COVID -19 and Endocrine Function : Exploring the unexplored

Michigan State Medical Society
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COVID 19 and Endocrine function –Disclosures

NONE

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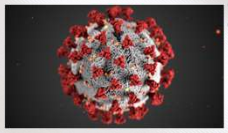
COVID-19 and Endocrine Function. Exploring the unexplored



Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus.(SARS-COV-2).

First noted in Wuhan Province in China – Dec 2019.

Epidemic in China –Feb 26,2020

WHO declares Pandemic –March 11,2020

Region	Infections	Deaths
World	220.5 million	4.5 million
USA	39.6 million	640,000
India	33.0 million	440,000

Source WHO Coronavirus (COVID-19)dashboard . Sept 6, 2021

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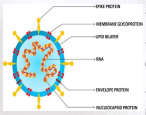
COVID -19 and Endocrine Function



- SARS- CoV-2 (COVID -19) is a single stranded RNA virus.
- ACE-2 is the binding site for the virus entry into the host cell.
- ACE-2 is expressed in lungs ,CV system ,GI System and also **many endocrine tissues including ,Pancreas ,Testis ,Ovaries, Adrenal ,Pituitary and Thyroid glands**
- **Endocrine effects : unexplored**

J Endocrinol Invest. 2020 May 2 : 1–5.
doi: 10.1007/s40618-020-01276-8 [Epub ahead of print]
PMCID: PMC7195612
PMID: 32361826
COVID-19 and the endocrine system: exploring the unexplored
R. Pal [1] and M. Banerjee [2]

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COVID -19 and Endocrine function - Diabetes

Worldwide 415 million adults have diabetes .
By the year 2040 this will increase to 642 million
34.2 million Americans (Just over 1 in 10) have diabetes
88 million Americans (Approx 1 in 3) have prediabetes

IDF diabetes atlas- 9th edition 2019

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Covid-19 and endocrine function. – Pancreas

- COVID-19 has been associated with damage to exocrine and endocrine components of Pancreas
- β cell may get damaged directly or by immune mechanisms (Cytokines)
- DM may down regulate ACE2 ,there by increasing the levels of Angiotensin II ,leading to delayed insulin secretion, local inflammation ,apoptosis of Islet cells
- A significant number of COVID-19 patients present with hyperglycemia (Not previously known DM), Including DKA and mixed DKA + HHS.
- Hyperglycemia: associated with dysfunction of phagocytosis, impaired neutrophil chemotaxis and impaired cell mediated immunity.

Lindholm MD et al .J Endo society 4;2020.https://doi.org10.1210/jendoso/bvaa144
Singh AK etal Diabetes Metab syndr. 2020;14(4):303-310
Huang I .Diabetes Metab syndr.2020;14(4):395-403

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COVID -19 and Endocrine Function.-Diabetes

- Diabetes is a "risk factor for poor outcome in pts with COVID-19.
- Increased incidence of COVID-19 among hospitalized patients with DM.
- In a meta- analysis (n=6452) DM was associated with increased severity, increased frequency of ARDS and higher mortality in patients with COVID-19
- DM may persist in "long haulers"

Lundholm M et al .J of endocrine society;4:2020https://doi.org/10.1210/jendso/bvaa144
Singh AK etal Diabetes Metab syndr. 2020;14(4):303-310
Huang,I Diabetes Metab syndr 2020;14(4): 395-403

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COVID -19 and Endocrine Function –Diabetes drugs

Recommendations for antihyperglycemic drugs for pts with Diabetes

Medication class	Outpatient use	Inpatient use	Comments
Insulin (Basal or Bolus)	X	X	May be added or increased to improve glycemic control
Metformin	X		Risk of Lactic acidosis, esp with Organ dysfunction. Hold if nausea ,vomiting or diarrhea
Sulfonylureas	X	X*	Risk of hypoglycemia. Hold , if poor dietary intake
Meglitinides	X	X*	Risk of hypoglycemia . Hold ,if poor intake
DPP4 inhibitors	X	X*	
GLP-1 agonists	X		May worsen nausea , vomiting or diarrhea
SGLT2 inhibitors	X		Risk of hypotension and Euglycemic DKA. Hold if poor intake

- *Although use of these drugs is not contraindicated in the inpatient setting, they are often withheld as they may not be well tolerated and safety data on inpatient use of oral medications is limited.
- Adapted from Lundholm MD et al J endo Society 2020;4(11) 1-13

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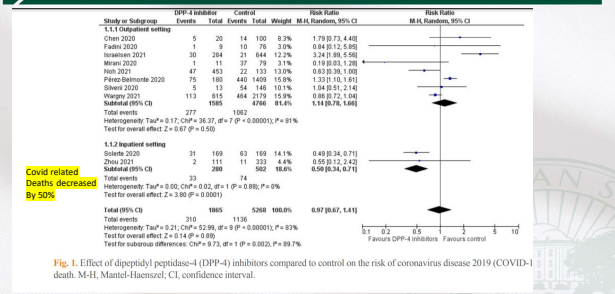
COVID-19 and Endocrine function- DPP4 inhibitors



Covid related Deaths decreased By 50%

Fig. 1. Effect of dipeptidyl peptidase-4 (DPP-4) inhibitors compared to control on the risk of coronavirus disease 2019 (COVID-1 death. M-H, Mantel-Haenszel; CI, confidence interval.

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Endocrinol Metab 2021 Forthcoming. https://doi.org/10.3803/EnM.2021.1048 pISSN 2093-596X · eISSN 2093-5978

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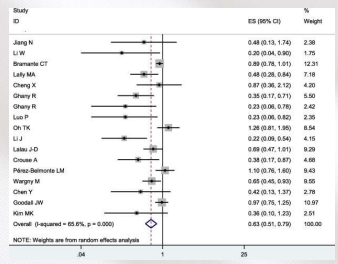
Covid- 19 and Endocrine function . Diabetes ;Metformin

Meta-analysis 17 studies ,n=20,719.



Overall, metformin was associated with significantly decreased mortality and severity in COVID-19 patients with diabetes
OR for mortality = 0.64 (0.51-0.79)

OR for severity = 0.81 (0.66–0.99)

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The effect of Metformin on mortality and severity in COVID-19 patients with Diabetes mellitus
Wenseng Y,Xurhong S,Jun Z, Kui Z. Diab Res Clin Pract

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COVID -19 and Endocrine function. Control of Diabetes

Retrospective study: n=7336 with COVID-19

N=810 with Diabetes

Measure	Poorly controlled n=528	Well controlled n=282	P value
HbA1c	8.3%	7.3%.	<.001
O2 saturation <95%	22.7%	12.6%	<.001
ARDS	21.4%	7.1%	<.001
Acute Head Injury	9.9%	1.4%	<.001
Acute kidney injury	3.8%	0.7%	<.0019
Septic Shock	4.7%	0.0%	
All Cause mortality		HR =.13 (0.04-0.44)	<.001

Zhu L,et al Cell Metab.2020;31:1-10. doi 10.1016J.Cmet 2020.04.021

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COVID-19 and Endocrine Function.-Diabetes summary

- For patients with DM, the risk of contracting a viral illness is no greater than those without Diabetes.
- Diabetes is a risk factor for increased morbidity and mortality from COVID -19
- Continued use of DPP-4 inhibitors and Metformin maybe helpful
- Tight glucose control in the outpatient and inpatient settings is crucial to prevent complications and poor outcomes

JCEM 2020;105:1299-1301.
J endo society 2020;4(11): bvaa144.https://doi.org/10.1210/jendosoc/bvaa144

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COVID -19 and Endocrine function –Obesity

•The US obesity prevalence was 42.4% in 2017 – 2018.

•From 1999 –2000 through 2017 –2018, US obesity prevalence increased from 30.5% to 42.4%.

•During the same time, the prevalence of severe obesity increased from 4.7% to 9.2%.

•Cost of obesity-147 billion (2008)

•$1429 higher medical cost compared to those with healthy weight

https://www.cdc.gov/obesity/index.html

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COVID-19 and Endocrine Function :Obesity

- obesity may triple the risk of hospitalization due to a COVID-19 infection(CDC)
- Obesity is associated with increased risk for complicated COVID -19 and related mortality.
- Chinese study: Obesity was associated with 142% higher risk for developing severe pneumonia(1)
- UK Study: 72.1% of patients with confirmed COViD-19 were overweight or obese(2)
- Pts with BMI>30 who had undergone ICU care 60.9% died(2)
- New York study: n=4103. BMI of >40kg/m^2 was the 2nd strongest independent predictor of hospitalization after old age (3)

(1) Qingxian C etal https://www.ssrn.com/abstract=3556658
(2) Intensive care and National audit research Center(Internet) Cited May21,2020.https://www.icnarc.org
(3) Petrilli CM etal Intensive and critical care medicine2020 April. BMJ doi10.1136/bmj.m1966

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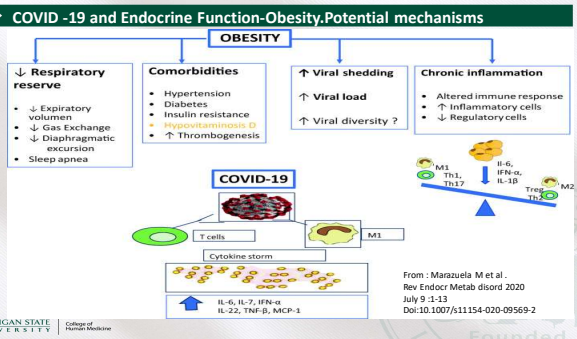
COVID -19 and Endocrine Function-Obesity.Potential mechanisms



From : Marazuela M et al . Rev Endocr Metab disord 2020 July 9 :1-13 Doi:10.1007/s11154-020-09569-2

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COVID-19 and Endocrine Function :Obesity

- It is critical that obese patients ,esp those with BMI >40 (critical cut-off for mortality risk) to take all possible precautions to avoid infection
- Lowering weight ,blood pressure and controlling blood sugar have always been important to prevent serious health consequences .
- COVID-19 infection might now be another important reason to focus on these health issues

Marazuela M etal Rev Endocr Metab disord 2020 July 9:1-13.doi.10.1007/s11154-2020-09569-2

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COVID-19 and Endocrine function – Post COVID syndrome

N=2469 post COVID discharge patients.(6 months after discharge)

736 excluded.1733 followed up.
Median age =57.0 years. Men =897 (52%) Women =836 (48%)

Symptom	Number	Symptom	Number
Any one of the following	76%	Dizziness	6%
Fatigue or muscle weakness	63%	Diarrhea or Vomiting	5%
Sleep difficulties	26%	Chest pain	5%
Hair loss	22%	Sore throat/ difficulty Swallowing	4%
Smell disorders	11%	Skin rash	3%
Palpitations	9%	Myalgia	2%
Joint pain	9%	Headache	2%
Decreased appetite	8%	Low grade fever	<1%
Taste disorders	7%		

Huang C et al Lancet 2021;397:220-232.

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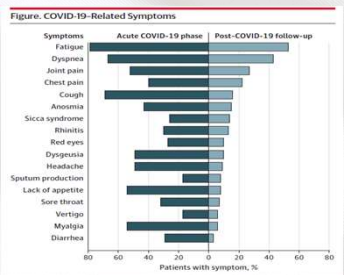
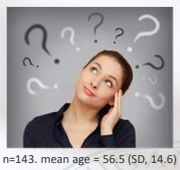
COVID -19 and Endocrine function.-Post Covid syndrome





n=143. mean age = 56.5 (SD, 14.6) years.
(range, 19-84 years)
women= 53 (37%).
Pts were assessed 60.3(13.6) days after the onset of symptoms
Only 18 (12.6 %) were completely free of symptoms

Carfi A et al JAMA 2020;324(6)603-605

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COVID-19 and Endocrine function.New Eng J Medicine

Perspective :Confronting Our Next National Health Disaster — Long-Haul Covid.

"long-haul Covid" (or "long Covid") is our next public health disaster in the making.

No one knows what the time course of long Covid will be or what proportion of patients will recover or have long-term symptoms. It is a frustratingly perplexing condition.

Addressing this post infection condition effectively is bound to be an extended and complex endeavor for the health care system and society as well as for affected patients themselves.

•Steven Phillips, M.D., M.P.H., and Michelle A. Williams, Sc.D.
N Engl J Med 2021; 385:577-579.DOI: 10.1056/NEJMp2109285
August 12, 2021

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AMA AMERICAN MEDICAL ASSOCIATION

The COVID-19 "long-hauler" syndrome – facts, fallacies and the unknown

Sunday, June 6 | 12N – 1 pm CDT

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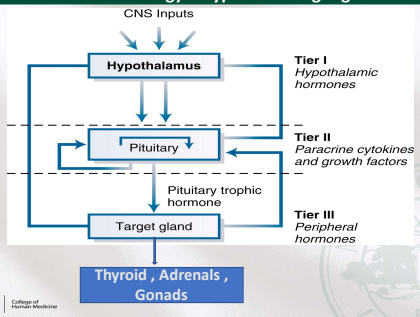
COVID-19 and Endocrinology – Hypo –Pit –target glands axis



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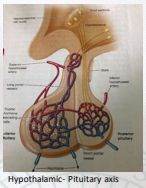
COVID -19 and Endocrine function- Pituitary

- ACE-2 is expressed in the pituitary and cerebral vascular endothelium.(1)
- SARS-CoV-2 has been hypothesized to enter the brain through the olfactory nerve or could pass through the BBB or directly reach the median eminence.(where BBB is lacking)(2)


Hypothalamic- Pituitary axis

(1) J Neuro sci 2020;412:116824.
(2) Chem Neuro Sci 2020;11(11):1520-1522

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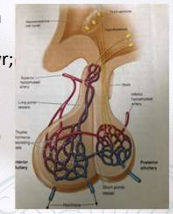
COVID -19 and Endocrine function- Pituitary apoplexy

- Pituitary Apoplexy: acute emergency due to sudden hemorrhage and infarction of the Pituitary gland, typically with in a tumor.(incidence=0.17/100,000/yr; prevalence 6.2/100.000).(1)
- Occurs in 6-12% of patients with Pit adenomas
- Previous studies have shown a possible relationship with Viral infections.(2)
- COVID -19 can induce thrombocytopenia, coagulopathy and platelet dysfunction.(3)


Hypothalamic –pituitary axis

(1) Neurosurg Clin N Am 2019;30(4) 457-463 .(2) Endocr Pract 2014;20(4) e58-e64
(3) ACS chem Neurosci 2020 11(11):1520-1522

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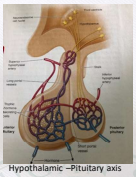
COVID -19 and Endocrine function- Pituitary apoplexy

- Several case reports of Pituitary apoplexy associated with COVID 19. have been described(1)
- Increased awareness of this complication is needed for predisposed patients(Pts with macroadenoma on dopaminergic agents , anticoagulant therapy(1)


Hypothalamic –Pituitary axis

(1) Pituitary 2020,May 3:1-17 .doi 10.1007/s11102-021-01148-1

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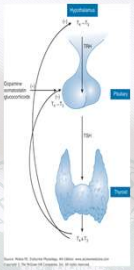
COVID-19 and Endocrine Function – Pit –Thyroid axis

- ACE-2 is expressed in Thyroid
- In postmortem studies, No pathological change was found in Thyroid gland except lymphocytic infiltration in one study.
- SARS Co-V-2 was not found in the thyroid by immunohistochemistry or polymerase chain reaction analysis in the Thyroid tissue .
- 32/50 (64%) patients had abnormal thyroid functions during COVID and after recovery.(1)
- 247 noncritical hospitalized patients for CoVID-19 -20.2% had thyrotoxicosis and 5% had Hypothyroidism ;214 (74.6%) had normal Thyroid functions(2)



(1)Chen M ,Zhou WB et al.Thyroid .2021;31:8-11.
(2) Lania A, Sandri MT et al Eur J endocrinol 2020;183:381-387

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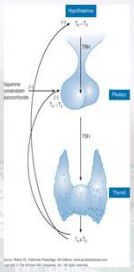
COVID -19 and Endocrine function- Thyroid

- Approximately 15% patients with mild to moderate COVID may have thyroid dysfunction.(1)
- COVID -19 may aggravate AITD through its effects on immune system.(2)
- Graves' disease (GD) may be triggered by COVID-19 (2)
- Regular monitoring of TFT in patients with GD who are infected with COVID -19 is advised.(2)
- The possibility that Thyroid dysfunction may also increase susceptibility to COVID-19 deserves further investigation(2)



(1) Lui DTW et al JCEM 2021;106:(2) e926-e935
(2) Duntas LH et al J of the Endo society 2021;5:8-11

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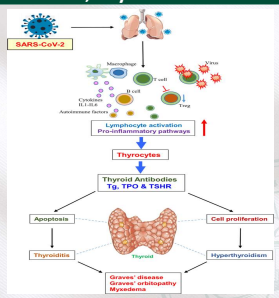
COVID-19 and Endocrine function; Thyroid disease

Postulated mechanisms :



Murugan, A.K., Alzahrani, A.S. SARS-CoV-2 plays a pivotal role in inducing hyperthyroidism of Graves' disease. *Endocrine* **73**, 243–254 (2021). https://doi.org/10.1007/s12020-021-02770-6

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COVID -19 and Endocrinology . Pit –Thyroid axis

Diagnosis	Thyroid functions	Mechanism
Non-Thyroidal illness	Low TSH ,Low T3 ,low or normal T4	Potential effect of systemic inflammation
Subacute Thyroiditis	Varies by the stage *	Viral infection Thyroid
Central Hypothyroidism **	Low TSH ,Low T4 ,Low T3	Dysfunction of Hypo-Pit axis

- *Initially hyperthyroidism ,followed by Hypothyroidism and recovery
- ** may be associated with low cortisol levels also

Chen W, Yuang T et al Endocrinology 2021 March 162 (3) bqab004doi 10.1210 endocr/bqab004

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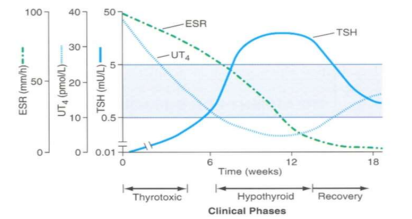
Covid -19 and Endocrine function– Subacute Thyroiditis



Prevalence of SAT in high intensity ICUs was 10 % in patients infected with COVID -19.
compared to 0.5 % in patients with HICU, not infected with COVID-19 (1).

Jameson JL, Weetman AP. Disorders of Thyroid gland In ;Harrison's Endocrinology. 2006; 95
(1) Muller I et al Lancet ,Diab Endocrinol 2020;8(9):739-741

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COVID -19 and Endocrine function-Case presentation

Feb 28,2020:

- 18 yr old Female – tested due to father being hospitalized for COVID-19. +ive for SARS CoV-2.
- Next few days –developed URI (Rhinorrhea and cough)
  Not treated – recovered in 4 days (additional swabs March 13 and 14 neg for SARS Cov-2)
- March 17 –sudden fatigue ,palpitations and anterior neck pain
- P/E Heart rate 90/min Thyroid painful and tender

J Clin Endocrinol Metab. 2020 Jul; 105(7): dgaa276.
Published online 2020 May 21. doi: 10.1210/clinem/dgaa276

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COVID -19 and Endocrine function –Case presentation

Measure	Reference range	February 21	March 19	April 1	April 27
FT4, nmol/L	11-23	15.4	27.2	21.7	16.2
FT3, pmol/L	4.6-8.4	5.5	8.7	7.5	5.3
TSH, mIU/L	0.5-4.1	2.1	< 0.04	0.2	2.9
TgAb, IU/mL	< 30	< 30	120.2		
TPOAb, IU/mL	< 10	< 10	< 10		
TRAb, IU/mL	< 1.5		< 1.5		
Tg, µg/L			5.6		
White cell count, per L	3800-11 000		11 200	6900	6600
ESR, mm/h	0-13		90	28	2
CRP, mg/L	< 2		6.9	1.2	0.9

Thyroid U/S multiple hypoechoic areas (unremarkable).Begun on Prednisone. Neck pain and fever subsided in 2 days. (the authors claim that this is the first case of SAT with SARS CoV-2)

J Clin Endocrinol Metab. 2020 Jul; 105(7): dgaa276.
Published online 2020 May 21. doi: 10.1210/clinem/dgaa276

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COVID -19 and Endocrine function – Subacute Thyroiditis

Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Postvaccination ASIA* Syndrome

Burçin Gönül İremli, Süleyman Nahit Şendur, Uğur Ünlütürk

The Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 9, September 2021, Pages 2600–2605, https://doi.org/10.1210/clinem/dgab373

Published:
27 May 2021

* Autoimmune syndrome induced by adjuvants

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COVID -19 and Endocrinology . Pit –Adrenal axis

- ACE -2 is expressed in Pituitary and Adrenal glands.(1)
- Microscopic changes of adrenal necrosis, hemorrhage and vascular thrombosis in adrenal glands has been reported (2).
- Bilateral adrenal hemorrhage leading to adrenal insufficiency has been reported (3)
- 32% patients with COVID had evidence of adrenal insufficiency(4).
- The benefit of Steroids may be related to adrenal insufficiency(1)
- Pts with Adrenal insufficiency can be assumed to be high risk for COVID -19 and complications including Adrenal crisis(1)

(1) J of the Endocrine society.2020;4:issue 11.(2).Am J trop Med Hyg 2020;103:1604-1607
(3).JCEM 2020;105:3745-9 (4)Endo Pract .2021;27(2) 83-89

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COVID-19 and Endocrine function. Adrenal glands

Cortisol and ACTH levels on repeated testing of 28 patients admitted to hospital with COVID -19

	Test 1.n=28. days 1-2	Test 2 .n=20. days 3-5	Test 3.n=15. days 8-11
Cortisol (median ,range) nmol/L*	196 (31-587)	314 (27-644)	238 (57-94)
Level <100 (3.6µg/dl)	8(26%)	2(10%)	3(20%)
Level <200 (7.2µg/dl)	14(50%)	6(30%)	6(40%)
Level <300 (10.8µg/dl)	18(64.3%)	9(45%)	9(60%)
ACTH(median,range). ng/dL**	18.5(4-38)	27 (2-59)	16.5 (3.1-50.2)
Level<10	7 (25%)	-	5(33.3%)
Level<20	17 (60.7%)	-	8 (53.3%)
Level <30	23(82.1%)	-	10 (66.6%)

- to convert nmol/L to µg/dl divide by 27.6
- ** upper normal range =60ng/dl

Alzahrani AS,etal Endo pract 2021;27:83-89

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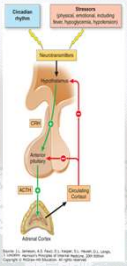
COVID -19 and Endocrine function :Adrenal insufficiency

- Both Primary and secondary adrenal insufficiency has been reported with COVID -19.
- COVID -19 may precipitate acute adrenal insufficiency (Adrenal crisis)
- Pts with known adrenal insufficiency should be counseled on "sick day rules" immediately at the onset of symptoms suspicious for COVID -19.
- These should continue until symptoms resolve.



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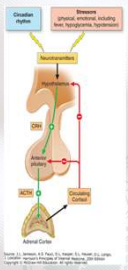
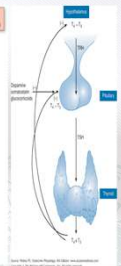
Covid -19 and Endocrine function. Thyroid and Adrenal function

Normal Adrenal and Thyroid Function in Patients Who Survive COVID-19 Infection

N=70: 3months after recovery from COVID-19
44 (62.9%) were C/O fatigue
26 (37 %) did not C/O fatigue
N=68 – Thyroid functions were normal
(TSH ,Free T4 and Free T3).

symptoms of fatigue were not accounted for by alterations in adrenal or thyroid function.





J Clin Endocrinol metab.2021;106(8): 2208-2220 , https://doi.org/10.1210/clinem/dgab349.

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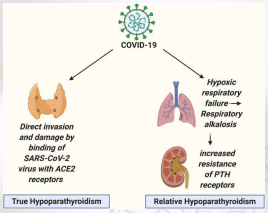
COVID -19 and Endocrine function. Hypocalcemia & Hypo PTH

Chinese study: Severe COVID 19.(1)
n=107. Hypocalcemia –n=67; Normal Ca-n=40

Severe illness*: Hypocalcemia (32/67;(47.8%)
Normal Ca (10/40 ;(25%)

Hypocalcemia : associated with high levels Of CRP ,Procalcitonin ,IL-6 , D dimers and poor outcomes (Mech Ventilation , ICU care or death) :

Case reports: low PTH (2)
Severe hypocalcemia – Vit D deficiency (3)



From :A Abobaker and Abobaker A.J infect pub health 2021 Jun 14(6) 724-725

*Severity defined by WHO criteria Respiratory distress ,RR >30/min, Pulse O2<93%

(1)Liu et al *J Infect Public Health.* 2020;13(9):1224–1228.
(2) J.Inf pub health 2021 Jun;14(6):724-725. doi: 10.1016/j.jiph.2021.04.002. Epub 2021 Apr 12
(3) Endo Diab Metab 2021,issue 1.https://doi.10.1530/EDM-20-0097

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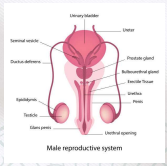
COVID -19 and Endocrine function: Male reproduction

- ACE -2 is present in testes
- Increased susceptibility for the rate of severe symptoms and mortality in men (compared to women)
- Studies from China – Decreased sexual activity during the pandemic
- Studies from Bangladesh, Nepal and India- No change or slight increase.
- COVID-19 has been associated with Orchitis.
- Conflicting date about presence of virus in the semen
- Normal or Impaired spermatogenesis (decreased count and motility)



Fertility sterility 2021;115 (4) :813-823
Reproduction 2021; 161(2):

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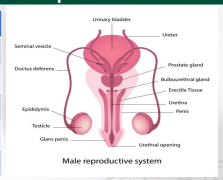
COVID -19 and Endocrine function: Male reproduction

Hormone	Levels
L H	Increased
LH :T ratio	Increased
Testosterone	No change
Prolactin	Increased
Estradiol	decreased /no change

In one Italian study .n=4532 .Men with prostate cancer receiving Androgen deprivation therapy(ADT) had significantly lower risk of disease (COVID)than those without ADT



Fertility sterility 2021;115(4):813-823
Reproduction 2021;161(2):
Ann Onc 2020; 31:1040-1045

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COVID -19 and Endocrine function: Female reproduction

Not many studies
Retrospective study: n=237 women. Age =18-45 yrs

N=177 ,analyzed for menstrual changes:

Condition	No Change	Decrease	Increase
Menstrual Volume	132 (75%)	36(20%)	9 (5%)

Cycle Length

<28 days	28-32 days	33-37 days	>37 days
25(14%)	66 (37%)	31(18%)	43(24%)

No significant change in LH ,FSH Estradiol ,Progesterone , Testosterone and AMH, Compared to the control group

Kezhen Li et al Repro Biomed on line 2021;Jan 42:9(1) 260-267

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COVID -19 and Endocrine function: Menstrual functions

MSU- New Grant :

(1)Is infection with the COVID-19 virus associated with heavier or irregular menstruation or pelvic pain?

(2) Is vaccination for the virus associated with changes in menstruation or pelvic pain?

(3) Are pandemic-related anxiety and stress having an impact on menstrual characteristics?

Stacy Missmer Sc.D .Michigan State University

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COVID -19 and Endocrine function-Pregnancy

n=23434 symptomatic pregnant
n=386,028 symptomatic non pregnant with COVID -19. Age =15-44 yrs

Condition	aRR for pregnant
Admission to ICU	3.0 (2.6-3.4)
Mechanical Ventilation	2.9 (2.3-3.8)
Extracorporeal O2	2.4 (1.15- 4.0)
Death	1.7 (1.2-2.4)

aRR adjusted relative risk.Adjusted for age, race ,ethnicity
And presence of underlying conditions

MMWR. Morbid mortal wkly repo.2020;69:1641-1657
Fertil steril2021;115(4)824-830

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COVID-19 and Endocrine function: pregnancy-maternal outcome -i

703 hospitals (Premier health care data base)

N=489 471 delivery hospitalizations.

Outcome	COVID-19 (n=6550)	NO COVID-19 (n=482 921)	Adjusted RR
Any adverse outcome	372 (5.7)	20 402 (4.2%)	1.2(1.1-1.3)
Preterm delivery	315 (4.8)	17 392 (3.6)	1.2(1.1-1.3)
Any maternal complication	291(4.4)	3400 (0.7)	6.3 (5.5-7.3)
Acute renal failure	41(0.6)	734 (0.2)	3.5 (2.5-5.0)
Adverse cardiac outcome	41 (0.6)	1560 (0.3)	2.2 (1.6-2.9)
Thromboembolic disease	19 (0.3)	527 (0.1)	2.7(1.7-4.4)
ARDS	218 (3.3)	426 (0.1)	34.4(29.0-40.8)
Shock	30 (0.5)	374 (0.1)	5.1 (3.4-7.8)

Ko JY et al Clinical Infectious diseases 2021;73 (S1) S24-31

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COVID-19 and Endocrine function: pregnancy-maternal outcome-ii

703 hospitals (Premier health care data base)

N=489 471 delivery hospitalizations

Outcome	COVID-19 (n=6550)	NO COVID - 19 (n= 482 921	Adjusted RR
Any maternal severe illness	307 (4.7)	7593 (1.6)	3.5 (92.8-4.3
ICU admission	293 (4.5)	7389 (1.5)	3.6 (2.8-4.5)
Mechanical Ventilation	105 (1.6)	583(0.1)	12.7 (9.2-17.5)
Death	9 (0.1)	32 (0.0)	17.0 (8.2-35.4)
Discharged home	6403 (97.8)	477 682 (98.9)	1.0 (1.0-1.0)
Readmission within 30 days	99 (1.5)	5834 (1.2)	1.2 (1.0-1.4)

Ko JY et al. Clinical Infectious diseases 2021;73 (S1) S24-31

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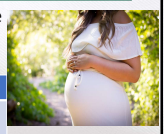
COVID -19 and Endocrine function-Pregnancy

- Rate of spontaneous abortions does not appear to be increased
- Increased risk for Obstetrical complications

Condition	SARS CoV-2 positive	SARS CoV-2 negative
C Section	46.7% in symptomatic 45.5% in asymptomatic	30.9% ,p=.044 (1)
Preterm birth	23%	8% (2)
Still births	3.2%	0.6% (3)



No difference in Neonatal complications:
(low birth weight, difficulty breathing , apnea or respiratory infections)

- Intrauterine transmission may occur

(1)BJOG 2020;127:1548-156.
(2) COVID-NET 13 states.March 1-Aug 22.2020;69:1347-1354
(3) Mark mast mortal wkly rep 2020;69:1355-1359

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COVID-19 and Endocrine function :Pregnancy

- n=1554--14 US medical centers (17 hospitals)
  - -490 with SARS CoV2.-Symptomatic =314 (64.1%).
  - -Asymptomatic =176 (35.9%).
- Delivery @<37 weeks 73 (14.8%) with COVID Vs 98 (10.2%) controls
- Other Obstetrical outcomes and neonatal complications no different compared to controls
- Symptomatic COVID pts had:
  - -increased C section rate (81/176) compared to Controls (331/964).aOR =2.08(1.29-3.36).
  - -longer PP stay in the hospital (3.8 Vs 1.9 days) .aOR=1.18-2.60.
- These differences were not seen in asymptomatic patients

Katz D,et al Anesthesia & Analgesia: August 2021 - Volume 133 - Issue 2 - p 462-473
doi: 10.1213/ANE.0000000000005592

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COVID-19 and Endocrine function :Pregnancy-Summary

- It appears that :
  pregnant women are at higher risk for complications related to COVID-19.(Mechanical ventilation , ICU admission ,ARDS and death)
- Higher rates of preterm delivery.
- Higher rate of C sections
- Obstetrical complications and neonatal complications –controversial

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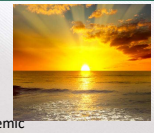
COVID -19 and Endocrine function -Vit D

- Vit D is an immune modulator:
  - -ACE-2 receptor modulation(1)
  - -maintenance of Pulmonary barrier function(1)
  - -reduces the damage caused by pro-inflammatory cytokines(1)
  - -boosts the innate immune response in the acute viremic phase(2)
- Lower levels of 25(OH) D are associated with increased risk of acute respiratory infections (3)
- Vit D supplementation has been associated with protection against acute respiratory infections(4)



(1)Grellier CL eta. Nutrients 2015;7(6):4240-4270.
(2)Bikkle DD et al Chem Biol 2014 ;21(3):319-329
(3)Cannel JJ et al Epidemiol Inf .2006;356:1129-1140
(4) BMJ 2017;356 :i6583

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COVID -19 and Endocrinology . Vitamin D

- The role of Vit D in COVID -19 is controversial.(3,4).
- An association of Vit D deficiency and increased risk of hospitalization and mortality from COVID-19 has been described (5).
- A single high dose of Vit D among Hospitalized patients did not reduce length of hospital stay(6)
- A recent meta-analyses concluded that Vit D supplementation did not alter mortality, ICU admission rates and mechanical ventilation.(7)
- Trials are underway – await results.

(3) Hastle CE et al Diabetology and Metab Syndrome 2020;14:561-565.
(4)Meltzer DO et al .JAMA 2020.3(9) e 219722.doi.10.1001/jamanetworkopen.2020.19722
(5) Periera M et al Crit Rev Food Sci Nutr 2020.Nov 4:1-9 doi:10.1080/10408398.2020.1841090.
(6)Murai IH .JAMA 2021;325(11) 1053-1060 .doi.10.1001/jama .202026848
(7) Rawat D et al Diabetes and Met Syndr clin Res Reviews 2021;15:102189

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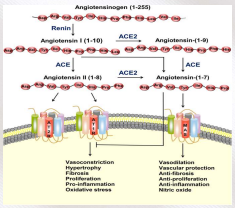
COVID -19 and Endocrine function – RAAS



Administration of ACEi and ARBs increased messenger RNA expression of ACE2 (1)

ACEi and ARBs increase ACE-2 expression in Brain ,heart and Kidneys but not in Lungs(2)

Use of ACEi and ARBs was not associated with increased severity of the disease but was accompanied by decreased mortality (3)

(1) Ferrario CM et al. *Circulation.* 2005;111(20):2605–2610. doi: 10.1161/CIRCULATIONAHA.104.510461.
(2) Cure E etal. *Diabetes Metab Syndr.* 2020;14(4):349–350. doi: 10.1016/j.dsx.2020.04.019.
(3) Guo X et al *Hypertension.* 2020;76:e13–e14.

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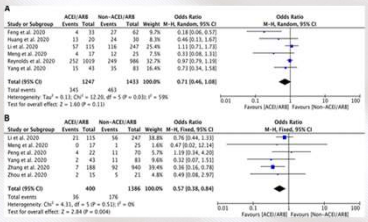
COVID 19 and Endocrine Function. RAAS; metanalysis



9 studies.n=3936

ACEi ,ARBs were not associated with disease severity (OR=0.71(0.46-1.08)

but was associated with lower mortality in pts with hypertension and COVID-19(OR =0.57 (0.38-0.84.p<0.004)

https://doi.org/10.1161/HYPERTENSIONAHA.120.15572Hypertension. 2020;76:e13–e14

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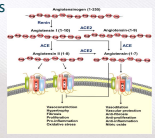
COVID-19 and Endocrine function ;RAAS

- Retrospective study: followed 9,101 household contacts of patients who tested positive for COVID-19.
- Among the contacts, 1,499 were taking (ACEI) or (ARB) at study entry
- After multivariate analysis* ACEI/ARB use was associated with a significantly decreased risk of a COVID-19 diagnosis (OR, 0.60; P=0.00)
- The results were similar when ACEI and ARB use were analyzed separately
- No other medication classes were associated with reduced risk of COVID-19
- These findings support the current professional recommendations that use of ACEI and ARBs should not be discontinued because of concern about COVID-19



*adjustment for age, gender, race/ethnicity, English proficiency, comorbid conditions and date of study entry.
Armstrong et al PLoSOne 16(3)e024758

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COVID-19 and Endocrine Function.ACEi and ARBs

"The Council on Hypertension strongly recommends that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEIs or ARBs should be discontinued because of the COVID-19 infection."[1] (European society of Cardiology)

On March 17, 2020, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology put out a joint statement advocating for patients to continue ACEIs and ARBs as prescribed and that changes in medications in the setting of COVID-19 should be completed only after careful assessment.[2] American Heart Association. HFSA/ACC/AHA

1.https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang
2.https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp

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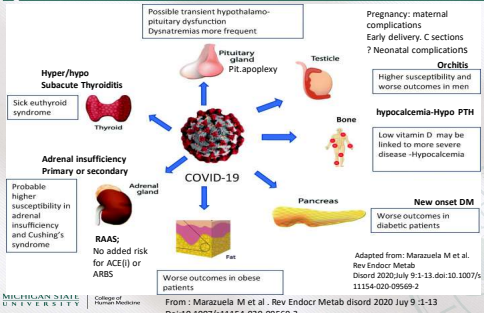
COVID -19 and Endocrine Function :Summary



From : Marazuela M et al . Rev Endocr Metab disord 2020 Juy 9 :1-13
Doi:10.1007/s11154-020-09569-2

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COVID -19 And Endocrine Function: Exploring the Unexplored

THANK YOU

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