vaccination against SARS-CoV-2 remains an important measure to prevent serious infection.
- Misinformation and doubts regarding the vaccines should be properly addressed.
- Studies published so far report no association between covid19 vaccines and fertility.
- Future studies should focus on longer follow up time, systematic investigation, and representativeness.

So far, there is no scientific proof of any association between COVID-19 vaccines and fertility impairment in men or women. Considering that COVID-19 infection could pose a threat to the human reproductive health, vaccination represents an important choice to prevent adverse COVID-19 outcomes.

?

FLCCC
ALLIANCE
EDUCATIONAL
CONFERENCE
2022

https://www.sciencedirect.com/science/article/pii/S0264410X22011185?via%3Dihub

HPG axis in females with SARS-CoV-2 spike protein

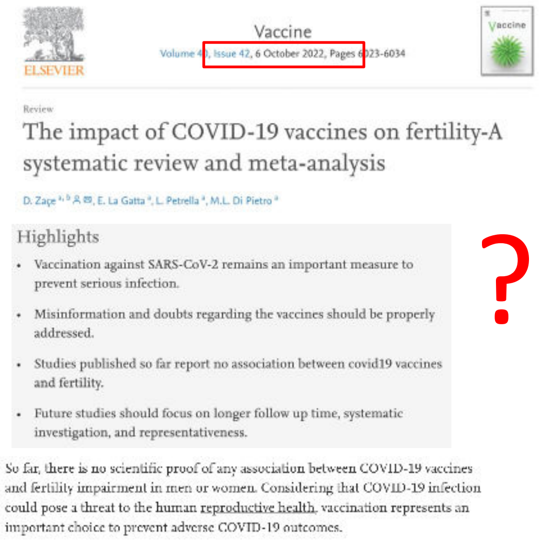
Hypothalamus

Pituitary

Anterior Pituitary

HPG axis – GnRH-LH/FSH-Egg/E2/P

SHBG


ELSEVIER

Vaccine

Volume 40, Issue 42, 6 October 2022, Pages 6023-6034

Review

The impact of COVID-19 vaccines on fertility-A systematic review and meta-analysis

D. Zaçe [a, b], E. La Gatta [a], L. Petrella [a], M.L. Di Pietro [a]

Highlights

- Vaccination against SARS-CoV-2 remains an important measure to prevent serious infection.
- Misinformation and doubts regarding the vaccines should be properly addressed.
- Studies published so far report no association between covid19 vaccines and fertility.
- Future studies should focus on longer follow up time, systematic investigation, and representativeness.

So far, there is no scientific proof of any association between COVID-19 vaccines and fertility impairment in men or women. Considering that COVID-19 infection could pose a threat to the human reproductive health, vaccination represents an important choice to prevent adverse COVID-19 outcomes.

?

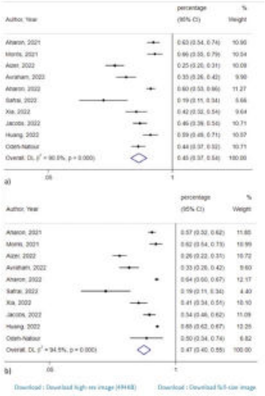


Fig. 6. Clinical pregnancy rate in the a) vaccinated and b) non vaccinated group.

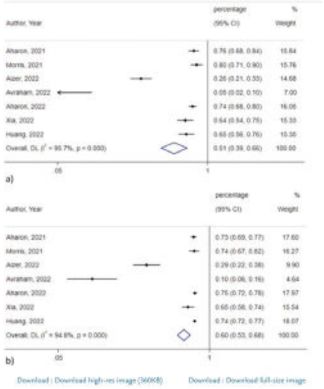


Fig. 5. Biochemical pregnancy rate in the a) vaccinated and b) non vaccinated group.

SARS-CoV-2 vaccine

↓ 20% biochemical pregnancy rate

↓ 5% clinical pregnancy rate

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

https://www.sciencedirect.com/science/article/pii/S0264410X22011185?via%3Dihub

Pancreas and SARS-CoV-2 spike protein

Pancreas

Insulin

Glucagon

- SARS-CoV-2 vaccines → potential to impair glucose metabolism

- Post-vaccination immune response

→ Transient worsening of hyperglycemia and hyperglycemic emergencies

- Individual Case Safety Reports (ICSRs) in the European database (Eudravigilance, EV).

- 4275 impaired glucose metabolism events:

Most reported event → "High glucose levels" (n=2012; 47.06%).

Yakou F, Saburi M, Hirose A, Akaoka H, Hirota Y, Kobayashi T, Awane N, Asahi N, Amagawa T, Ozawa S, Ohno A, Matsushita T. A Case Series of Ketoacidosis After Coronavirus Disease 2019 Vaccination in Patients With Type 1 Diabetes. Front Endocrinol (Lausanne). 2022 Mar 18;13:840580. doi: 10.3389/fendo.2022.840580.
di Mauro G, Mascolo A, Longo M, Maiorino MI, Scappaticcio L, Bellastella G, Esposito K, Capuano A. European Safety Analysis of mRNA and Viral Vector COVID-19 Vaccines on Glucose Metabolism Events. Pharmaceuticals (Basel). 2022 May 27;15(6):677. doi: 10.3390/ph15060677.
Yano M, Morioka T, Natsuki Y, Sasaki K, Kakutani Y, Ochi A, Yamazaki Y, Shoji T, Emoto M. New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination. Intern Med. 2022 Apr 15;61(8):1197-1200. doi: 10.2169/internalmedicine.9004-21.
Sasaki H, Itoh A, Watanabe Y, Nakajima Y, Saisho Y, Irie J, Meguro S, Itoh H. Newly developed type 1 diabetes after coronavirus disease 2019 vaccination: A case report. J Diabetes Investig. 2022 Jun;13(6):1105-1108. doi: 10.1111/jdi.13757.
Sakurai K, Narita D, Saito N, Ueno T, Sato R, Niitsuma S, Takahashi K, Arihara Z. Type 1 diabetes mellitus following COVID-19 RNA-based vaccine. J Diabetes Investig. 2022 Jul;13(7):1290-1292. doi: 10.1111/jdi.13781.
Ganakumar V, Jethwani P, Roy A, Shukla R, Mittal M, Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination. Diabetes Metab Syndr. 2022 Jan;16(1):102371. doi: 10.1016/j.dsx.2021.102371.
Mishra A., Ghosh A., Dutta K., Tyagi K., Misra A. Exacerbation of hyperglycemia in patients with type 2 diabetes after vaccination for COVID19: Report of three cases. *Diabetes Metab. Syndr.* 2021;15:102151. doi: 10.1016/j.dsx.2021.05.024.
Heald A., Rea R., Horne L., Metters A., Steele T., Leivesley K., Whyte M.B., Stedman M., Ollier W. Analysis of continuous glucose tracking data in people with Type 1 Diabetes (T1DM) after COVID-19 Vaccination reveals unexpected link between immune and metabolic response, augmented by adjunctive oral medication. *Int. J. Clin. Pract.* 2021;75:e14714. doi: 10.1111/ijcp.14714.

Pancreas and SARS-CoV-2 spike protein

- mRNA SARS-CoV-2 vaccines →

a. ↑86% T1DM (ROR 1.86; 95% CI 1.33-2.60)

b. ↑ 58% Type 2 diabetes mellitus (T2DM) (ROR 1.58; 95% CI 1.03-2.42)

c. ↑ 16% ”High glucose levels" (ROR 1.16; 95% CI 1.06-1.27)

d. ↑ 63% ”Uncontrolled DM" (ROR 1.63; 95% CI 1.25-2.11)

e. ↑ 62% ”Hypoglycemia" (ROR 1.62; 95% CI 1.41-1.86)

Compared to viral vector SARS-CoV-2 vaccines.

→ → → mRNA SARS-CoV-2 vaccines → Substantially more harmful to glucose metabolism

- Viral vector and innactivated vaccines →

Severe diabetic ketoacidosis in previously controlled T1DM

Yakou F, Saburi M, Hirose A, Akaoka H, Hirota Y, Kobayashi T, Awane N, Asahi N, Amagawa T, Ozawa S, Ohno A, Matsushita T. A Case Series of Ketoacidosis After Coronavirus Disease 2019 Vaccination in Patients With Type 1 Diabetes. Front Endocrinol (Lausanne). 2022 Mar 18;13:840580. doi: 10.3389/fendo.2022.840580.
di Mauro G, Mascolo A, Longo M, Maiorino MI, Scappaticcio L, Bellastella G, Esposito K, Capuano A. European Safety Analysis of mRNA and Viral Vector COVID-19 Vaccines on Glucose Metabolism Events. Pharmaceuticals (Basel). 2022 May 27;15(6):677. doi: 10.3390/ph15060677.
Yano M, Morioka T, Natsuki Y, Sasaki K, Kakutani Y, Ochi A, Yamazaki Y, Shoji T, Emoto M. New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination. Intern Med. 2022 Apr 15;61(8):1197-1200. doi: 10.2169/internalmedicine.9004-21.
Sasaki H, Itoh A, Watanabe Y, Nakajima Y, Saisho Y, Irie J, Meguro S, Itoh H. Newly developed type 1 diabetes after coronavirus disease 2019 vaccination: A case report. J Diabetes Investig. 2022 Jun;13(6):1105-1108. doi: 10.1111/jdi.13757.
Sakurai K, Narita D, Saito N, Ueno T, Sato R, Niitsuma S, Takahashi K, Arihara Z. Type 1 diabetes mellitus following COVID-19 RNA-based vaccine. J Diabetes Investig. 2022 Jul;13(7):1290-1292. doi: 10.1111/jdi.13781.
Ganakumar V, Jethwani P, Roy A, Shukla R, Mittal M, Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination. Diabetes Metab Syndr. 2022 Jan;16(1):102371. doi: 10.1016/j.dsx.2021.102371.
Mishra A., Ghosh A., Dutta K., Tyagi K., Misra A. Exacerbation of hyperglycemia in patients with type 2 diabetes after vaccination for COVID19: Report of three cases. *Diabetes Metab. Syndr.* 2021;15:102151. doi: 10.1016/j.dsx.2021.05.024.
Heald A., Rea R., Horne L., Metters A., Steele T., Leivesley K., Whyte M.B., Stedman M., Ollier W. Analysis of continuous glucose tracking data in people with Type 1 Diabetes (T1DM) after COVID-19 Vaccination reveals unexpected link between immune and metabolic response, augmented by adjunctive oral medication. *Int. J. Clin. Pract.* 2021;75:e14714. doi: 10.1111/ijcp.14714.

Pancreas and SARS-CoV-2 spike protein

Pancreas

Insulin

Glucagon

- Illustrative case reports:

- mRNA vaccine (Moderna) - 73 y/o woman – 8 weeks after - new-onset type 1 diabetes

- mRNA vaccine - 36 y/o woman – 3-10 days later - new-onset type 1 diabetes discovered through diabetic ketoacidosis with negative islet-related autoantibodies

- mRNA vaccine - 58 y/o man - 2 days later (21 days after 1st dose)- Hyperosmolar Hyperglycemic State in non-previous T2DM (Nocturia, polyuria, polydipsia, altered mental status, weight loss

- Viral vector - 3 cases – 50-60 y/o - Exacerbation of hyperglycemia in pre-existing Type 2 Diabetes Mellitus

- 20 patients – 8 mRNA / 12 viral vector - Transient hypoglycemia in T1DM

- mRNA vaccine - Case 1. Insulin + SGLT-2 inhibitor | Case 2. Insulin

Yakou F, Saburi M, Hirose A, Akaoka H, Hirota Y, Kobayashi T, Awane N, Asahi N, Amagawa T, Ozawa S, Ohno A, Matsushita T. A Case Series of Ketoacidosis After Coronavirus Disease 2019 Vaccination in Patients With Type 1 Diabetes. Front Endocrinol (Lausanne). 2022 Mar 18;13:840580. doi: 10.3389/fendo.2022.840580.
di Mauro G, Mascolo A, Longo M, Maiorino MI, Scappaticcio L, Bellastella G, Esposito K, Capuano A. European Safety Analysis of mRNA and Viral Vector COVID-19 Vaccines on Glucose Metabolism Events. Pharmaceuticals (Basel). 2022 May 27;15(6):677. doi: 10.3390/ph15060677.
Yano M, Morioka T, Natsuki Y, Sasaki K, Kakutani Y, Ochi A, Yamazaki Y, Shoji T, Emoto M. New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination. Intern Med. 2022 Apr 15;61(8):1197-1200. doi: 10.2169/internalmedicine.9004-21.
Sasaki H, Itoh A, Watanabe Y, Nakajima Y, Saisho Y, Irie J, Meguro S, Itoh H. Newly developed type 1 diabetes after coronavirus disease 2019 vaccination: A case report. J Diabetes Investig. 2022 Jun;13(6):1105-1108. doi: 10.1111/jdi.13757.
Sakurai K, Narita D, Saito N, Ueno T, Sato R, Niitsuma S, Takahashi K, Arihara Z. Type 1 diabetes mellitus following COVID-19 RNA-based vaccine. J Diabetes Investig. 2022 Jul;13(7):1290-1292. doi: 10.1111/jdi.13781.
Ganakumar V, Jethwani P, Roy A, Shukla R, Mittal M, Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination. Diabetes Metab Syndr. 2022 Jan;16(1):102371. doi: 10.1016/j.dsx.2021.102371.
Mishra A., Ghosh A., Dutta K., Tyagi K., Misra A. Exacerbation of hyperglycemia in patients with type 2 diabetes after vaccination for COVID19: Report of three cases. *Diabetes Metab. Syndr.* 2021;15:102151. doi: 10.1016/j.dsx.2021.05.024.
Heald A., Rea R., Horne L., Metters A., Steele T., Leivesley K., Whyte M.B., Stedman M., Ollier W. Analysis of continuous glucose tracking data in people with Type 1 Diabetes (T1DM) after COVID-19 Vaccination reveals unexpected link between immune and metabolic response, augmented by adjunctive oral medication. *Int. J. Clin. Pract.* 2021;75:e14714. doi: 10.1111/ijcp.14714.

Pancreas and SARS-CoV-2 spike protein - Summary

Pancreas

Insulin

Glucagon

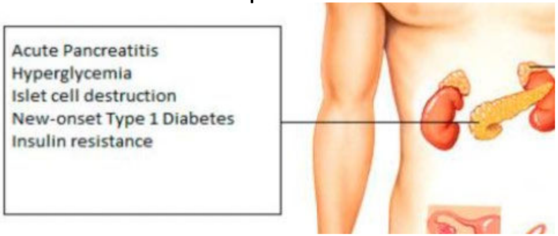
Early

1. Hyperglycemia on admission/during hospitalization
2. New presentation of DM with DKA or hyperosmolarity
3. DM or precipitation of T1DM
4. Aggravation of glycemic control in preexisting DM

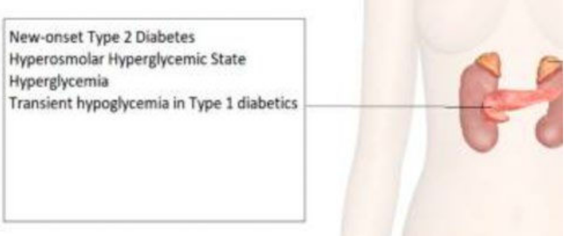
Late

1. Permanent dysregulation of glucose homeostasis
2. T1DM or T2DM
3. Alteration of pathophysiology of DM

Expected



Confirmed



FLCCC
ALLIANCE
EDUCATIONAL CONFERENCE
2022

Yakou F, Saburi M, Hirose A, Akaoka H, Hirota Y, Kobayashi T, Awane N, Asahi N, Amagawa T, Ozawa S, Ohno A, Matsushita T. A Case Series of Ketoacidosis After Coronavirus Disease 2019 Vaccination in Patients With Type 1 Diabetes. Front Endocrinol (Lausanne). 2022 Mar 18;13:840580. doi: 10.3389/fendo.2022.840580.
di Mauro G, Mascolo A, Longo M, Maiorino MI, Scappaticcio L, Bellastella G, Esposito K, Capuano A. European Safety Analysis of mRNA and Viral Vector COVID-19 Vaccines on Glucose Metabolism Events. Pharmaceuticals (Basel). 2022 May 27;15(6):677. doi: 10.3390/ph15060677.
Yano M, Morioka T, Natsuki Y, Sasaki K, Kakutani Y, Ochi A, Yamazaki Y, Shoji T, Emoto M. New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination. Intern Med. 2022 Apr 15;61(8):1197-1200. doi: 10.2169/internalmedicine.9004-21.
Sasaki H, Itoh A, Watanabe Y, Nakajima Y, Saisho Y, Irie J, Meguro S, Itoh H. Newly developed type 1 diabetes after coronavirus disease 2019 vaccination: A case report. J Diabetes Investig. 2022 Jun;13(6):1105-1108. doi: 10.1111/jdi.13757.
Sakurai K, Narita D, Saito N, Ueno T, Sato R, Niitsuma S, Takahashi K, Arihara Z. Type 1 diabetes mellitus following COVID-19 RNA-based vaccine. J Diabetes Investig. 2022 Jul;13(7):1290-1292. doi: 10.1111/jdi.13781.
Ganakumar V, Jethwani P, Roy A, Shukla R, Mittal M, Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination. Diabetes Metab Syndr. 2022 Jan;16(1):102371. doi: 10.1016/j.dsx.2021.102371.
Mishra A., Ghosh A., Dutta K., Tyagi K., Misra A. Exacerbation of hyperglycemia in patients with type 2 diabetes after vaccination for COVID19: Report of three cases. *Diabetes Metab. Syndr.* 2021;15:102151. doi: 10.1016/j.dsx.2021.05.024.
Heald A., Rea R., Horne L., Metters A., Steele T., Leivesley K., Whyte M.B., Stedman M., Ollier W. Analysis of continuous glucose tracking data in people with Type 1 Diabetes (T1DM) after COVID-19 Vaccination reveals unexpected link between immune and metabolic response, augmented by adjunctive oral medication. *Int. J. Clin. Pract.* 2021;75:e14714. doi: 10.1111/ijcp.14714.

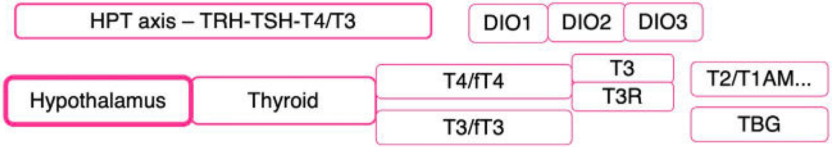
Pancreas and SARS-CoV-2 spike protein - Summary

Proposed mechanisms

1. Pancreatic β-cell loss or malfunction: cytolytic effect of the virus on β-cells
2. Morphological, transcriptional, and functional changes of β-cells by SARS-CoV-2 infection
3. Effect of the virus on exocrine pancreas (pancreatitis)
4. Hyperinflammation/cytokine storm
5. Hypokalemia through reduction of ACE2 expression may decrease insulin secretion
6. Drugs (corticosteroids, antivirals)
7. Cahexia, muscle weakness, rhabdomyolysis lead to decreased insulin sensitivity
8. DPP4 potential SARS-CoV-2 receptor

Yakou F, Saburi M, Hirose A, Akaoka H, Hirota Y, Kobayashi T, Awane N, Asahi N, Amagawa T, Ozawa S, Ohno A, Matsushita T. A Case Series of Ketoacidosis After Coronavirus Disease 2019 Vaccination in Patients With Type 1 Diabetes. Front Endocrinol (Lausanne). 2022 Mar 18;13:840580. doi: 10.3389/fendo.2022.840580.
di Mauro G, Mascolo A, Longo M, Maiorino MI, Scappaticcio L, Bellastella G, Esposito K, Capuano A. European Safety Analysis of mRNA and Viral Vector COVID-19 Vaccines on Glucose Metabolism Events. Pharmaceuticals (Basel). 2022 May 27;15(6):677. doi: 10.3390/ph15060677.
Yano M, Morioka T, Natsuki Y, Sasaki K, Kakutani Y, Ochi A, Yamazaki Y, Shoji T, Emoto M. New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination. Intern Med. 2022 Apr 15;61(8):1197-1200. doi: 10.2169/internalmedicine.9004-21.
Sasaki H, Itoh A, Watanabe Y, Nakajima Y, Saisho Y, Irie J, Meguro S, Itoh H. Newly developed type 1 diabetes after coronavirus disease 2019 vaccination: A case report. J Diabetes Investig. 2022 Jun;13(6):1105-1108. doi: 10.1111/jdi.13757.
Sakurai K, Narita D, Saito N, Ueno T, Sato R, Niitsuma S, Takahashi K, Arihara Z. Type 1 diabetes mellitus following COVID-19 RNA-based vaccine. J Diabetes Investig. 2022 Jul;13(7):1290-1292. doi: 10.1111/jdi.13781.
Ganakumar V, Jethwani P, Roy A, Shukla R, Mittal M, Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination. Diabetes Metab Syndr. 2022 Jan;16(1):102371. doi: 10.1016/j.dsx.2021.102371.
Mishra A., Ghosh A., Dutta K., Tyagi K., Misra A. Exacerbation of hyperglycemia in patients with type 2 diabetes after vaccination for COVID19: Report of three cases. *Diabetes Metab. Syndr.* 2021;15:102151. doi: 10.1016/j.dsx.2021.05.024.
Heald A., Rea R., Horne L., Metters A., Steele T., Leivesley K., Whyte M.B., Stedman M., Ollier W. Analysis of continuous glucose tracking data in people with Type 1 Diabetes (T1DM) after COVID-19 Vaccination reveals unexpected link between immune and metabolic response, augmented by adjunctive oral medication. *Int. J. Clin. Pract.* 2021;75:e14714. doi: 10.1111/ijcp.14714.

Thyroid and SARS-CoV-2 spike protein



HPT axis – TRH-TSH-T4/T3

DIO1 DIO2 DIO3

Hypothalamus

Thyroid

T4/fT4

T3/fT3

T3

T3R

T2/T1AM...

TBG

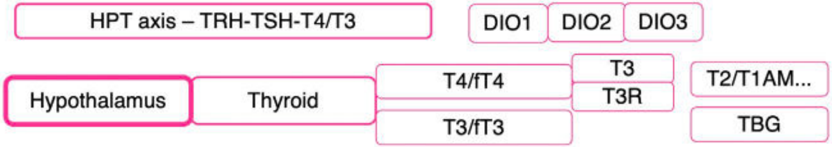
- Almost 90% of thyroid tissues are affected
  - SARS-CoV-2 spike protein → All tissue (seen in autopsies)
  - SARS-CoV-2 mRNA (follicular cells)

- Thyroiditis
  - Linked to COVID-19 vaccines
  - Not linked to COVID-19 infection as per population-based prospective studies

- ACE-2, TMPRSS-2, and furin (main proteins for SARS-CoV-2 cell entry)
  - Previously: Not described on the thyroid
  - Now: SARS-CoV-2 receptors are ubiquitously present

Macedo S, Pestana A, Santos L, Neves C, Guimarães S, Duarte-Neto A, Dolhnikoff M, Saldiva P, Alves G, Oliveira R, Cabanes D, Carneiro F, Sobrinho-Simões M, Soares P. Detection of SARS-CoV-2 infection in thyroid follicular cells from a COVID-19 autopsy series. Eur Thyroid J. 2022 Jul 19;11(4):e220074. doi: 10.1530/ETJ-22-0074.
Oğuz SH, Şendur SN, İremli BG, Gürlek A, Erbas T, Ünlütürk U. SARS-CoV-2 Vaccine-induced Thyroiditis: Safety of Revaccinations and Clinical Follow-up. J Clin Endocrinol Metab. 2022 Apr 19;107(5):e1823-e1834. doi: 10.1210/clinem/dgac049.
Wang XM, Mannan R, Xiao L, Abdulfatah E, Qiao Y, Farver C, Myers JL, Zelenka-Wang S, McMurry L, Su F, Wang R, Pantanowitz L, Jentzen J, Wilson A, Zhang Y, Cao X, Chinnaiyan AM, Mehra R. Characterization of SARS-CoV-2 and host entry factors distribution in a COVID-19 autopsy series. Commun Med (Lond). 2021 Aug 23;1:24. doi: 10.1038/s43856-021-00025-z.
Weintraub MA, Ameer B, Sinha Gregory N. Graves Disease Following the SARS-CoV-2 Vaccine: Case Series. J Investig Med High Impact Case Rep. 2021 Jan-Dec;9:23247096211063356. doi: 10.1177/23247096211063356.
Siolos A, Gartzonika K, Tigas S. Thyroiditis following vaccination against COVID-19: Report of two cases and review of the literature. Metabol Open. 2021 Dec;12:100136. doi: 10.1016/j.metop.2021.100136.
Bahçecioğlu AB, Karahan ZC, Aydoğan BI, Kalkan IA, Azap A, Erdoğan MF. Subacute thyroiditis during the COVID-19 pandemic: a prospective study. J Endocrinol Invest. 2022 Apr;45(4):865-874. doi: 10.1007/s40618-021-01718-x.
Vu TB, Chu DT, Le DT, Hoang TTD, Gautret P, Hoang VT. Subacute thyroiditis after receiving the vaccine for COVID-19: a case report and literature review. Clin Exp Vaccine Res. 2022 May;11(2):226-229. doi: 10.7774/cevr.2022.11.2.226.

Thyroid and SARS-CoV-2 spike protein



Mechanisms of thryoid dysfunction with SARS-CoV-2 spike protein:
(mRNA and viral vector vaccines)

1. Molecular mimicry:

a. Genetic similarity or homology with a sequences of thyroid peoxidase (TPO) + human leucocytes antigen (HLA) genes →

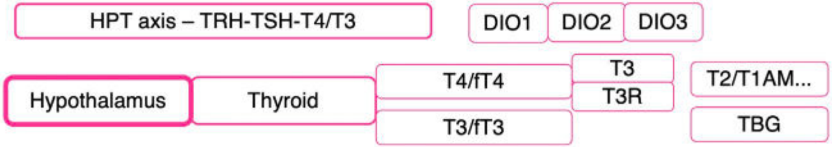
b. Cross-reaction with thyroid antigens in follicular cells + alteration of HLA structure and function →

c. Mitochondrial damage + immune-mediated destruction of the thyroid follicular cells →

d. Thyroid dysfunctions.

Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Domiguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Thyroid and
SARS-CoV-2 spike protein



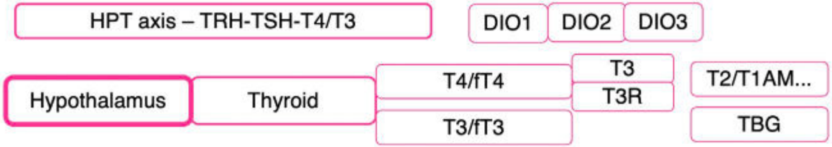
Mechanisms of thryoid dysfunction with SARS-CoV-2 spike protein:

2. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) (described in 2011 by Shoenfeld and Agmon-Levin):

a. Resulted from the dysregulation of immune system following exposure to adjuvants. Adjuvants →
b. Enhancement of the immunogenicity of vaccines →
c. Increase of both innate and adaptive immune responses →
d. Formation of autoantibodies +
e. Local and systemic inflammation

Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Domiguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Thyroid and SARS-CoV-2 spike protein


HPT axis – TRH-TSH-T4/T3
DIO1 DIO2 DIO3
Hypothalamus
Thyroid
T4/fT4
T3/fT3
T3
T3R
T2/T1AM…
TBG

Causes:

a. (Inactivated vaccine – CoronaVac) Aluminium hydroxide or aluminium salts

b. (Viral vector – AZ) Polysorbate 80

c. (mRNA vaccine) Polyethylene glycol (PEG) lipid conjugates (to stabilise the lipid nanoparticles)

d. Oil-in-water emulsion

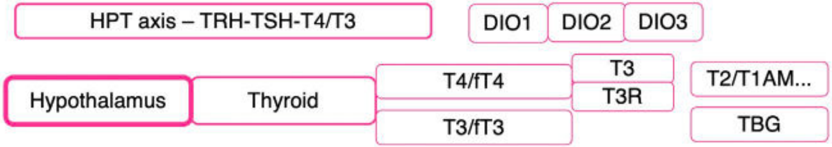
Previously described:

1. Type 1 diabetes mellitus | 2. Primary ovarian failure | 3. Adrenal insufficiency | 4. Autoimmune thyroid diseases

In: 1. HPV | 2. Influenza | 3. Hepatitis B vaccines → And now, after Covid-19 vaccines.

Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Domiguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Thyroid and SARS-CoV-2 spike protein


HPT axis – TRH-TSH-T4/T3

DIO1 DIO2 DIO3

Hypothalamus

Thyroid

T4/fT4

T3/fT3

T3

T3R

T2/T1AM...

TBG

Mechanisms of thryoid dysfunction with SARS-CoV-2 spike protein:

3. Genetic predisposition:

Full spectrum of autoimmune with personal and/or family history of autoimmune disorders - genetic predisposition

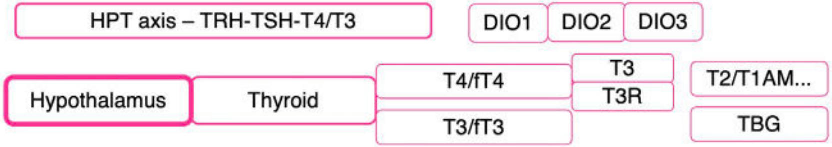
“Despite a mass immunisation campaign against Covid-19 infection, thyroid adverse effects appear to be rare” → “Rare” or rarely diagnosed?

a. T lymphocytes → Excessively sensitised to the TSH receptor antigen and vaccines

b. B lymphocytes → Produce and secrete autoantibodies against the TSH receptor → Graves disease

Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Domiguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves’ Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Thyroid and
SARS-CoV-2 spike protein



- SARS-CoV-2 vaccines: 48 new diagnoses of Graves Diseases (GD) and 15 recurrences or relapses

- mRNA or viral vector SARS-CoV-2 vaccines (inactivated vírus vaccines seem to be safe for GD) - higher immunogenicity with cross-reactivity?

- Other triggered thyroid diaseases:

1. Painful thyroiditis (Quervain)
2. Subacute thyroiditis,
3. Co-occurrence of subacute thyroiditis and Graves' disease

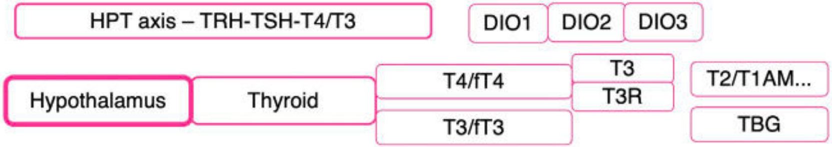
How to differentiate subacute thyroiditis from GD?

- fT4 → higher in GD ($p = 0.001$)

- Thyrotoxicosis within a few days of the 1st dose of SARS-CoV-2 vaccines → Aggravation of a chronic (previously undiagnosed) autoimmune thyroiditis

Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Domiguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Thyroid and SARS-CoV-2 spike protein



- Illustrative case reports:

- Viral vector vaccine (AZ) - 4 days after - 1st dose (2 previous doses of inactivated vírus vaccine) - 0 y/o Woman - Decompensation of a previously pharmacologically controlled Graves Diseases that did not respond to high doses of methimazole

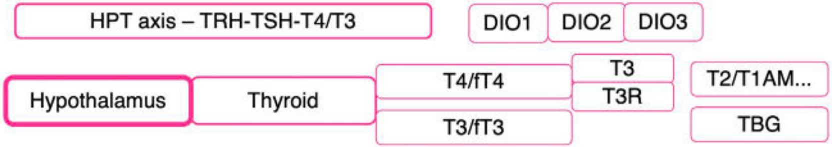
- mRNA vaccine (Pfizer) – a few days later - 2 cases of Graves' Ophthalmopathy (GD) relapse

- Attenuated virus vaccine (CoronaVac) – 3 females 34-37 y/o - Subacute Thyroiditis (secondary to ASIA syndrome) (+ Recurrent myalgia and neck pain in patient 2)

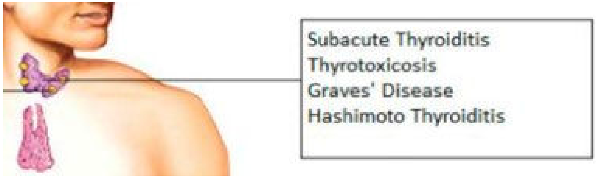
- 1 mRNA, 1 viral vector, 1 unknown - 3 additional cases of subacute thyroiditis

Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Dominguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Thyroid and SARS-CoV-2 spike protein - Summary

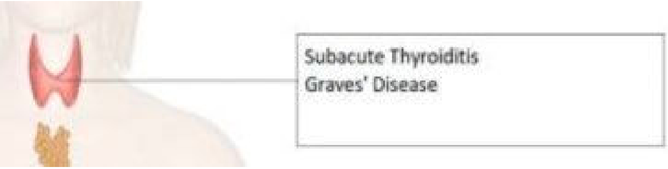


Expected



Subacute Thyroiditis
Thyrotoxicosis
Graves' Disease
Hashimoto Thyroiditis

Confirmed



Subacute Thyroiditis
Graves' Disease

Early

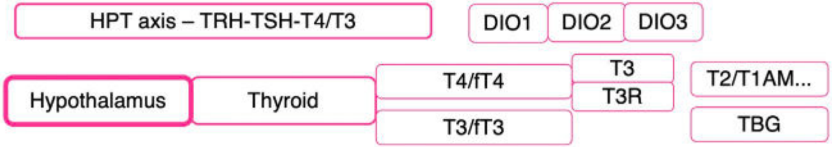
1. Low T3 concentrations
2. Thyrotoxicosis
3. Subacute thyroiditis

Late

1. Low T3 concentrations
2. Low TSH concentrations
3. Hypothyroidism

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Dominguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Thyroid and SARS-CoV-2 spike protein - Summary



HPT axis – TRH-TSH-T4/T3

DIO1

DIO2

DIO3

Hypothalamus

Thyroid

T4/fT4

T3/fT3

T3

T3R

T2/T1AM...

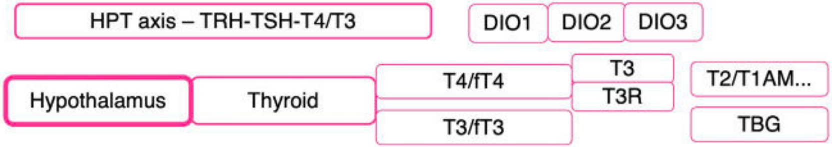
TBG

Proposed mechanisms

1. Direct virus effect on follicular cells
2. Immune mechanisms
3. Euthyroid sick syndrome
4. Hypothalamic-pituitary dysfunction due to edema and neuronal degeneration
5. Drugs (glucocorticoids, heparin)

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Domiguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Thyroid and SARS-CoV-2 spike protein - Summary



HPT axis – TRH-TSH-T4/T3

DIO1 DIO2 DIO3

Hypothalamus

Thyroid

T4/fT4

T3/fT3

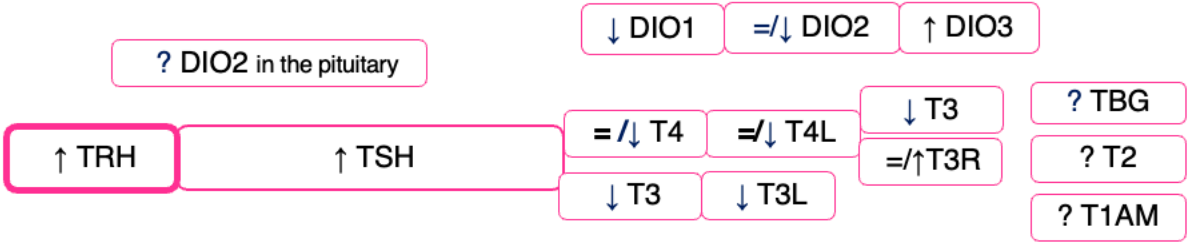
T3

T3R

T2/T1AM...

TBG

Predicted (not based on current evidence)



↓ DIO1

=/↓ DIO2

↑ DIO3

? DIO2 in the pituitary

↑ TRH

↑ TSH

= /↓ T4

=/↓ T4L

↓ T3

↓ T3L

↓ T3

=/↑T3R

? TBG

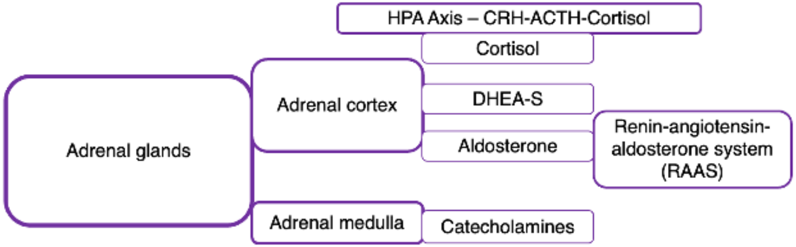
? T2

? T1AM

SARS-CoV-2 reservoir/sanctuary? (speculative)

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Sriphrapradang C. Aggravation of hyperthyroidism after heterologous prime-boost immunization with inactivated and adenovirus-vectored SARS-CoV-2 vaccine in a patient with Graves' disease. Endocrine. 2021 Nov;74(2):226-227. doi: 10.1007/s12020-021-02879-8.
Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V, Antonelli A, Fallahi P. Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review. Vaccines (Basel). 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445.
Patrizio A, Ferrari SM, Antonelli A, Fallahi P. Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev. 2022 Jul;21(7):103096. doi: 10.1016/j.autrev.2022.103096.
Ruggeri RM, Giovanellla L, Campennì A. SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature. J Endocrinol Invest. 2022 Jul 12:1–7. doi: 10.1007/s40618-022-01863-x.
Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022 Jun 28:1–12. doi: 10.1007/s12020-022-03118-4.
Iremli B.G., Sendur S.N., Unluturk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome. J. Clin. Endocrinol. Metab. 2021;106:2600–2605. doi: 10.1210/clinem/dgab373.
Franquemont S., Galvez J. Subacute Thyroiditis After mRNA Vaccine for Covid-19. J. Endocr. Soc. 2021;5:A956–A957. doi: 10.1210/jendso/bvab048.1954.
Oyibo S.O. Subacute Thyroiditis After Receiving the Adenovirus-Vectored Vaccine for Coronavirus Disease (COVID-19) Cureus. 2021;13:e16045. doi: 10.7759/cureus.16045.
Sahin Tekin M., Saylisoy S., Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: A case report. Hum. Vaccines Immunother. 2021;17:4090–4092. doi: 10.1080/21645515.2021.1947102.
Vera-Lastra O., Ordinola Navarro A., Cruz Domiguez M.P., Medina G., Sanchez Valadez T.I., Jara L.J. Two Cases of Graves’ Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid. 2021;31:1436–1439. doi: 10.1089/thy.2021.0142.

Adrenal glands and SARS-CoV-2 spike protein



HPA Axis – CRH-ACTH-Cortisol

Adrenal glands

Adrenal cortex

Cortisol

DHEA-S

Aldosterone

Renin-angiotensin-aldosterone system (RAAS)

Adrenal medulla

Catecholamines

The adrenal glands are a prominent target for SARS-CoV-2 and ensuing cellular damage, which could trigger a predisposition for adrenal dysfunction.

Mechanisms →

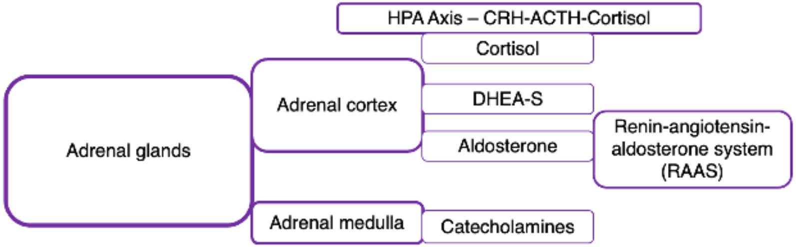
1. Inflammation
2. Inflammatory cell death
3. Widespread microthrombosis
4. Severe direct adrenal injury.
5. Reduction of cortisone (increased 11betaHSD-type 1 activity)
6. Induction of adrenalitis.

Paul T, Ledderose S, Bartsch H, Sun N, Soliman S, Märkl B, Ruf V, Herms J, Stern M, Keppler OT, Delbridge C, Müller S, Piontek G, Kimoto YS, Schreiber F, Williams TA, Neumann J, Knösel T, Schulz H, Spallek R, Graw M, Kirchner T, Walch A, Rudelius M. Adrenal tropism of SARS-CoV-2 and adrenal findings in a post-mortem case series of patients with severe fatal COVID-19. Nat Commun. 2022 Mar 24;13(1):1589. doi: 10.1038/s41467-022-29145-3.

Kanczkowski W, Evert K, Stadtmüller M, Haberecker M, Laks L, Chen LS, Frontzek K, Pablik J, Hantel C, Beuschlein F, Kurth T, Gruber S, Aguzzi A, Varga Z, Bornstein SR. COVID-19 targets human adrenal glands. Lancet Diabetes Endocrinol. 2022 Jan;10(1):13-16. doi: 10.1016/S2213-8587(21)00291-6.

Kanczkowski W, Beuschlein F, Bornstein SR. Is there a role for the adrenal glands in long COVID? Nat Rev Endocrinol. 2022 Aug;18(8):451-452. doi: 10.1038/s41574-022-00700-8.

Adrenal glands and SARS-CoV-2 spike protein



HPA Axis – CRH-ACTH-Cortisol

Cortisol

Adrenal glands

Adrenal cortex

DHEA-S

Aldosterone

Renin-angiotensin-aldosterone system (RAAS)

Adrenal medulla

Catecholamines

- SARS-CoV-2 spike protein entry

- ACE2 → ++ adrenal cortical cells | +++ intervening capillaries

- TMPRSS2 → + adrenal cells

- SARS-CoV-2 spike protein + mRNA →

45% to 100% of subjects with severe COVID-19

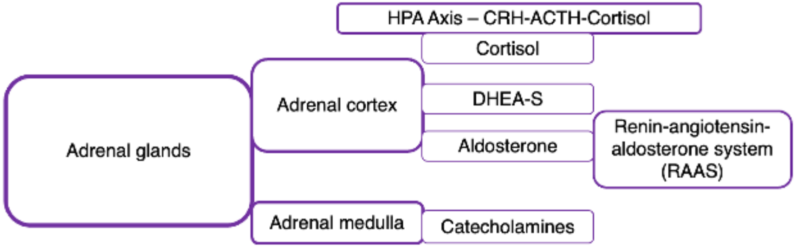
And SARS-CoV-2 mRNA vaccine?

Paul T, Ledderose S, Bartsch H, Sun N, Soliman S, Märkl B, Ruf V, Herms J, Stern M, Keppler OT, Delbridge C, Müller S, Piontek G, Kimoto YS, Schreiber F, Williams TA, Neumann J, Knösel T, Schulz H, Spallek R, Graw M, Kirchner T, Walch A, Rudelius M. Adrenal tropism of SARS-CoV-2 and adrenal findings in a post-mortem case series of patients with severe fatal COVID-19. Nat Commun. 2022 Mar 24;13(1):1589. doi: 10.1038/s41467-022-29145-3.

Kanczkowski W, Evert K, Stadtmüller M, Haberecker M, Laks L, Chen LS, Frontzek K, Pablik J, Hantel C, Beuschlein F, Kurth T, Gruber S, Aguzzi A, Varga Z, Bornstein SR. COVID-19 targets human adrenal glands. Lancet Diabetes Endocrinol. 2022 Jan;10(1):13-16. doi: 10.1016/S2213-8587(21)00291-6.

Kanczkowski W, Beuschlein F, Bornstein SR. Is there a role for the adrenal glands in long COVID? Nat Rev Endocrinol. 2022 Aug;18(8):451-452. doi: 10.1038/s41574-022-00700-8.

Adrenal glands and SARS-CoV-2 spike protein



HPA Axis – CRH-ACTH-Cortisol

Adrenal glands

Adrenal cortex

Cortisol

DHEA-S

Aldosterone

Renin-angiotensin-aldosterone system (RAAS)

Adrenal medulla

Catecholamines

- Specific features:

1. No vascular endothelialitis | No microthrombosis in pre-capillary in COVID-19 infection

2. Microthrombi in capillary → 58%

3. Ischemia or hemorrhage in adrenal córtex or medulla → 16%

4. Disruption of the adrenal zonation → 100%

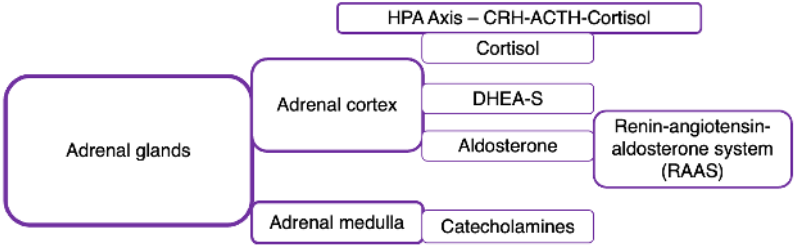
5. Disruption of the adrenal metabolism→ 100%

6. Numerous SARS-CoV-2 virus-like particles

7. Direct necroptosis activation in adrenocortical cells
→ Necroptosis activation in adrenomedullary cells → Exclusive to SARS-CoV-2 vaccies?

Paul T, Ledderose S, Bartsch H, Sun N, Soliman S, Märkl B, Ruf V, Herms J, Stern M, Keppler OT, Delbridge C, Müller S, Piontek G, Kimoto YS, Schreiber F, Williams TA, Neumann J, Knösel T, Schulz H, Spallek R, Graw M, Kirchner T, Walch A, Rudelius M. Adrenal tropism of SARS-CoV-2 and adrenal findings in a post-mortem case series of patients with severe fatal COVID-19. Nat Commun. 2022 Mar 24;13(1):1589. doi: 10.1038/s41467-022-29145-3.
Kanczkowski W, Evert K, Stadtmüller M, Haberecker M, Laks L, Chen LS, Frontzek K, Pablik J, Hantel C, Beuschlein F, Kurth T, Gruber S, Aguzzi A, Varga Z, Bornstein SR. COVID-19 targets human adrenal glands. Lancet Diabetes Endocrinol. 2022 Jan;10(1):13-16. doi: 10.1016/S2213-8587(21)00291-6.
Kanczkowski W, Beuschlein F, Bornstein SR. Is there a role for the adrenal glands in long COVID? Nat Rev Endocrinol. 2022 Aug;18(8):451-452. doi: 10.1038/s41574-022-00700-8.

Adrenal glands and SARS-CoV-2 spike protein



Adrenal insufficiency → Several weeks after COVID-19

→ Late-onset of adrenal insufficiency

1. Persisting dysregulation of the HPA axis*
2. Reactivation of latent viral infections
3. Autoimmune response
4. High molecular similarity between SARS-CoV-2 peptides and ACTH

<u>→ → → Triggered | Enhanced by mRNA SARS-CoV-2 vaccines</u>

Paul T, Ledderose S, Bartsch H, Sun N, Soliman S, Märkl B, Ruf V, Herms J, Stern M, Keppler OT, Delbridge C, Müller S, Piontek G, Kimoto YS, Schreiber F, Williams TA, Neumann J, Knösel T, Schulz H, Spallek R, Graw M, Kirchner T, Walch A, Rudelius M. Adrenal tropism of SARS-CoV-2 and adrenal findings in a post-mortem case series of patients with severe fatal COVID-19. Nat Commun. 2022 Mar 24;13(1):1589. doi: 10.1038/s41467-022-29145-3.

Kanczkowski W, Evert K, Stadtmüller M, Haberecker M, Laks L, Chen LS, Frontzek K, Pablik J, Hantel C, Beuschlein F, Kurth T, Gruber S, Aguzzi A, Varga Z, Bornstein SR. COVID-19 targets human adrenal glands. Lancet Diabetes Endocrinol. 2022 Jan;10(1):13-16. doi: 10.1016/S2213-8587(21)00291-6.

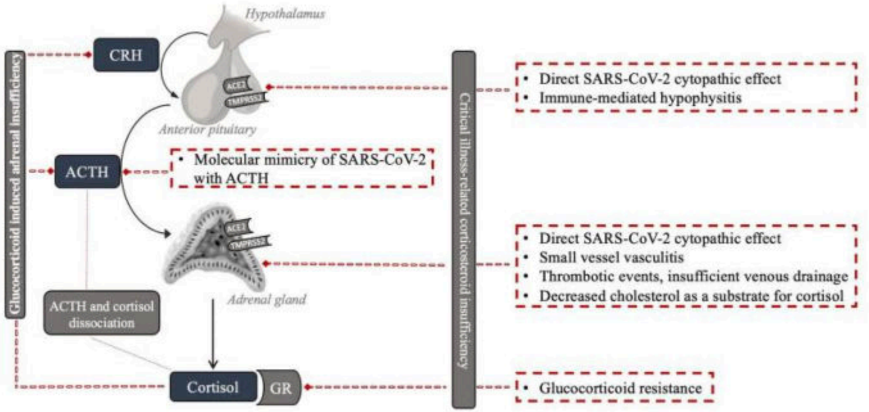
Kanczkowski W, Beuschlein F, Bornstein SR. Is there a role for the adrenal glands in long COVID? Nat Rev Endocrinol. 2022 Aug;18(8):451-452. doi: 10.1038/s41574-022-00700-8.

Adrenal glands and
SARS-CoV-2 spike protein

*Additional harm caused in the HPA axis – disruption of the system:

1. Increased cortisol/cortisone ratio
2. Impaired post-receptor signaling
3. Resistance of cortisol receptors
4. Dissociation of ACTH and cortisol regulation
5. IL-6 (replaces ACTH) →

Stimulates cortisol without influencing DHEA and aldosterone



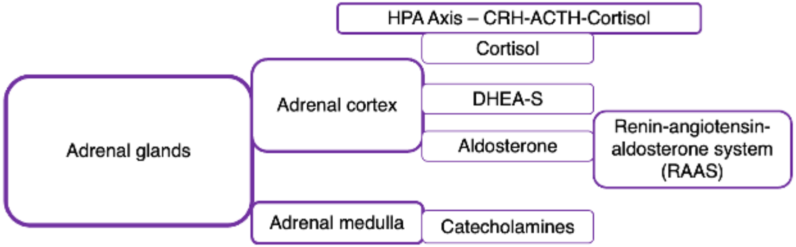
FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Paul T, Ledderose S, Bartsch H, Sun N, Soliman S, Märkl B, Ruf V, Herms J, Stern M, Keppler OT, Delbridge C, Müller S, Piontek G, Kimoto YS, Schreiber F, Williams TA, Neumann J, Knösel T, Schulz H, Spallek R, Graw M, Kirchner T, Walch A, Rudelius M. Adrenal tropism of SARS-CoV-2 and adrenal findings in a post-mortem case series of patients with severe fatal COVID-19. Nat Commun. 2022 Mar 24;13(1):1589. doi: 10.1038/s41467-022-29145-3.

Kanczkowski W, Evert K, Stadtmüller M, Haberecker M, Laks L, Chen LS, Frontzek K, Pablik J, Hantel C, Beuschlein F, Kurth T, Gruber S, Aguzzi A, Varga Z, Bornstein SR. COVID-19 targets human adrenal glands. Lancet Diabetes Endocrinol. 2022 Jan;10(1):13-16. doi: 10.1016/S2213-8587(21)00291-6.

Kanczkowski W, Beuschlein F, Bornstein SR. Is there a role for the adrenal glands in long COVID? Nat Rev Endocrinol. 2022 Aug;18(8):451-452. doi: 10.1038/s41574-022-00700-8.

Adrenal glands and SARS-CoV-2 spike protein



HPA Axis – CRH-ACTH-Cortisol

Adrenal glands

Adrenal cortex

Cortisol

DHEA-S

Aldosterone

Renin-angiotensin-aldosterone system (RAAS)

Adrenal medulla

Catecholamines

Illustrative case reports → Bilateral Adrenal Hemorrhage + VITT + adrenal insufficiency

1. Viral vector (AZ) – 8 days after 1st dose 38 y/o male

2. Viral vector (AZ) – 8 days after 1st dose – 55 y/o female

3. Viral vector (AZ) – 16 days after - 23 y/o woman - overt and unrecovered adrenal insuficiency
High anti-spike titre and positive anti-nucleocapsid titres for SARS-CoV-2 – post-COVID vaccination?

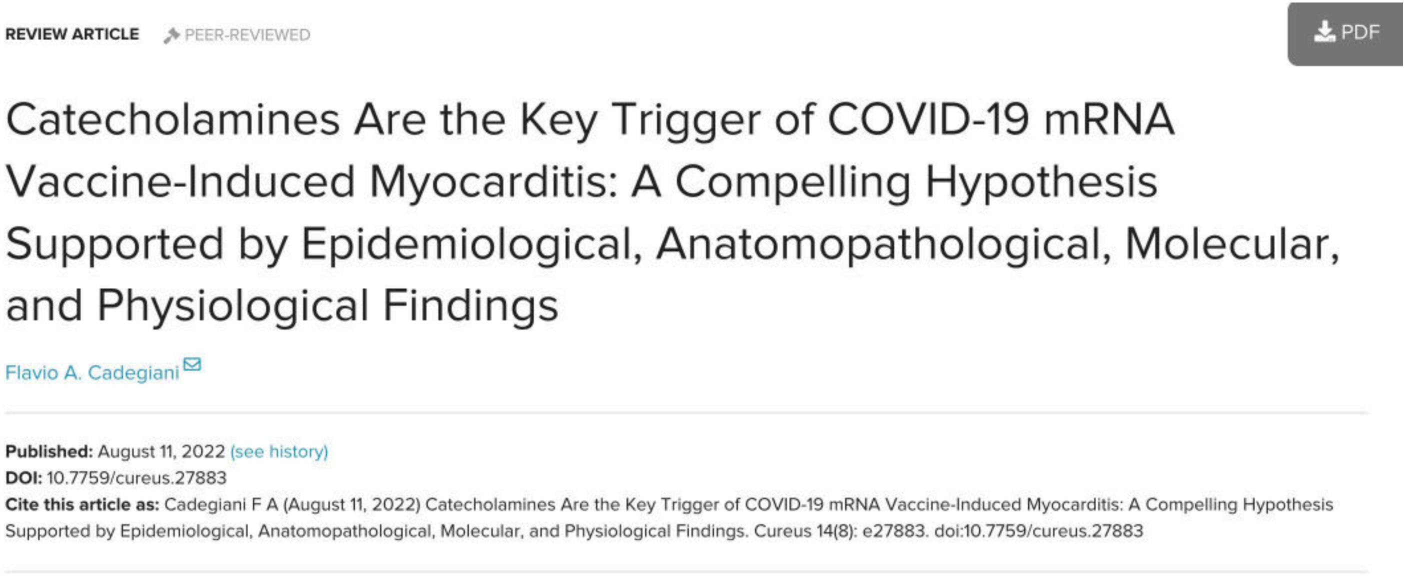
4. Viral vector (JJ) – 10 days after - 39 y/o

5. Viral vector (AZ) – 10 days after - 47 y/o man - overt adrenal insuficiency

6. mRNA vaccine – hours after 2nd dose – worsening of secondary adrenal insufficiency

Efthymiadis A, Khan D, Pavord S, Pal A. A case of ChAdOx1 vaccine-induced thrombocytopenia and thrombosis syndrome leading to bilateral adrenal haemorrhage and adrenal insufficiency. Endocrinol Diabetes Metab Case Rep. 2022 Jun 1;2022:22-0239. doi: 10.1530/EDM-22-0239.
Tews HC, Driendl SM, Kandulski M, Buechler C, Heiss P, Stöckert P, Heissner K, Paulus MG, Kunst C, Müller M, Schmid S. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia with Venous Thrombosis, Pulmonary Embolism, and Adrenal Haemorrhage: A Case Report with Literature Review. Vaccines (Basel). 2022 Apr 12;10(4):595. doi: 10.3390/vaccines10040595.
Taylor P, Allen L, Shrikrishnapalasuriyar N, Stechman M, Rees A. Vaccine-induced thrombosis and thrombocytopenia with bilateral adrenal haemorrhage. Clin Endocrinol (Oxf). 2022 Jul;97(1):26-27. doi: 10.1111/cen.
Tha T, Martini I, Stefan E, Redla S. Bilateral adrenal haemorrhage with renal infarction after ChAdOx1 nCoV-19 AstraZeneca vaccination. BJR Case Rep. 2022 Jan 10;8(2):20210139. doi: 10.1259/bjrcr.20210139.
Boyle L.D., Morganstein D.L., Mitra I., Nogueira E.F. A rare case of multiple thrombi and left adrenal haemorrhage following COVID-19 vaccination. Endocr. Abstr. 2021;74:NCC4. doi: 10.1530/endoabs.74.NCC4.
Varona JF, García-Isidro M, Moeinvaziri M, Ramos-López M, Fernández-Domínguez M. Primary adrenal insufficiency associated with Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia (VITT). Eur J Intern Med. 2021 Sep;91:90-92. doi: 10.1016/j.ejim.2021.06.025.
Markovic N, Faizan A, Boradia C, Nambi S. Adrenal Crisis Secondary to COVID-19 Vaccination in a Patient With Hypopituitarism. AACE Clin Case Rep. 2022 Jul-Aug;8(4):171-173. doi: 10.1016/j.aace.2022.04.004.

Adrenal glands, SARS-CoV-2 spike protein, and **myocarditis**



REVIEW ARTICLE PEER-REVIEWED

Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings

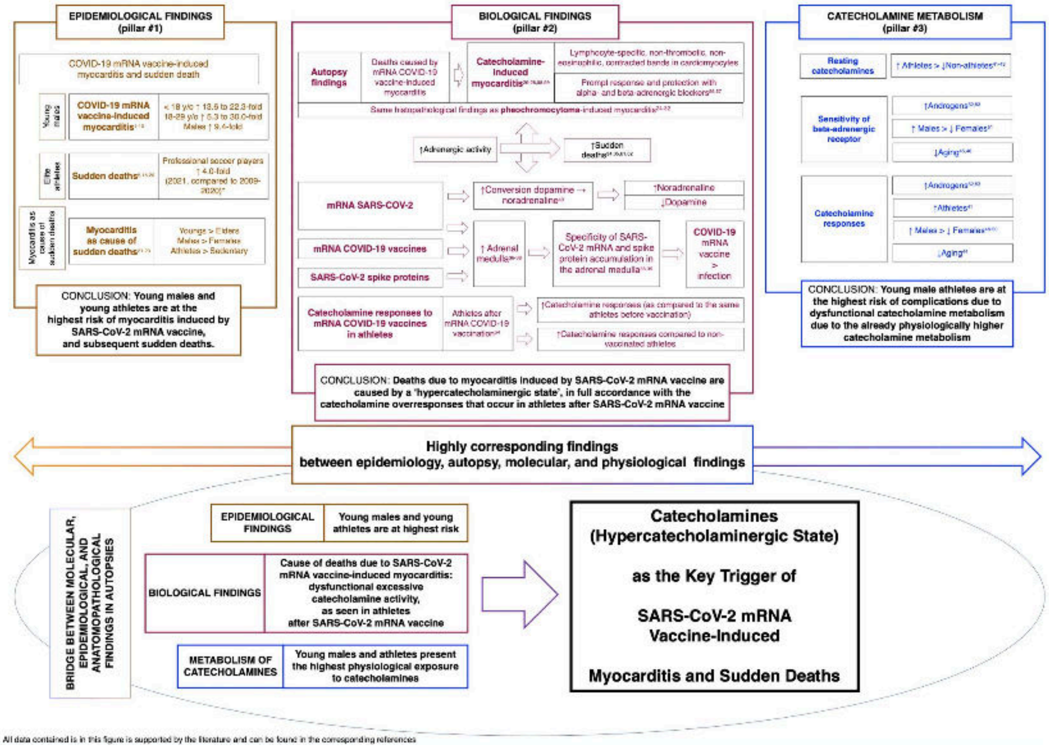
Flavio A. Cadegiani

Published: August 11, 2022 (see history)
DOI: 10.7759/cureus.27883
Cite this article as: Cadegiani F A (August 11, 2022) Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus 14(8): e27883. doi:10.7759/cureus.27883

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

Adrenal glands, SARS-CoV-2 spike protein, and **myocarditis**



EPIDEMIOLOGICAL FINDINGS (pillar #1)

COVID-19 mRNA vaccine-induced myocarditis and sudden death

Young males — **COVID-19 mRNA vaccine-induced myocarditis** — < 18 y/o ↑ 13.5 to 22.3-fold; 18-29 y/o ↑ 5.3 to 30.0-fold; Males ↑ 9.4-fold

Elite athletes — **Sudden deaths** — Professional soccer players ↑ 4.0-fold (2021, compared to 2009-2020)

Myocarditis as cause of sudden deaths — **Myocarditis as cause of sudden deaths** — Youngs > Elders; Males > Females; Athletes > Sedentary

CONCLUSION: **Young males and young athletes are at the highest risk of myocarditis induced by SARS-CoV-2 mRNA vaccine, and subsequent sudden deaths.**

BIOLOGICAL FINDINGS (pillar #2)

Autopsy findings — Deaths caused by mRNA COVID-19 vaccine-induced myocarditis ⇒ **Catecholamine-induced myocarditis** — Lymphocyte-specific, non-thrombotic, non-eosinophilic, contracted bands in cardiomyocytes; Prompt response and protection with alpha- and beta-adrenergic blockers

Same histopathological findings as **pheochromocytoma**-induced myocarditis[21-22]

↑Adrenergic activity ⇒ ↑Sudden deaths

mRNA SARS-COV-2 ⇒ ↑Conversion dopamine → noradrenaline ⇒ ↑Noradrenaline; ↓Dopamine

mRNA SARS-COV-2, **mRNA COVID-19 vaccines**, **SARS-CoV-2 spike proteins** ⇒ ↑ Adrenal medulla ⇒ Specificity of SARS-CoV-2 mRNA and spike protein accumulation in the adrenal medulla ⇒ **COVID-19 mRNA vaccine > infection**

Catecholamine responses to mRNA COVID-19 vaccines in athletes — Athletes after mRNA COVID-19 vaccination ⇒ ↑Catecholamine responses (as compared to the same athletes before vaccination); ⇒ ↑Catecholamine responses compared to non-vaccinated athletes

CONCLUSION: **Deaths due to myocarditis induced by SARS-CoV-2 mRNA vaccine are caused by a 'hypercatecholaminergic state', in full accordance with the catecholamine overresponses that occur in athletes after SARS-CoV-2 mRNA vaccine**

CATECHOLAMINE METABOLISM (pillar #3)

Resting catecholamines — ↑ Athletes > ↓Non-athletes

Sensitivity of beta-adrenergic receptor — ↑Androgens; ↑ Males > ↓ Females; ↓Aging

Catecholamine responses — ↑Androgens; ↑Athletes; ↑ Males > ↓ Females; ↓Aging

CONCLUSION: **Young male athletes are at the highest risk of complications due to dysfunctional catecholamine metabolism due to the already physiologically higher catecholamine metabolism**

Highly corresponding findings between epidemiology, autopsy, molecular, and physiological findings

BRIDGE BETWEEN MOLECULAR, EPIDEMIOLOGICAL, AND ANATOMOPATHOLOGICAL FINDINGS IN AUTOPSIES

EPIDEMIOLOGICAL FINDINGS	Young males and young athletes are at highest risk
BIOLOGICAL FINDINGS	Cause of deaths due to SARS-CoV-2 mRNA vaccine-induced myocarditis: dysfunctional excessive catecholamine activity, as seen in athletes after SARS-CoV-2 mRNA vaccine
METABOLISM OF CATECHOLAMINES	Young males and athletes present the highest physiological exposure to catecholamines

⇒

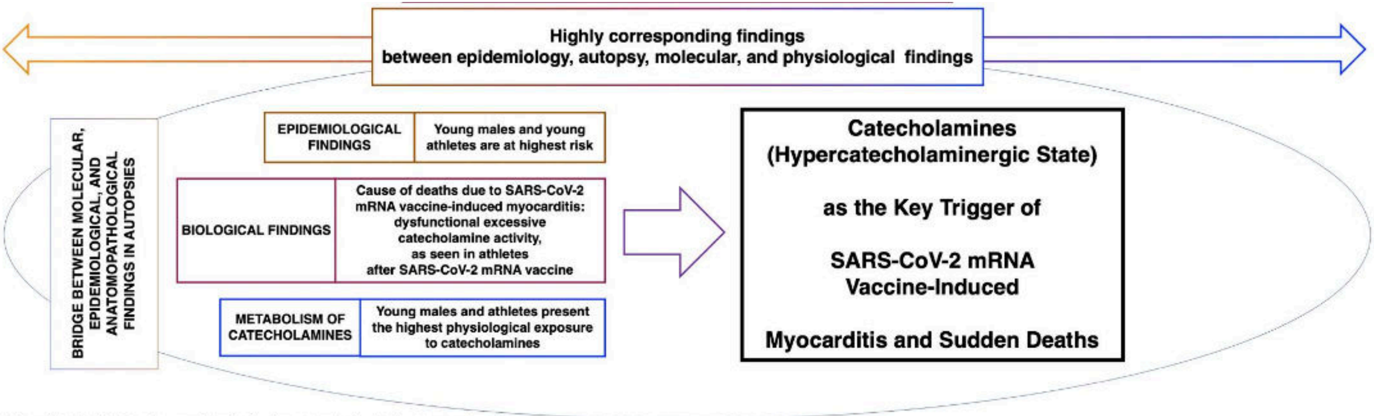
Catecholamines (Hypercatecholaminergic State) as the Key Trigger of SARS-CoV-2 mRNA Vaccine-Induced Myocarditis and Sudden Deaths

All data contained is in this figure is supported by the literature and can be found in the corresponding references

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

Adrenal glands, SARS-CoV-2 spike protein, and **myocarditis**



Highly corresponding findings
between epidemiology, autopsy, molecular, and physiological findings

BRIDGE BETWEEN MOLECULAR, EPIDEMIOLOGICAL, AND ANATOMOPATHOLOGICAL FINDINGS IN AUTOPSIES

EPIDEMIOLOGICAL FINDINGS	Young males and young athletes are at highest risk
BIOLOGICAL FINDINGS	Cause of deaths due to SARS-CoV-2 mRNA vaccine-induced myocarditis: dysfunctional excessive catecholamine activity, as seen in athletes after SARS-CoV-2 mRNA vaccine
METABOLISM OF CATECHOLAMINES	Young males and athletes present the highest physiological exposure to catecholamines

Catecholamines (Hypercatecholaminergic State)

as the Key Trigger of

SARS-CoV-2 mRNA Vaccine-Induced

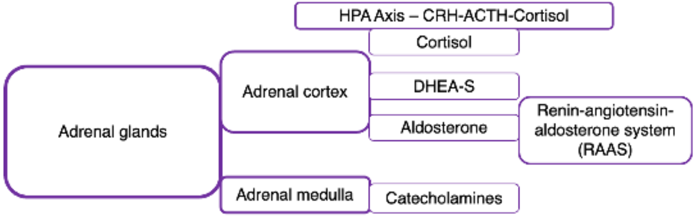
Myocarditis and Sudden Deaths

All data contained is in this figure is supported by the literature and can be found in the corresponding references

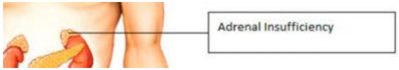
FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Cadegiani FA. Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. Cureus. 2022 Aug 11;14(8):e27883. doi: 10.7759/cureus.27883.

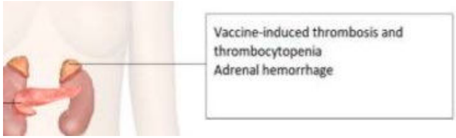
Adrenal glands and SARS-CoV-2 spike protein - Summary



Expected



Confirmed



Early

1. Possible adrenal insufficiency

Later

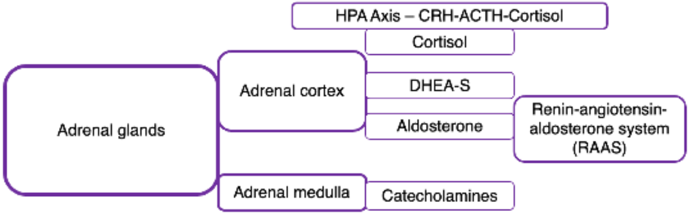
1. Possible adrenal insufficiency

Proposed mechanisms

1. Adrenal hemorrhage
2. Adrenal micro-infarction
3. Ischemic necrosis
4. Adrenalitis

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Efthymiadis A, Khan D, Pavord S, Pal A. A case of ChAdOx1 vaccine-induced thrombocytopenia and thrombosis syndrome leading to bilateral adrenal haemorrhage and adrenal insufficiency. Endocrinol Diabetes Metab Case Rep. 2022 Jun 1;2022:22-0239. doi: 10.1530/EDM-22-0239.
Tews HC, Driendl SM, Kandulski M, Buechler C, Heiss P, Stöckert P, Heissner K, Paulus MG, Kunst C, Müller M, Schmid S. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia with Venous Thrombosis, Pulmonary Embolism, and Adrenal Haemorrhage: A Case Report with Literature Review. Vaccines (Basel). 2022 Apr 12;10(4):595. doi: 10.3390/vaccines10040595.
Taylor P, Allen L, Shrikrishnapalasuriyar N, Stechman M, Rees A. Vaccine-induced thrombosis and thrombocytopenia with bilateral adrenal haemorrhage. Clin Endocrinol (Oxf). 2022 Jul;97(1):26-27. doi: 10.1111/cen.
Tha T, Martini I, Stefan E, Redla S. Bilateral adrenal haemorrhage with renal infarction after ChAdOx1 nCoV-19 AstraZeneca vaccination. BJR Case Rep. 2022 Jan 10;8(2):20210139. doi: 10.1259/bjrcr.20210139.
Boyle L.D., Morganstein D.L., Mitra I., Nogueira E.F. A rare case of multiple thrombi and left adrenal haemorrhage following COVID-19 vaccination. Endocr. Abstr. 2021;74:NCC4. doi: 10.1530/endoabs.74.NCC4.
Varona JF, García-Isidro M, Moeinvaziri M, Ramos-López M, Fernández-Domínguez M. Primary adrenal insufficiency associated with Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia (VITT). Eur J Intern Med. 2021 Sep;91:90-92. doi: 10.1016/j.ejim.2021.06.025.
Markovic N, Faizan A, Boradia C, Nambi S. Adrenal Crisis Secondary to COVID-19 Vaccination in a Patient With Hypopituitarism. AACE Clin Case Rep. 2022 Jul-Aug;8(4):171-173. doi: 10.1016/j.aace.2022.04.004.

Adrenal glands and SARS-CoV-2 spike protein - Expected

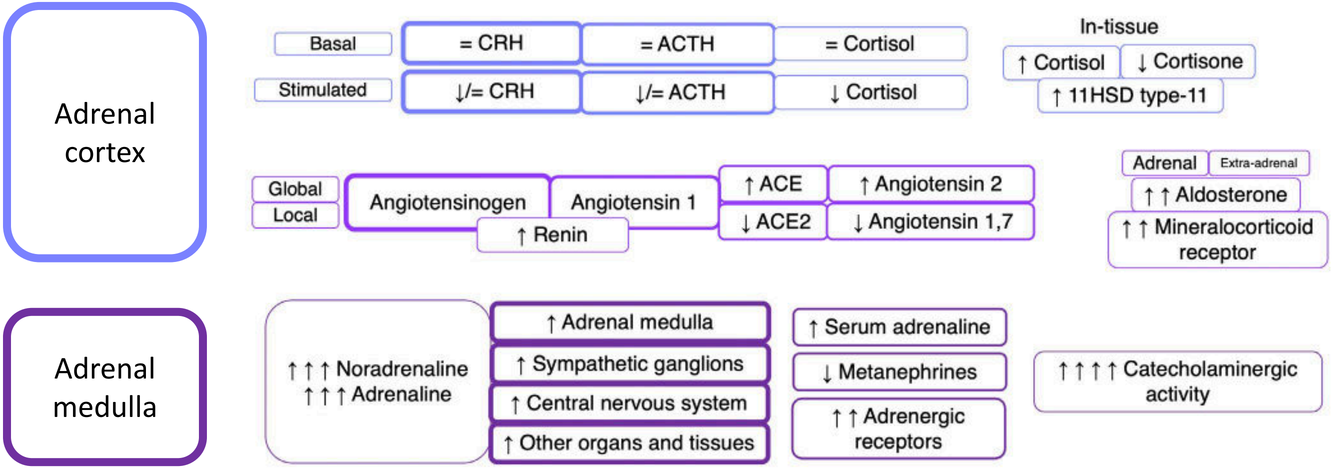

HPA Axis – CRH-ACTH-Cortisol

Adrenal glands

Adrenal cortex
- Cortisol
- DHEA-S
- Aldosterone
  - Renin-angiotensin-aldosterone system (RAAS)

Adrenal medulla
- Catecholamines

Predicted (not based on current evidence)


Adrenal cortex

Basal	= CRH	= ACTH	= Cortisol
Stimulated	↓/= CRH	↓/= ACTH	↓ Cortisol

In-tissue
- ↑ Cortisol
- ↓ Cortisone
- ↑ 11HSD type-11

Global / Local

Angiotensinogen → Angiotensin 1 (↑ Renin)
- ↑ ACE → ↑ Angiotensin 2
- ↓ ACE2 → ↓ Angiotensin 1,7

Adrenal / Extra-adrenal
- ↑ ↑ Aldosterone
- ↑ ↑ Mineralocorticoid receptor

Adrenal medulla

↑ ↑ ↑ Noradrenaline
↑ ↑ ↑ Adrenaline

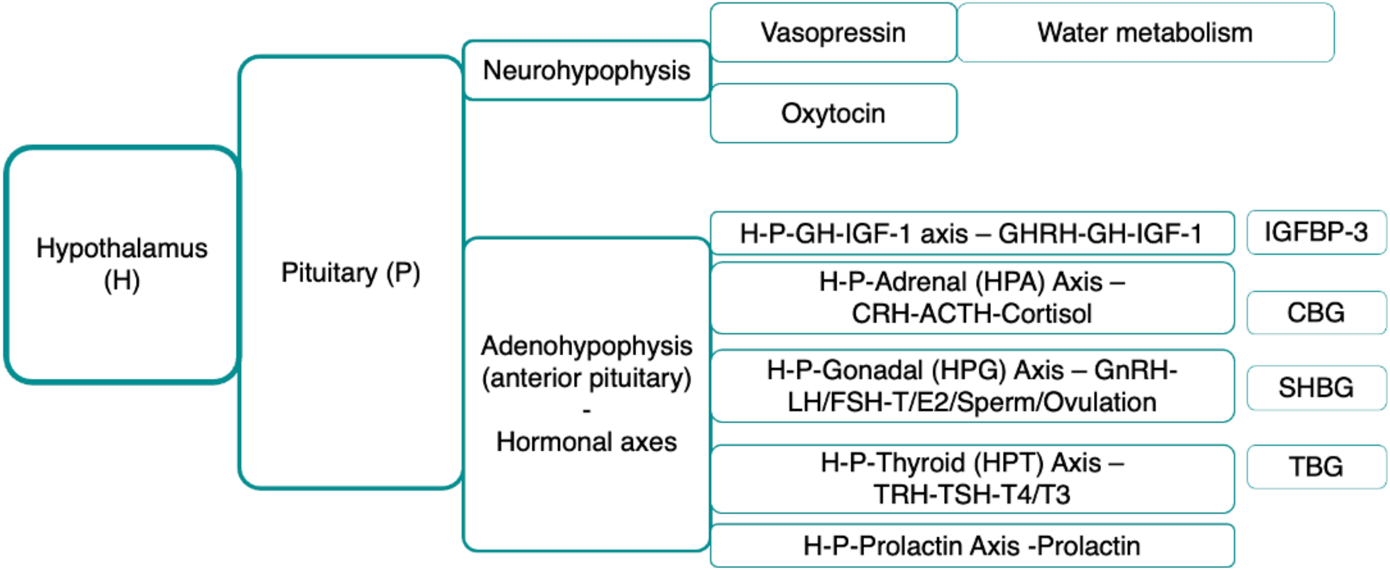
- ↑ Adrenal medulla
- ↑ Sympathetic ganglions
- ↑ Central nervous system
- ↑ Other organs and tissues

- ↑ Serum adrenaline
- ↓ Metanephrines
- ↑ ↑ Adrenergic receptors

↑ ↑ ↑ ↑ Catecholaminergic activity

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Paul T, Ledderose S, Bartsch H, Sun N, Soliman S, Märkl B, Ruf V, Herms J, Stern M, Keppler OT, Delbridge C, Müller S, Piontek G, Kimoto YS, Schreiber F, Williams TA, Neumann J, Knösel T, Schulz H, Spallek R, Graw M, Kirchner T, Walch A, Rudelius M. Adrenal tropism of SARS-CoV-2 and adrenal findings in a post-mortem case series of patients with severe fatal COVID-19. Nat Commun. 2022 Mar 24;13(1):1589. doi: 10.1038/s41467-022-29145-3.
Kanczkowski W, Evert K, Stadtmüller M, Haberecker M, Laks L, Chen LS, Frontzek K, Pablik J, Hantel C, Beuschlein F, Kurth T, Gruber S, Aguzzi A, Varga Z, Bornstein SR. COVID-19 targets human adrenal glands. Lancet Diabetes Endocrinol. 2022 Jan;10(1):13-16. doi: 10.1016/S2213-8587(21)00291-6.
Kanczkowski W, Beuschlein F, Bornstein SR. Is there a role for the adrenal glands in long COVID? Nat Rev Endocrinol. 2022 Aug;18(8):451-452. doi: 10.1038/s41574-022-00700-8.

Pituitary and SARS-CoV-2 spike protein



Hypothalamus (H)

Pituitary (P)

Neurohypophysis

Vasopressin

Water metabolism

Oxytocin

Adenohypophysis (anterior pituitary) - Hormonal axes

H-P-GH-IGF-1 axis – GHRH-GH-IGF-1

IGFBP-3

H-P-Adrenal (HPA) Axis – CRH-ACTH-Cortisol

CBG

H-P-Gonadal (HPG) Axis – GnRH-LH/FSH-T/E2/Sperm/Ovulation

SHBG

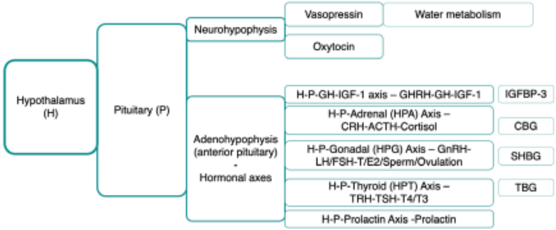
H-P-Thyroid (HPT) Axis – TRH-TSH-T4/T3

TBG

H-P-Prolactin Axis -Prolactin

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.

Pituitary and SARS-CoV-2 spike protein



Hypothalamus (H)

Pituitary (P)

Neurohypophysis

Vasopressin

Water metabolism

Oxytocin

Adenohypophysis (anterior pituitary) - Hormonal axes

H-P-GH-IGF-1 axis – GHRH-GH-IGF-1

IGFBP-3

H-P-Adrenal (HPA) Axis – CRH-ACTH-Cortisol

CBG

H-P-Gonadal (HPG) Axis – GnRH-LH/FSH-T/E2/Sperm/Ovulation

SHBG

H-P-Thyroid (HPT) Axis – TRH-TSH-T4/T3

TBG

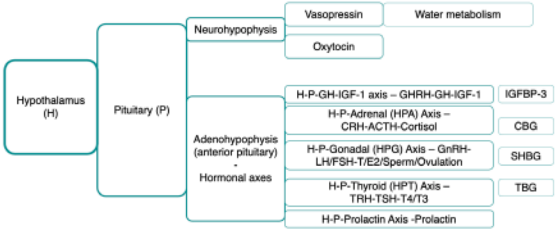
H-P-Prolactin Axis -Prolactin

- Pituitary disorders → challenges for the diagnoses

1. Centrally located hormonal disturbances are harder to be biochemically detected – less frank alterations in exams
2. Slowly progressive conditions
3. Only detectable through basal biochemistry (i.e., not stimulated, not using functional tests) when severely affected
4. Non-specific manifestations

Abdillah DA, Kereilwe O, Ferdousy RN, Saito R, Kadokawa H. Spike protein of SARS-CoV-2 suppresses gonadotrophin secretion from bovine anterior pituitaries. J Reprod Dev. 2022 Apr 1;68(2):152-159. doi: 10.1262/jrd.2021-126.
Gu WT, Zhou F, Xie WQ, Wang S, Yao H, Liu YT, Gao L, Wu ZB. A potential impact of SARS-CoV-2 on pituitary glands and pituitary neuroendocrine tumors. Endocrine. 2021 May;72(2):340-348. doi: 10.1007/s12020-021-02697-y.
Poma AM, Proietti A, Macerola E, Bonuccelli D, Conti M, Salvetti A, Dolo V, Chillà A, Basolo A, Santini F, Toniolo A, Basolo F. Suppression of Pituitary Hormone Genes in Subjects Who Died From COVID-19 Independently of Virus Detection in the Gland. J Clin Endocrinol Metab. 2022 Jul 14;107(8):2243-2253. doi: 10.1210/clinem/dgac312.
Jensterle M, Herman R, Janež A, Mahmeed WA, Al-Rasadi K, Al-Alawi K, Banach M, Banerjee Y, Ceriello A, Cesur M, Cosentino F, Galia M, Goh SY, Kalra S, Kempler P, Lessan N, Lotufo P, Papanas N, Rizvi AA, Santos RD, Stoian AP, Toth PP, Viswanathan V, Rizzo M. The Relationship between COVID-19 and Hypothalamic-Pituitary-Adrenal Axis: A Large Spectrum from Glucocorticoid Insufficiency to Excess-The CAPISCO International Expert Panel. Int J Mol Sci. 2022 Jun 30;23(13):7326. doi: 10.3390/ijms23137326.
Yavropoulou MP, Filippa MG, Mantzou A, Ntziora F, Mylona M, Tektonidou MG, Vlachogiannis NI, Paraskevis D, Kaltsas GA, Chrousos GP, Sfikakis PP. Alterations in cortisol and interleukin-6 secretion in patients with COVID-19 suggestive of neuroendocrine-immune adaptations. Endocrine. 2022 Feb;75(2):317-327. doi: 10.1007/s12020-021-02968-8.

Pituitary and SARS-CoV-2 spike protein



Hypothalamus (H)

Pituitary (P)

Neurohypophysis

Vasopressin

Water metabolism

Oxytocin

Adenohypophysis (anterior pituitary) - Hormonal axes

H-P-GH-IGF-1 axis – GHRH-GH-IGF-1

IGFBP-3

H-P-Adrenal (HPA) Axis – CRH-ACTH-Cortisol

CBG

H-P-Gonadal (HPG) Axis – GnRH-LH/FSH-T/E2/Sperm/Ovulation

SHBG

H-P-Thyroid (HPT) Axis – TRH-TSH-T4/T3

TBG

H-P-Prolactin Axis -Prolactin

- SARS-CoV-2 spike protein →

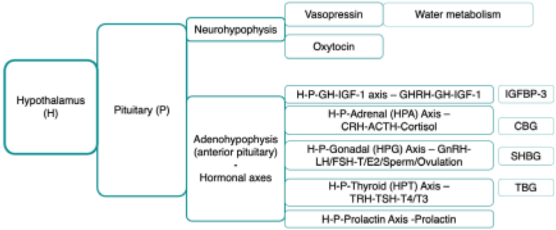
- Detected in 61% of subjects exposed, in both neuro- and adenohypophisis

- Impacts in both hypothalamus and pituitary through:

1. Direct cytopathic effects
2. Immune-mediated inflammation
3. Small vessel vasculitis
4. Microthrombotic events

Abdillah DA, Kereilwe O, Ferdousy RN, Saito R, Kadokawa H. Spike protein of SARS-CoV-2 suppresses gonadotrophin secretion from bovine anterior pituitaries. J Reprod Dev. 2022 Apr 1;68(2):152-159. doi: 10.1262/jrd.2021-126.
Gu WT, Zhou F, Xie WQ, Wang S, Yao H, Liu YT, Gao L, Wu ZB. A potential impact of SARS-CoV-2 on pituitary glands and pituitary neuroendocrine tumors. Endocrine. 2021 May;72(2):340-348. doi: 10.1007/s12020-021-02697-y.
Poma AM, Proietti A, Macerola E, Bonuccelli D, Conti M, Salvetti A, Dolo V, Chillà A, Basolo A, Santini F, Toniolo A, Basolo F. Suppression of Pituitary Hormone Genes in Subjects Who Died From COVID-19 Independently of Virus Detection in the Gland. J Clin Endocrinol Metab. 2022 Jul 14;107(8):2243-2253. doi: 10.1210/clinem/dgac312.
Jensterle M, Herman R, Janež A, Mahmeed WA, Al-Rasadi K, Al-Alawi K, Banach M, Banerjee Y, Ceriello A, Cesur M, Cosentino F, Galia M, Goh SY, Kalra S, Kempler P, Lessan N, Lotufo P, Papanas N, Rizvi AA, Santos RD, Stoian AP, Toth PP, Viswanathan V, Rizzo M. The Relationship between COVID-19 and Hypothalamic-Pituitary-Adrenal Axis: A Large Spectrum from Glucocorticoid Insufficiency to Excess-The CAPISCO International Expert Panel. Int J Mol Sci. 2022 Jun 30;23(13):7326. doi: 10.3390/ijms23137326.
Yavropoulou MP, Filippa MG, Mantzou A, Ntziora F, Mylona M, Tektonidou MG, Vlachogiannis NI, Paraskevis D, Kaltsas GA, Chrousos GP, Sfikakis PP. Alterations in cortisol and interleukin-6 secretion in patients with COVID-19 suggestive of neuroendocrine-immune adaptations. Endocrine. 2022 Feb;75(2):317-327. doi: 10.1007/s12020-021-02968-8.

Pituitary and SARS-CoV-2 spike protein



- SARS-CoV-2 spike protein →

- Causes hypophisitis – long-term consequences unknown

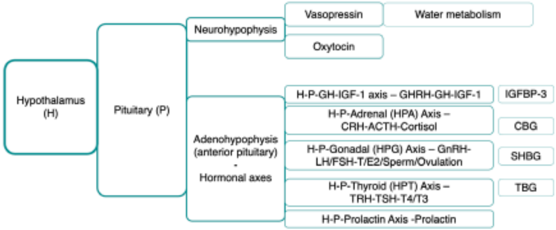
- Suppression of mRNA transcripts of pituitary hormones and pituitary developmental/regulatory genes – IRRESPECTIVE of COVID-19 infection

- Agonist or antagonist that suppresses gonadotrophs through ACE2 - suppressed LH secretion (both basal and stimulated by GnRH) and GnRH-stimulated FSH secretion.

- Activates ACTH (corticotrophs) through ACE2 → Disrupted circadian cycle, increased accumulated cortisol release, and all the consequences

Abdillah DA, Kereilwe O, Ferdousy RN, Saito R, Kadokawa H. Spike protein of SARS-CoV-2 suppresses gonadotrophin secretion from bovine anterior pituitaries. J Reprod Dev. 2022 Apr 1;68(2):152-159. doi: 10.1262/jrd.2021-126.
Gu WT, Zhou F, Xie WQ, Wang S, Yao H, Liu YT, Gao L, Wu ZB. A potential impact of SARS-CoV-2 on pituitary glands and pituitary neuroendocrine tumors. Endocrine. 2021 May;72(2):340-348. doi: 10.1007/s12020-021-02697-y.
Poma AM, Proietti A, Macerola E, Bonuccelli D, Conti M, Salvetti A, Dolo V, Chillà A, Basolo A, Santini F, Toniolo A, Basolo F. Suppression of Pituitary Hormone Genes in Subjects Who Died From COVID-19 Independently of Virus Detection in the Gland. J Clin Endocrinol Metab. 2022 Jul 14;107(8):2243-2253. doi: 10.1210/clinem/dgac312.
Jensterle M, Herman R, Janež A, Mahmeed WA, Al-Rasadi K, Al-Alawi K, Banach M, Banerjee Y, Ceriello A, Cesur M, Cosentino F, Galia M, Goh SY, Kalra S, Kempler P, Lessan N, Lotufo P, Papanas N, Rizvi AA, Santos RD, Stoian AP, Toth PP, Viswanathan V, Rizzo M. The Relationship between COVID-19 and Hypothalamic-Pituitary-Adrenal Axis: A Large Spectrum from Glucocorticoid Insufficiency to Excess-The CAPISCO International Expert Panel. Int J Mol Sci. 2022 Jun 30;23(13):7326. doi: 10.3390/ijms23137326.
Yavropoulou MP, Filippa MG, Mantzou A, Ntziora F, Mylona M, Tektonidou MG, Vlachogiannis NI, Paraskevis D, Kaltsas GA, Chrousos GP, Sfikakis PP. Alterations in cortisol and interleukin-6 secretion in patients with COVID-19 suggestive of neuroendocrine-immune adaptations. Endocrine. 2022 Feb;75(2):317-327. doi: 10.1007/s12020-021-02968-8.

Pituitary and SARS-CoV-2 spike protein



Hypothalamus (H)

Pituitary (P)

Neurohypophysis

Vasopressin

Water metabolism

Oxytocin

Adenohypophysis (anterior pituitary) - Hormonal axes

H-P-GH-IGF-1 axis – GHRH-GH-IGF-1

IGFBP-3

H-P-Adrenal (HPA) Axis – CRH-ACTH-Cortisol

CBG

H-P-Gonadal (HPG) Axis – GnRH-LH/FSH-T/E2/Sperm/Ovulation

SHBG

H-P-Thyroid (HPT) Axis – TRH-TSH-T4/T3

TBG

H-P-Prolactin Axis -Prolactin

- Illustrative case reports:

- Undetermined vaccine - 48 y/o woman - 2 days later - Diabetes *insipidus (*flu-like symptoms, headache, myalgia, polydipsia, and polyuria) - thickening of the pituitary stalk persisted after 03 months

- mRNA vaccine (Pfizer) - 31 y/o man – 2nd dose – 4 days later – isolated secondary adrenal insufficiency - atrophic pituitary gland (general fatigue, fever, headache, nausea, diarrhea, slight disorientation, hyponatremia, hypoglycemia – Undectable ACTH and and extremely low cortisol)

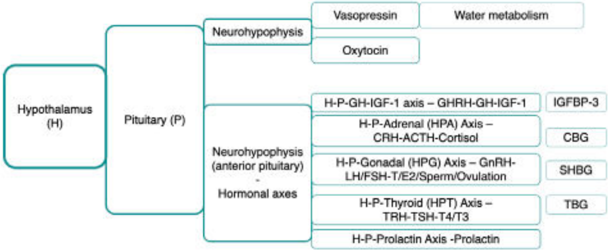
- Viral vector vaccine (AZ) - 37 y/o woman - 5 days later – adenohypophysis hemorrhagic bleeding and possible 10 mm intraglandular adenoma - (high-intensity frontal headache)

- Viral vector vaccine (AZ) - 28 y/o woman - long-lasting tension-type headache, hyperprolactinemia and menstrual changes

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Ankireddypalli AR, Chow LS, Radulescu A, Kawakami Y, Araki T. A Case of Hypophysitis Associated With SARS-CoV-2 Vaccination. AACE Clin Case Rep. 2022 Sep-Oct;8(5):204-209. doi: 10.1016/j.aace.2022.06.001.
Morita S, Tsuji T, Kishimoto S, Uraki S, Takeshima K, Iwakura H, Furuta H, Nishi M, Inaba H, Matsuoka TA. Isolated ACTH deficiency following immunization with the BNT162b2 SARS-CoV-2 vaccine: a case report. BMC Endocr Disord. 2022 Jul 19;22(1):185. doi: 10.1186/s12902-022-01095-3.
Piñar-Gutiérrez A, Remón-Ruiz P, Soto-Moreno A. Case report: Pituitary apoplexy after COVID-19 vaccination. Med Clin (Barc). 2022 May 27;158(10):498-499. doi: 10.1016/j.medcli.2021.09.028.
Roncati L, Manenti A. Pituitary apoplexy following adenoviral vector-based COVID-19 vaccination. Brain Hemorrhages. 2022 Apr 19. doi: 10.1016/j.hest.2022.04.002.

Pituitary and SARS-CoV-2 spike protein - Summary



Hypothalamus (H)

Pituitary (P)

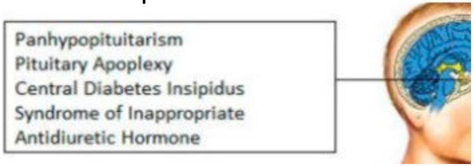
Neurohypophysis

- Vasopressin — Water metabolism
- Oxytocin

Neurohypophysis (anterior pituitary) - Hormonal axes

H-P-GH-IGF-1 axis – GHRH-GH-IGF-1	IGFBP-3
H-P-Adrenal (HPA) Axis – CRH-ACTH-Cortisol	CBG
H-P-Gonadal (HPG) Axis – GnRH-LH/FSH-T/E2/Sperm/Ovulation	SHBG
H-P-Thyroid (HPT) Axis – TRH-TSH-T4/T3	TBG
H-P-Prolactin Axis -Prolactin	

Expected



Panhypopituitarism
Pituitary Apoplexy
Central Diabetes Insipidus
Syndrome of Inappropriate Antidiuretic Hormone

Early

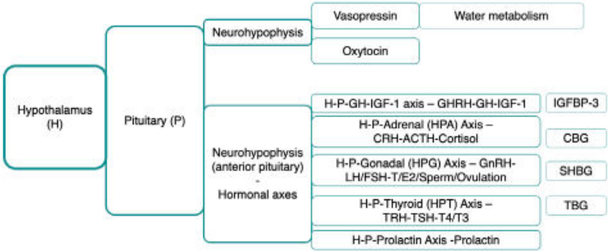
1. Possible hyponatremia

Proposed mechanisms

1. Possible inappropriate antidiuretic hormone secretion syndrome

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Ankireddypalli AR, Chow LS, Radulescu A, Kawakami Y, Araki T. A Case of Hypophysitis Associated With SARS-CoV-2 Vaccination. AACE Clin Case Rep. 2022 Sep-Oct;8(5):204-209. doi: 10.1016/j.aace.2022.06.001.
Morita S, Tsuji T, Kishimoto S, Uraki S, Takeshima K, Iwakura H, Furuta H, Nishi M, Inaba H, Matsuoka TA. Isolated ACTH deficiency following immunization with the BNT162b2 SARS-CoV-2 vaccine: a case report. BMC Endocr Disord. 2022 Jul 19;22(1):185. doi: 10.1186/s12902-022-01095-3.
Piñar-Gutiérrez A, Remón-Ruiz P, Soto-Moreno A. Case report: Pituitary apoplexy after COVID-19 vaccination. Med Clin (Barc). 2022 May 27;158(10):498-499. doi: 10.1016/j.medcli.2021.09.028.
Roncati L, Manenti A. Pituitary apoplexy following adenoviral vector-based COVID-19 vaccination. Brain Hemorrhages. 2022 Apr 19. doi: 10.1016/j.hest.2022.04.002.

Pituitary and SARS-CoV-2 spike protein - Expected



Hypothalamus (H)

Pituitary (P)

Neurohypophysis

Vasopressin

Water metabolism

Oxytocin

Neurohypophysis (anterior pituitary) - Hormonal axes

H-P-GH-IGF-1 axis – GHRH-GH-IGF-1

IGFBP-3

H-P-Adrenal (HPA) Axis – CRH-ACTH-Cortisol

CBG

H-P-Gonadal (HPG) Axis – GnRH-LH/FSH-T/E2/Sperm/Ovulation

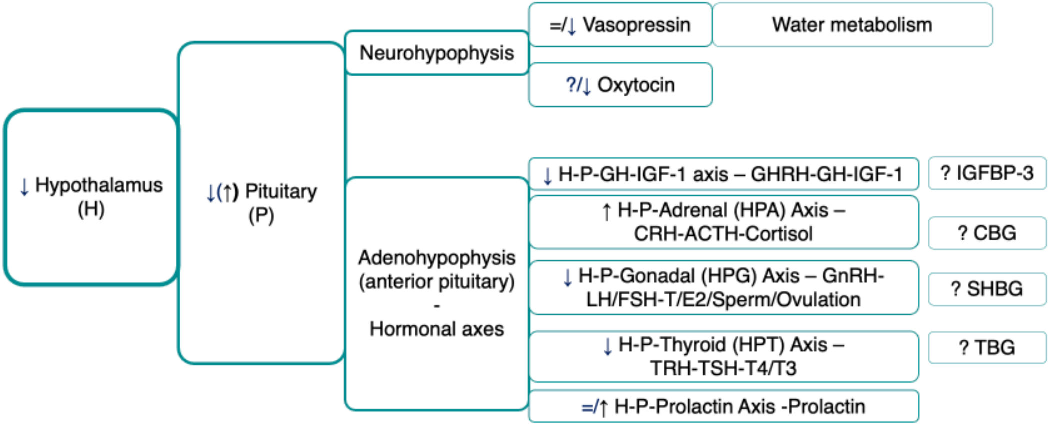
SHBG

H-P-Thyroid (HPT) Axis – TRH-TSH-T4/T3

TBG

H-P-Prolactin Axis -Prolactin

Predicted (not based on current evidence)



↓ Hypothalamus (H)

↓(↑) Pituitary (P)

Neurohypophysis

=/↓ Vasopressin

Water metabolism

?/↓ Oxytocin

Adenohypophysis (anterior pituitary) - Hormonal axes

↓ H-P-GH-IGF-1 axis – GHRH-GH-IGF-1

? IGFBP-3

↑ H-P-Adrenal (HPA) Axis – CRH-ACTH-Cortisol

? CBG

↓ H-P-Gonadal (HPG) Axis – GnRH-LH/FSH-T/E2/Sperm/Ovulation

? SHBG

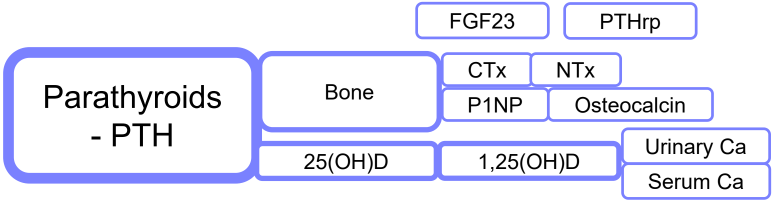
↓ H-P-Thyroid (HPT) Axis – TRH-TSH-T4/T3

? TBG

=/↑ H-P-Prolactin Axis -Prolactin

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Ankireddypalli AR, Chow LS, Radulescu A, Kawakami Y, Araki T. A Case of Hypophysitis Associated With SARS-CoV-2 Vaccination. AACE Clin Case Rep. 2022 Sep-Oct;8(5):204-209. doi: 10.1016/j.aace.2022.06.001.
Morita S, Tsuji T, Kishimoto S, Uraki S, Takeshima K, Iwakura H, Furuta H, Nishi M, Inaba H, Matsuoka TA. Isolated ACTH deficiency following immunization with the BNT162b2 SARS-CoV-2 vaccine: a case report. BMC Endocr Disord. 2022 Jul 19;22(1):185. doi: 10.1186/s12902-022-01095-3.
Piñar-Gutiérrez A, Remón-Ruiz P, Soto-Moreno A. Case report: Pituitary apoplexy after COVID-19 vaccination. Med Clin (Barc). 2022 May 27;158(10):498-499. doi: 10.1016/j.medcli.2021.09.028.
Roncati L, Manenti A. Pituitary apoplexy following adenoviral vector-based COVID-19 vaccination. Brain Hemorrhages. 2022 Apr 19. doi: 10.1016/j.hest.2022.04.002.

Parathyroid, vitamin D, calcium and bone, and SARS-CoV-2 spike protein



FGF23
PTHrp
Parathyroids - PTH
Bone
CTx
NTx
P1NP
Osteocalcin
25(OH)D
1,25(OH)D
Urinary Ca
Serum Ca

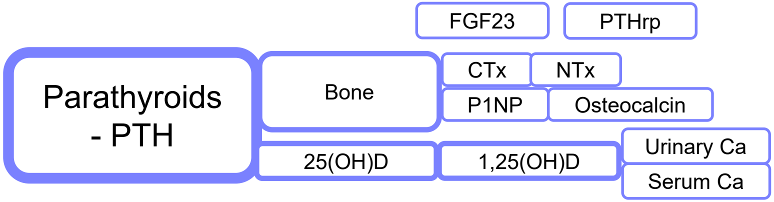
SARS-CoV-2 spike protein →
- Present in the parathyroids
- Potentially interferes in the vitamin D receptor (VDR)
- Directly and indirectly (through reduction of PTH) reduces 1alpha-reductase activity → Reduction of activation of vitamin D (25(OH)D → 1,25(OH)D)
- Functional hypoparathyroidism

Effects →
- Not dependent on vitamin D status
- Exacerbated or triggered by low vitamin D status

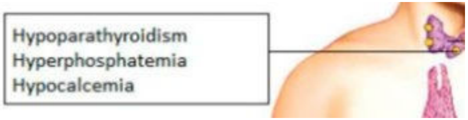
Main manifestations →
- Hypocalcemia + hyperphosphatemia
- Chronic fatigue (fluctuable), weakness
- Vertebral fractures
- Immunologic disorders and immunesuppression
- Viral reactivation

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.

Parathyroid, vitamin D, calcium and bone, and SARS-CoV-2 spike protein - Summary



Expected



Early

1. Complicated recovery in patients with vitamin D deficiency and hypocalcemia
2. Vertebral fractures

Late

1. Vitamin D deficiency
2. Increased PTH

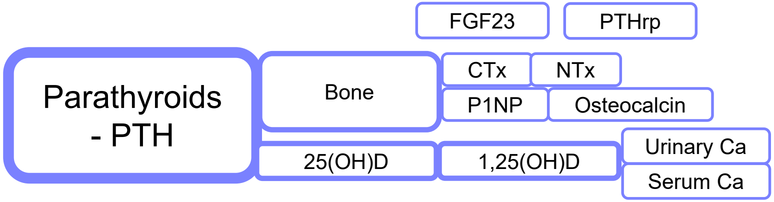
Proposed mechanisms

1. Home isolation and low sun exposure during lockdowns

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.
Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. BMC Endocr Disord. 2020 Sep 29;20(1):149. doi: 10.1186/s12902-020-00626-0.

Parathyroid, vitamin D, calcium and bone, and SARS-CoV-2 spike protein - Expected



FGF23

PTHrp

Parathyroids - PTH

Bone

CTx

NTx

P1NP

Osteocalcin

25(OH)D

1,25(OH)D

Urinary Ca

Serum Ca

Predicted (not based on current evidence)

? FGF23

~~PTHrp~~

Parathyroids - =/↓ PTH

Bone

↑ CTx

↑ NTx

↑ P1NP

↓ Osteocalcin

=/↑ 25(OH)D

↓1,25(OH)D

↓ Urinary Ca

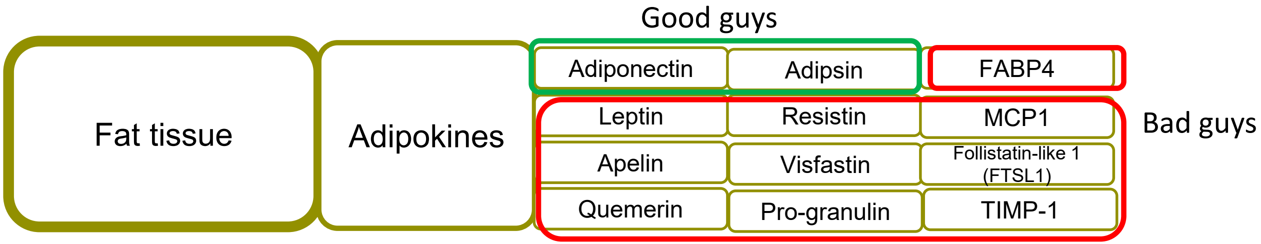
=/↓ Serum Ca

FLCCC ALLIANCE EDUCATIONAL CONFERENCE 2022

Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. Endocr Connect. 2021 Sep 20;10(9):R229-R239. doi: 10.1530/EC-21-0184.

Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. BMC Endocr Disord. 2020 Sep 29;20(1):149. doi: 10.1186/s12902-020-00626-0.

Fat tissue and
SARS-CoV-2 spike protein



Good guys

Bad guys

Fat tissue	Adipokines	Adiponectin	Adipsin	FABP4
		Leptin	Resistin	MCP1
		Apelin	Visfastin	Follistatin-like 1 (FTSL1)
		Quemerin	Pro-granulin	TIMP-1

SARS-CoV-2 spike protein (speculative) →

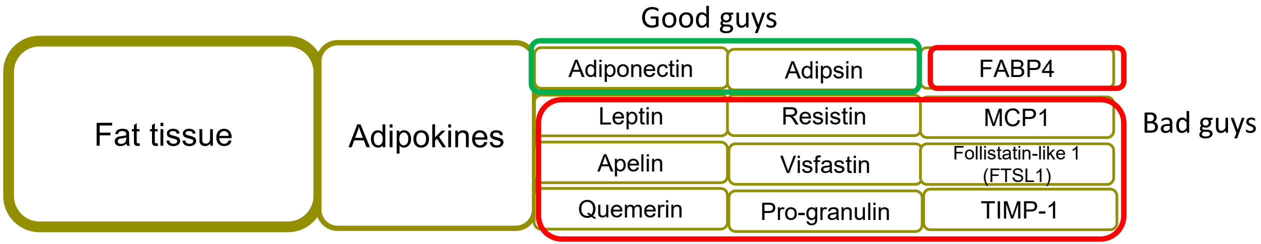
- Increase of pro-inflammatory adipokines and reduction of anti-inflammatory adipokines for a determined type and adipocyte volume
- Reduces lipogenesis and adipogenesis in subcutaneous fat →
- Predisposition for hypertrophy of ectopic, dysfunctional adipocyte

Effects →

- Exacerbation of metabolic diseases
- Increased risks in the presence of metabolic diseases
- Increased mortality due to:

1. Cardiovascular diseases | 2. Diabetes | 3. Cancer | 4. Dementia (among > 200 other diseases)

Fat tissue and SARS-CoV-2 spike protein - Expected

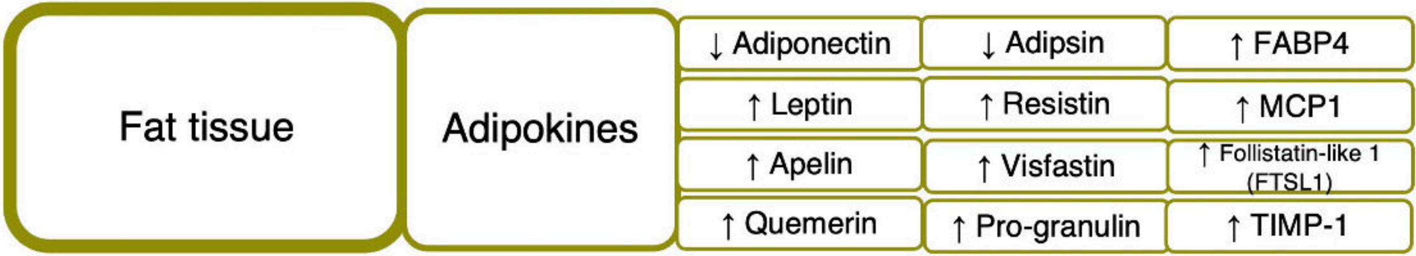


Good guys

Bad guys

Fat tissue	Adipokines	Adiponectin	Adipsin	FABP4
		Leptin	Resistin	MCP1
		Apelin	Visfastin	Follistatin-like 1 (FTSL1)
		Quemerin	Pro-granulin	TIMP-1

Predicted (not based on current evidence)



Fat tissue	Adipokines	↓ Adiponectin	↓ Adipsin	↑ FABP4
		↑ Leptin	↑ Resistin	↑ MCP1
		↑ Apelin	↑ Visfastin	↑ Follistatin-like 1 (FTSL1)
		↑ Quemerin	↑ Pro-granulin	↑ TIMP-1

Fang D, Shi X, Jia X, Yang C, Wang L, Du B, et al. Ups and Downs: The PPARgamma/p-PPARgamma Seesaw of Follistatin-Like 1 and Integrin Receptor Signaling in Adipogenesis. *Mol Metab* (2022) 55:101400. doi: 10.1016/j.molmet.2021.101400

Xu X, Zhang T, Mokou M, Li L, Li P, Song J, et al. 'Follistatin-Like 1 as a Novel Adipomyokine Related to Insulin Resistance and Physical Activity'. *J Clin Endocrinol Metab* (2020) 105:dgaa629. doi: 10.1210/clinem/dgaa629

Yang S, Dai H, Hu W, Geng S, Li L, Li X, et al. 'Association Between Circulating Follistatin-Like-1 and Metabolic Syndrome in Middle-Aged and Old Population: A Cross-Sectional Study'. *Diabetes Metab Res Rev* (2021) 37:e3373. doi: 10.1002/dmrr.3373

Biondi G, Marrano N, Borrelli A, Rella M, Palma G, Calderoni I, Siciliano E, Lops P, Giorgino F, Natalicchio A. Adipose Tissue Secretion Pattern Influences β-Cell Wellness in the Transition from Obesity to Type 2 Diabetes. Int J Mol Sci. 2022 May 15;23(10):5522. doi: 10.3390/ijms23105522.

Genchi, V.A.; D'oria, R.; Palma, G.; Caccioppoli, C.; Cignarelli, A.; Natalicchio, A.; Laviola, L.; Giorgino, F.; Perrini, S. Impaired leptin signalling in obesity: Is leptin a new thermolipokine? Int. J. Mol. Sci. 2021, 22, 6445

Kawai, T.; Autieri, M.V.; Scalia, R. Adipose Tissue Inflammation and Metabolic Dysfunction in Obesity. Am. J. Physiol. Cell Physiol. 2021, 320, C375–C391.

Porro, S.; Genchi, V.A.; Cignarelli, A.; Natalicchio, A.; Laviola, L.; Giorgino, F.; Perrini, S. Dysmetabolic adipose tissue in obesity: Morphological and functional characteristics of adipose stem cells and mature adipocytes in healthy and unhealthy obese subjects. J. Endocrinol. Investig. 2021, 44, 921–941.

Cheng, L.; Wang, J.; Dai, H.; Duan, Y.; An, Y.; Shi, L.; Lv, Y.; Li, H.; Wang, C.; Ma, Q.; et al. Brown and beige adipose tissue: A novel therapeutic strategy for obesity and type 2 diabetes mellitus. *Adipocyte* 2021, *10*, 48–65.

Vecchiola A, Fuentes CA, Solar I, et al. Eplerenone Implantation Improved Adipose Dysfunction Averting RAAS Activation and Cell Division. *Front Endocrinol (Lausanne)*. 2020;11:223. Published 2020 Apr 21.

Imai Y, Kuba K, Ohto-Nakanishi T, Penninger JM. Angiotensin-Converting Enzyme 2 (ACE2) in Disease Pathogenesis. Circ J. 2010;74(3):405–10.

Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. *Biomed Pharmacother*. 2017;94:317–325.

Feraco A, Armani A, Mammi C, Fabbri A, Rosano GM, Caprio M. Role of mineralocorticoid receptor and renin-angiotensin-aldosterone system in adipocyte dysfunction and obesity. *J Steroid Biochem Mol Biol*. 2013;137:99-106.

Weisberg, S.P.; McCann, D.; Desai, M.; Rosenbaum, M.; Leibel, R.L.; Ferrante, A.W., Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Investig.* 2003, *112*, 1796.

Wensveen, F.M.; Jelenčić, V.; Valentić, S.; Šestan, M.; Wensveen, T.T.; Theurich, S.; Glasner, A.; Mendrila, D.; Štimac, D.; Wunderlich, F.T.; et al. NK cells link obesity-induced adipose stress to inflammation and insulin resistance. *Nat. Immunol.* 2015, *16*, 376–385.

Jialal, I.; Adams-Huet, B.; Duong, F.; Smith, G. Relationship between retinol-binding protein-4/adiponectin and leptin/adiponectin ratios with insulin resistance and inflammation. Metab. Syndr. Relat. Disord. 2014, 12, 227–230.

Su, K.Z.; Li, Y.R.; Zhang, D.; Yuan, J.H.; Zhang, C.S.; Liu, Y.; Song, L.M.; Lin, Q.; Li, M.W.; Dong, J. Relation of circulating resistin to insulin resistance in type 2 diabetes and obesity: A systematic review and meta-analysis. Front. Physiol. 2019, 10, 1399.

Curat, C.A.; Wegner, V.; Sengenès, C.; Miranville, A.; Tonus, C.; Busse, R.; Bouloumié, A. Macrophages in human visceral adipose tissue: Increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia* 2006, *49*

Boucher, J.; Masri, B.; Daviaud, D.; Gesta, S.; Guigné, C.; Mazzucotelli, A.; Castan-Laurell, I.; Tack, I.; Knibiehler, B.; Carpéné, C.; et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. *Endocrinology* 2005, *146*, 1764–1771., 744–747.

Roca-Rivada, A.; Castelao, C.; Senin, L.L.; Landrove, M.O.; Baltar, J.; Crujeiras, A.B.; Seoane, L.M.; Casanueva, F.F.; Pardo, M. FNDC5/Irisin is not only a myokine but also an adipokine. *PLoS ONE* 2013, *8*, e60563.

Moreno-Navarrete, J.M.; Ortega, F.; Serrano, M.; Guerra, E.; Pardo, G.; Tinahones, F.; Ricart, W.; Fernández-Real, J.M. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. *J. Clin. Endocrinol. Metab.* 2013, *98*, 769–778.

Park, K.H.; Zaichenko, L.; Brinkoetter, M.; Thakkar, B.; Sahin-Efe, A.; Joung, K.E.; Tsoukas, M.A.; Geladari, E.V.; Huh, J.Y.; Dincer, F.; et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. *J. Clin. Endocrinol. Metab.* 2013, *98*, 4899–4907.

Cignarelli, A.; Genchi, V.A.; Perrini, S.; Natalicchio, A.; Laviola, L.; Giorgino, F. Insulin and Insulin Receptors in Adipose Tissue Development. *Int. J. Mol. Sci.* 2019, *20*, 759.

Hoffstedt, J.; Arvidsson, E.; Sjölin, E.; Wåhlén, K.; Arner, P. Adipose Tissue Adiponectin Production and Adiponectin Serum Concentration in Human Obesity and Insulin Resistance. J. Clin. Endocrinol. Metab. 2004, 89, 1391–1396

Gautier, A.; Bonnet, F.; Dubois, S.; Massart, C.; Grosheny, C.; Bachelot, A.; Aubé, C.; Balkau, B.; Ducluzeau, P.-H. Associations between Visceral Adipose Tissue, Inflammation and Sex Steroid Concentrations in Men. *Clin. Endocrinol.* 2013, *78*, 373–378.

Bełtowski J. Apelin and visfatin: unique "beneficial" adipokines upregulated in obesity? Med Sci Monit. 2006 Jun;12(6):RA112-9. Epub 2006 May 29. PMID: 16733497.

Horak M, Kuruczova D, Zlamal F, Tomandl J, Bienertova-Vasku J. 'Follistatin-Like 1 Is Downregulated in Morbidly and Super Obese Central-European Population'. *Dis Markers* (2018) 2018:4140815. doi: 10.1155/2018/414081

Fan N, Sun H, Wang Y, Wang Y, Zhang L, Xia Z, et al. Follistatin-Like 1: A Potential Mediator of Inflammation in Obesity. *Mediators Inflammation* (2013) 2013:752519. doi: 10.1155/2013/752519

Ernst MC, Haidl ID, Zuniga LA, Dranse HJ, Rourke JL, Zabel BA, et al. Disruption of the Chemokine-Like Receptor-1 (CMKLR1) Gene is Associated With Reduced Adiposity and Glucose Intolerance. *Endocrinology* (2012) 153:672–82. doi: 10.1210/en.2011-1490

Catalan V, Gomez-Ambrosi J, Rodriguez A, Ramirez B, Rotellar F, Valenti V, et al. Increased Levels of Chemerin and its Receptor, Chemokine-Like Receptor-1, in Obesity are Related to Inflammation: Tumor Necrosis Factor-Alpha Stimulates mRNA Levels of Chemerin in Visceral Adipocytes From Obese Patients. *Surg Obes Relat Dis* (2013) 9:306–14. doi: 10.1016/j.soard.2011.11.001

Fulop P, Seres I, Lorincz H, Harangi M, Somodi S, Paragh G. Association of Chemerin With Oxidative Stress, Inflammation and Classical Adipokines in non-Diabetic Obese Patients. *J Cell Mol Med* (2014) 18:1313–20. doi: 10.1111/jcmm.12282

Incretin system and SARS-CoV-2 spike protein - Expected

Intestine

Incretin system

GLP-1

GIP

Oxyntomodulin

CCK

PYY

GLP-2

SARS-CoV-2 spike protein (speculative) →

- Present in L and K cells in the intestine → dysregulation
- Reduction of GLP-1, GIP, and other incretins in response to meal
- Reduction of pancreas and body sensitivity to incretins
- (Disastrous) Consequences of a ‘global incretin reduction’

Intestine

↓ Incretin system

↓ GLP-1

↓ GIP

↓ Oxyntomodulin

↓ CCK

↓ PYY

↓ GLP-2

Osinski C, Moret D, Clément K, Serradas P, Ribeiro A. Enteroendocrine System and Gut Barrier in Metabolic Disorders. Int J Mol Sci. 2022 Mar 29;23(7):3732. doi: 10.3390/ijms23073732.

Jonik S, Marchel M, Grabowski M, Opolski G, Mazurek T. Gastrointestinal Incretins-Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-like Peptide-1 (GLP-1) beyond Pleiotropic Physiological Effects Are Involved in Pathophysiology of Atherosclerosis and Coronary Artery Disease-State of the Art. Biology (Basel). 2022 Feb 11;11(2):288. doi: 10.3390/biology11020288.

Rizvi AA, Rizzo M. The Emerging Role of Dual GLP-1 and GIP Receptor Agonists in Glycemic Management and Cardiovascular Risk Reduction. Diabetes Metab Syndr Obes. 2022 Apr 5;15:1023-1030. doi: 10.2147/DMSO.S351982.

Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. Diabetes Obes Metab. 2021 Sep;23 Suppl 3:5-29. doi: 10.1111/dom.14496.

Seon MJ, Hwang SY, Son Y, Song J, Kim OY. Circulating GLP-1 Levels as a Potential Indicator of Metabolic Syndrome Risk in Adult Women. Nutrients. 2021 Mar 6;13(3):865. doi: 10.3390/nu13030865.

Góralska J, Raźny U, Polus A, Dziewońska A, Gruca A, Zdzienicka A, Dembińska-Kieć A, Solnica B, Micek A, Kapusta M, Słowińska-Solnica K, Malczewska-Malec M. Enhanced GIP Secretion in Obesity Is Associated with Biochemical Alteration and miRNA Contribution to the Development of Liver Steatosis. Nutrients. 2020 Feb 13;12(2):476. doi: 10.3390/nu12020476.

Sarkar J, Nargis T, Tantia O, Ghosh S, Chakrabarti P. Increased Plasma Dipeptidyl Peptidase-4 (DPP4) Activity Is an Obesity-Independent Parameter for Glycemic Deregulation in Type 2 Diabetes Patients. Front Endocrinol (Lausanne). 2019 Jul 25;10:505. doi: 10.3389/fendo.2019.00505.

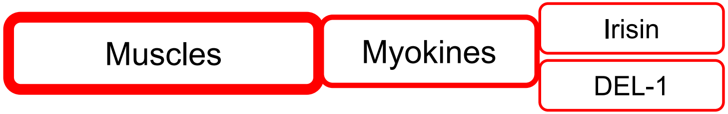
Madsbad S. The role of glucagon-like peptide-1 impairment in obesity and potential therapeutic implications. Diabetes Obes Metab. 2014 Jan;16(1):9-21. doi: 10.1111/dom.12119.

Sandoval DA, D'Alessio DA. Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. Physiol Rev. 2015 Apr;95(2):513-48. doi: 10.1152/physrev.00013.2014.

Carr, R.D.; Larsen, M.O.; Jelic, K.; Lindgren, O.; Vikman, J.; Holst, J.J.; Deacon, C.F.; Ahrén, B. Secretion and Dipeptidyl Peptidase-4-Mediated Metabolism of Incretin Hormones after a Mixed Meal or Glucose Ingestion in Obese Compared to Lean, Nondiabetic Men. *J. Clin. Endocrinol. Metab.* 2010, *95*, 872–878.

Steinert RE, Feinle-Bisset C, Asarian L, Horowitz M, Beglinger C, Geary N. Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory Controls and Physiological Roles in Eating and Glycemia in Health, Obesity, and After RYGB. Physiol Rev. 2017 Jan;97(1):411-463. doi: 10.1152/physrev.00031.2014.

Muscles and
SARS-CoV-2 spike protein - Expected


Muscles

Myokines

Irisin

DEL-1

SARS-CoV-2 spike protein (speculative) →

- Vastly present in all types of muscles and locations
- Reduction of its functionality
- Potential reduction of exercise-induced irisin secretion and basal DEL-1
- Potential acceleration of the process of muscle loss → Early, severe sarcopenia
- Multiple consequences of sarcopenia


Muscles

Myokines

↓ Irisin

↓ DEL-1

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

Ren Y, Zhao H, Yin C, Lan X, Wu L, Du X, Griffiths HR, Gao D. Adipokines, Hepatokines and Myokines: Focus on Their Role and Molecular Mechanisms in Adipose Tissue Inflammation. Front Endocrinol (Lausanne). 2022 Jul 14;13:873699. doi: 10.3389/fendo.2022.873699.

SARS-CoV-2 spike protein and Endocrinologic dysfunctions – Practical approach

Level (0-10)	Short term	Long term	Likelihood	Relevance	Level of priority
Male hypogonadism	5	7	5	8	7
Male infertility	3	9	6	10	10
Early menopause	4	8	6	10	10
Female infertility	3	6	4	10	10
Type 1 diabetes	7	4	5	7	7
Type 2 diabetes	2	8	6	9	10
Diabetic complications	6	7	6	8	6
Graves disease	8	1	3	2	1
Hashimoto's disease	3	6	6	7	7
Hypothyroidism	1	6	5	8	7
Impaired T4-T3 conversion	5	3	8	5	5
Thyroid cancer	0	3	2	6	3
Adrenal insufficiency	5	6	2	8	4
'Pseudocushing'	3	5	3	4	6
RAAS-related conditions	4	7	6	8	8
Catecholaminergic hyperactivity	9	5	8	8	8
Growth Hormone (GH) deficiency	2	7	5	9	4
Panhypopituitarism	3	5	3	9	4
'Functional' hypoparathyroidism	6	3	8	7	10
Low active vitamin D	8	3	8	9	10
Dysfunctional fat tissue	1	6	8	9	9
Sarcopenia	3	7	8	8	10

SARS-CoV-2 spike protein and Endocrinologic dysfunctions – Practical approach

	When	Blood work	‘Treatment’
Male hypogonadism	Suspected	LH, testosterone, SHBG, estradiol	Testosterone therapy
Male infertility	Selected	Sperm analysis	Clomiphene, HCG, recombinant FSH
Early menopause	Suspected	LH, FSH, estradiol	E2 +-P therapy
Female infertility	Selected	AMH, follicle counting	Multiple (protocols)
Type 1 diabetes	Suspected	Fasting glucose/insulin/peptide C, OGTT, HbA1c, anti-GAD, -insulin, -ICA512	Insulin (off-label: GLP1a, SGLT2i)
Type 2 diabetes	Screening	Fasting glucose, OGTT, HbA1c	Diet, exercise, metformin, GLP1a, SGLT2i
Diabetic complications	Screening*	24h urine, ENMG, retinography	Glucose control
Graves disease	Suspected	TSAb, TSI, TSH, thyroid scintigraphy	Methimazole, iodotherapy
Hashimoto’s disease	Screening?	Anti-TPO, anti-tireoglobulin	Levothyroxine, liothyronine, vit D, selenium
Hypothyroidism	Screening?	TSH, T4/fT4, T3/fT3	Levothyroxine, liothyronine, selenium
Impaired T4-T3 conversion	Selected	T3/T4 ratio, rT3/T3 ratio	Liothyronine
Thyroid cancer	Suspected	Thyroid/cervical ultrasonography	Surgery, +- iodotherapy
Adrenal insufficiency	Suspected	Basal cortisol/ACTH, cortisol stimulation test	Hydrocortisone, fludrocortisone
‘Pseudocushing’	Suspected	Post-dex cortisol, 24h-UFC, 11PM salivary cortisol	Ketoconazole, metformin
RAAS-related conditions	Clinical**	Renin, aldosterone	Spironolactone
Catecholaminergic hyperactivity	Suspected	Plasma/urinary catecholamines/metanephrines	Alpha- and beta-blockers
Growth Hormone (GH) deficiency	Suspected	IGF-1, GH stimulation test	GH, GHRH analogue
Panhypopituitarism	Suspected	ACTH/cortisol, IGF-1, TSH/T4?T3, LH/FSH/E2/T	Hydrocortisone, T4, T3, T or E2/P, GH
‘Functional’ hypoparathyroidism	Assumed	25(OH)D, 1,25(OH)D, serum Ca, PTH, DEXA	Calcifediol, calcitriol, cholecalciferol, Ca
Low active vitamin D	Assumed	25(OH)D, 1,25(OH)D, serum Ca, PTH	Calcifediol, calcitriol, cholecalciferol
Dysfunctional fat tissue	Assumed	Adiponectin, leptin, IL-6, hsCRP	Diet, exercise, anti-obesity interventions
Sarcopenia	Assumed	BIA, DEXA	High-protein diet, resistance exercise, hormone therapy>

‘Treatment’ = not considering preventing approaches

FLCCC ALLIANCE
EDUCATIONAL CONFERENCE
2022

Overall treatments in andSARS-CoV-2 spike-induced diseases that affects the endocrine system

1. Melatonin – multiple benefits in overall hormone regulation and metabolism
2. Oxytocin – mood disorders, fatigue, potentially including hormonal dysfunctions
3. LD naltrexone – multiple regulatory actions
4. Fludrocortisone, extended/dual-release hydrocortisone - Selected cases when not in overt adrenal insufficiency
5. DHEA
6. Tadalafil + L-arginine
7. Nandrolone, oxandrolone – sarcopenia, severe fatigue
8. Optimization of hormonal therapies
9. High-dose methylfolate + methylB12 + B6
10. LD lisdexamfetamine - Selected, refractory cases
11. Calcefidiol, calcitriol
12. Thioctic acid
13. Iron
14. Rhodiola rosea
15. Ashwaganda (Withania *somnifera*)
16. Vitamin C
17. Ginseng
18. Beta-alanine | HMB
19. 5-HTP
20. GABA
21. High-dose CoQ10
22. Probiotics (+ support to consolidate and maintain a healthy gut microbiota)
23. High-dose multisalt magnesium
24. Ozone?
25. Hydroxychloroquine?
26. Ivermectin?
27. Compounded intranasal ivermectin?
28. Ozone?
29. Intravenous high-dose amino acids?

Overall treatments in andSARS-CoV-2 spike-induced diseases that affects the endocrine system

Gerbarg PL, Brown RP. Pause menopause with Rhodiola rosea, a natural selective estrogen receptor modulator. Phytomedicine. 2016 Jun 15;23(7):763-9.
Lekomtseva Y, Zhukova I, Wacker A. Rhodiola rosea in Subjects with Prolonged or Chronic Fatigue Symptoms: Results of an Open-Label Clinical Trial. Complement Med Res. 2017;24(1):46-52.
Chaoyang Maa, Liming Hub, Guanjun Taoa, Wenping Lva, Hongxin Wanga, An UPLC-MS-based metabolomics investigation on the anti-fatigueeffect of salidroside in mice. Journal of Pharmaceutical and Biomedical Analysis 105 (2015) 84–90.
Ishaque S, Shamseer L, Bukutu C, Vohra S. Rhodiola rosea for physical and mental fatigue: a systematic review. BMC Complement Altern Med. 2012 May 29;12:70.
Kang DZ, Hong HD, Kim KI, Choi SY. Anti-Fatigue Effects of Fermented Rhodiola rosea Extract in Mice. Prev Nutr Food Sci. 2015 Mar;20(1):38-42.
Wallis A et al. Open-label pilot for treatment targeting gut dysbiosis in myalgic encephalomyelitis/chronic fatiguesyndrome: neuropsychological symptoms and sex comparisons. J Transl Med. 2018 Feb 6;16(1):24.
Litleskare S[1], Rortveit G[2], Eide GE[3], Hanevik K[4], Langeland N[4], Wensaas KA. Prevalence of Irritable Bowel Syndrome and Chronic Fatigue 10 Years after Giardia Infection. Clin Gastroenterol Hepatol. 2018 Jan 25.
Nagy-Szakal D et al. Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome. 2017 Apr 26;5(1):44.
Mandarano AH[1], Giloteaux L[1], Keller BA[2], Levine SM[1], Hanson MR. Eukaryotes in the gut microbiota in myalgic encephalomyelitis/chronic fatigue syndrome. PeerJ. 2018 Jan 22;6:e4282.
Evrensel A[1], Ceylan ME. Fecal Microbiota Transplantation and Its Usage in Neuropsychiatric Disorders. Clin Psychopharmacol Neurosci. 2016 Aug 31;14(3):231-7.
Lee N, Lee SH, Yoo HR, Yoo HS. Anti-Fatigue Effects of Enzyme-Modified Ginseng Extract: A Randomized, Double-Blind, Placebo-Controlled Trial. J Altern Complement Med. 2016 Nov;22(11):859-864.
Kim HG et al. Antifatigue effects of Panax ginseng C.A. Meyer: a randomised, double-blind, placebo-controlled trial. PLoS One. 2013 Apr 17;8(4):e61271.
Hsiao CY[1,2], Hsu YJ[3], Tung YT[4], Lee MC[3], Huang CC[3,4], Hsieh CC. Effects of Antrodia camphorata and Panax ginseng supplementation on anti-fatigue properties in mice. J Vet Med Sci. 2017 Dec 25.
Yennurajalingam S et al. A Double-Blind, Randomized, Placebo-Controlled Trial of Panax Ginseng for Cancer-Related Fatigue in Patients With Advanced C ncer. J Natl Compr Canc Netw. 2017 Sep;15(9):1111-1120.
Chang YD et al. Single Institute Experience With Methylphenidate and American Ginseng in Cancer-Related Fatigue. Am J Hosp Palliat Care. 2018 Jan;35(1):144-150.
Kalman D[1], Harvey PD[2], Perez Ojalvo S[3], Komorowski J. Randomized Prospective Double-Blind Studies to Evaluate the Cognitive Effects of Inositol-Stabilized Arginine Silicate in Healthy Physically Active Adults. Nutrients. 2016 Nov 18;8(11).
Silva EP Jr[1], Borges LS[1], Mendes-da-Silva C[2], Hirabara SM[1], Lambertucci RH. l-Arginine supplementation improves rats' antioxidant system and exercise performance. Free Radic Res. 2017 Mar;51(3):281-293.
Smriga M[1], Ando T, Akutsu M, Furukawa Y, Miwa K, Morinaga Y. Oral treatment with L-lysine and L-arginine reduces anxiety and basal cortisol levels in healthy humans. Biomed Res. 2007 Apr;28(2):85-90.
Siyambalapitiya S[1], Ibbotson V, Doane A, Ghigo E, Campbell MJ, Ross RJ. Combining growth hormone releasing hormone-arginine and synacthen testing diminishes the cortisol response. J Clin Endocrinol Metab. 2007 Mar;92(3):853-6.
Berti Zanella P1, Donner Alves F2, Guerini de Souza C. Effects of beta-alanine supplementation on performance and muscle fatigue in athletes and non-athletes of different sports: a systematic review. J Sports Med Phys Fitness. 2017 Sep;57(9):1132-1141
Russ DW et al. Dietary HMB and β-alanine co-supplementation does not improve in situ muscle function in sedentary, aged male rats. Appl Physiol Nutr Metab. 2015 Dec;40(12):1294-301.
Wu H et al. Effect of beta-hydroxy-beta-methylbutyrate supplementation on muscle loss in older adults: a systematic review and meta-analysis. Arch Gerontol Geriatr. 2015 Sep-Oct;61(2):168-75.
Holeček M. Beta-hydroxy-beta-methylbutyrate supplementation and skeletal muscle in healthy and muscle-wasting conditions. J Cachexia Sarcopenia Muscle. 2017 Aug;8(4):529-541.
Pinheiro CH et al. Metabolic and functional effects of beta-hydroxy-beta-methylbutyrate (HMB) supplementation in skeletal muscle. Eur J Appl Physiol. 2012 Jul;112(7):2531-7.
Kim JS1, Khamoui AV, Jo E, Park BS, Lee W . β-Hydroxy-β-methylbutyrate as a countermeasure for cancer cachexia: a cellular and molecular rationale. Anticancer Agents Med Chem. 2013 Oct;13(8):1188-96..
Mirza KA[1], Pereira SL[2], Voss AC[2], Tisdale MJ. Comparison of the anticatabolic effects of leucine and Ca-β-hydroxy-β-methylbutyrate in experimental models of cancer cachexia. Nutrition. 2014 Jul-Aug;30(7-8):807-13..
Das D[1], Sen C[1], Goswami A[1]. Effect of Vitamin C on adrenal suppression by etomidate induction in patients undergoing cardiac surgery: A randomized controlled trial. Ann Card Anaesth. 2016 Jul-Sep;19(3):410-7.
Olayaki LA[1], Sulaiman SO, Anoba NB. Vitamin C Prevents Sleep Deprivation-induced Elevation in Cortisol and Lipid Peroxidation in the Rat Plasma. Niger J Physiol Sci. 2015 Dec 20;30(1-2):5-9.
Montalvo CP[1], Díaz NH, Galdames LA, Andrés ME, Larraín RE. Short communication: effect of vitamins E and C on cortisol production by bovine adrenocortical cells in vitro. J Dairy Sci. 2011 Jul;94(7):3495-7.
Padayatty SJ et al. Human adrenal glands secrete vitamin C in response to adrenocorticotrophic hormone. Am J Clin Nutr. 2007 Jul;86(1):145-9.
Carr AC[1], Vissers MC[1], Cook JS[2]. The effect of intravenous vitamin C on cancer- and chemotherapy-related fatigue and quality of life. Front Oncol. 2014 Oct 16;4:283.
Huck CJ[1], Johnston CS, Beezhold BL, Swan PD. Vitamin C status and perception of effort during exercise in obese adults adhering to a calorie-reduced diet. Nutrition. 2013 Jan;29(1):42-5.
Biswal BM et al. Effect of Withania somnifera (Ashwagandha) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. Integr Cancer Ther. 2013 Jul;12(4):312-22.
Winters M. Ancient medicine, modern use: Withania somnifera and its potential role in integrative oncology. Altern Med Rev. 2006 Dec;11(4):269-77.
Mishra LC[1], Singh BB, Dagenais S. Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): a review. Altern Med Rev. 2000 Aug;5(4):334-46.
Singh A[1], Naidu PS, Gupta S, Kulkarni SK. Effect of natural and synthetic antioxidants in a mouse model of chronic fatigue syndrome. J Med Food. 2002 Winter;5(4):211-20.
Choudhary D[1], Bhattacharyya S[2], Joshi K[3]. Body Weight Management in Adults Under Chronic Stress Through Treatment With Ashwagandha Root Extract: A Double-Blind, Randomized, Placebo-Controlled Trial. J Evid Based Complementary Altern Med. 2017 Jan;22(1):96-106.
J Int Soc Sports Nutr. 2015 Nov 25;12:43. doi: 10.1186/s12970-015-0104-9. eCollection 2015.
Wankhede S[1], Langade D[2], Joshi K[3], Sinha SR[4], Bhattacharyya S[5]. Examining the effect of Withania somnifera supplementation on muscle strength and recovery: a randomized controlled trial. J Int Soc Sports Nutr. 2015 Nov 25;12:43.
Chandrasekhar K[1], Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012 Jul;34(3):255-62.
Sharma AK[1], Basu I[1], Singh S[1]. Efficacy and Safety of Ashwagandha Root Extract in Subclinical Hypothyroid Patients: A Double-Blind, Randomized Placebo-Controlled Trial. J Altern Complement Med. 2017 Aug 22.
Choudhary D[1], Bhattacharyya S[2], Bose S[2]. Efficacy and Safety of Ashwagandha (Withania somnifera (L.) Dunal) Root Extract in Improving Memory and Cognitive Functions. J Diet Suppl. 2017 Nov 2;14(6):599-612.
Choudhary B[1], Shetty A[2], Langade DG[3]. ,. Efficacy of Ashwagandha (Withania somnifera [L.] Dunal) in improving cardiorespiratory endurance in healthy athletic adults. Ayu. 2015 Jan-Mar;36(1):63-8..
Talbott SM[1], Talbott JA, Pugh M. Effect of Magnolia officinalis and Phellodendron amurense (Relora®) on cortisol and psychological mood state in moderately stressed subjects. J Int Soc Sports Nutr. 2013 Aug 7;10(1):37.
Kalman DS et al. Effect of a proprietary Magnolia and Phellodendron extract on stress levels in healthy women: a pilot, double-blind, placebo-controlled clinical trial. Nutr J. 2008 Apr 21;7:11.
Garrison R[1], Chambliss WG. Effect of a proprietary Magnolia and Phellodendron extract on weight management: a pilot, double-blind, placebo-controlled clinical trial. *Altern Ther Health Med. 2006 Jan-Feb; 12(1):50-4.*
Park S[1], Kim DS[1], Kang S[1], Shin BK[1]. Synergistic topical application of salt-processed Phellodendron amurense and Sanguisorba officinalis Linne alleviates atopic dermatitis symptoms by reducing levels of immunoglobulin E and pro-inflammatory cytokines in NC/Nga mice. Mol Med Rep. 2015 Nov;12(5):7657-64.
Li CG et al. Honokiol protects pancreatic β cell against high glucose and intermittent hypoxia-induced injury by activating Nrf2/ARE pathway in vitro and in vivo. Biomed Pharmacother. 2018 Jan;97:1229-1237.
Talarek S et al. Neuroprotective effects of honokiol: from chemistry to medicine. Biofactors. 2017 Nov;43(6):760-769.
Xian YF[1], Ip SP[2], Mao QQ[1], Lin ZX. Neuroprotective effects of honokiol against beta-amyloid-induced neurotoxicity via GSK-3β and β-catenin signaling pathway in PC12 cells. Neurochem Int. 2016 Jul;97:8-14.
Jangra A et al. Honokiol abrogates chronic restraint stress-induced cognitive impairment and depressive-like behaviour by blocking endoplasmic reticulum stress in the hippocampus of mice. Eur J Pharmacol. 2016 Jan 5;770:25-32.
Zhang Z et al. Magnolia bioactive constituent 4-O-methylhonokiol prevents the impairment of cardiac insulin signaling and the cardiac pathogenesis in high-fat diet-induced obese mice. Int J Biol Sci. 2015 Jun 5;11(8):879-91.
Zhang Z et al. The magnolia bioactive constituent 4-O-methylhonokiol protects against high-fat diet-induced obesity and systemic insulin resistance in mice. *Oxid Med Cell Longev. 2014; 2014:965954.*
Wang J et al. BL153 partially prevents high-fat diet induced liver damage probably via inhibition of lipid accumulation, inflammation, and oxidative stress. *Oxid Med Cell Longev. 2014; 2014:674690.*
Yamamoto T, Newsholme EA. Diminished central fatigue by inhibition of the L-system transporter for the uptake of tryptophan. Brain Res Bull. 2000 May 1;52(1):35-8.
Yamamoto T[1], Azechi H, Board M. Essential role of excessive tryptophan and its neurometabolites in fatigue. Can J Neurol Sci. 2012 Jan;39(1):40-7.
Cao Y[1], Li Q. The variation of the 5-hydroxytryptamine system between chronic unpredictable mild stress rats and chronic fatigue syndrome rats induced by forced treadmill running. Neuroreport. 2017 Aug 2;28(11):630-637.
Gibson EL et al. Tryptophan supplementation and serotonin function: genetic variations in behavioural effects. Tryptophan supplementation and serotonin function: genetic variations in behavioural effects.
Yamashita M[1], Yamamoto T. Tryptophan circuit in fatigue: From blood to brain and cognition. Brain Res. 2017 Nov 15;1675:116-126.
Leonte A, Colzato LS, Steenbergen L, Hommel B, Akyürek EG. Supplementation of gamma-aminobutyric acid (GABA) affects temporal, but not spatial visual attention. Brain Cogn. 2018 Feb;120:8-16.
Tabassum S et al. Impact of oral supplementation of Glutamate and GABA on memory performance and neurochemical profile in hippocampus of rats. Pak J Pharm Sci. 2017 May;30(3(Suppl.)):1013-1021.
Chen H et al. Extraction, purification and anti-fatigue activity of γ-aminobutyric acid from mulberry (Morus alba L.) leaves. Sci Rep. 2016 Jan 8;6:18933.
Powers M. GABA supplementation and growth hormone response. Med Sport Sci. 2012;59:36-46.
Teitelbaum J, Goudie S. An Open-Label, Pilot Trial of HRG80™ Red Ginseng in Chronic Fatigue Syndrome, Fibromyalgia, and Post-Viral Fatigue. Pharmaceuticals (Basel). 2021 Dec 29;15(1):43. doi: 10.3390/ph15010043.
Tirelli U, Franzini M, Valdenassi L, Pisconti S, Taibi R, Torrisi C, Pandolfi S, Chirumbolo S. Fatigue in post-acute sequelae of SARS-CoV2 (PASC) treated with oxygen-ozone autohemotherapy - preliminary results on 100 patients. Eur Rev Med Pharmacol Sci. 2021 Sep;25(18):5871-5875. doi: 10.26355/eurrev_202109_26809.
Castro-Marrero J, Domingo JC, Cordobilla B, Ferrer R, Giralt M, Sanmartin-Sentañes R, Alegre-Martin J. Does Dietary Coenzyme Q10 plus Selenium Supplementation Ameliorate Clinical Outcomes by Modulating Oxidative Stress and Inflammation in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome? Antioxid Redox Signal. 2022 Mar 1. doi: 10.1089/ars.2022.0018.
Nowak A[1], Boesch L, Andres E, Battegay E, Hornemann T, Schmid C, Bischoff-Ferrari HA, Suter PM, Krayenbuehl PA . Effect of vitamin D3 on self-perceived fatigue: A double-blind randomized placebo-controlled trial. Medicine (Baltimore). 2016 Dec;95(52):e5353. doi: 10.1097/MD.0000000000005353.

FLCCC
ALLIANCE
EDUCATIONAL
CONFERENCE
2022

THANK YOU