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MINI REVIEW

Influence of COVID-19 vaccines on endocrine system

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Abstract

The COVID-19 pandemic has posed a significant health threat globally. Timely and appropriate vaccination is a key step to reduce the morbidity and mortality from COVID-19. The clinical course of COVID-19 infection and the effects of COVID-19 vaccination are influenced by patients' health situations and involve a systemic physiological reaction. Just like an "endocrine phenotype" of COVID-19 infection, endocrine dysfunction after COVID-19 vaccination also acquired clinical concerns. In the present review, we briefly introduce the commonly available vaccines against SARS-CoV-2, summarize the influence of COVID-19 vaccines on the endocrine system, and explore the underlying pathogenic mechanisms.

Keywords COVID-19 vaccine · Side effects · Endocrine dysfunction

Introduction

Since the novel coronavirus pneumonia (COVID-19) outbreak in December 2019, the number of confirmed and death cases has increased rapidly [1]. The global spread of COVID-19 has posed a significant challenge to the worldwide healthcare system, leading to unprecedented medical, economic, and societal crises [2]. COVID-19 is initially defined as a potentially severe respiratory syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. With the deep understanding of this novel respiratory coronavirus, its scope has gone beyond the respiratory system [4].

Studies have shown that the pituitary, thyroid, pancreas, adrenals and gonads can all be affected by the virus, as they all express the angiotensin-converting enzyme 2 (ACE2) receptor which facilitates SARS-CoV-2 attachment and therefore induces cell damage [5–9]. The involvement of the endocrine system in COVID-19 is so relevant that an "endocrine phenotype" of COVID-19 has gradually acquired clinical concerns [10–12], ranging from pituitary apoplexy, thyroid dysfunction, hyperglycemia and diabetes, adrenal insufficiency to hypogonadism [13]. The COVID-19 infections cause impairment of endocrine organs, and similarly, the COVID-19 vaccinations also induce endocrine dysfunction. In this review, we summarize the influence of COVID-19 vaccines on the endocrine system, and explore the underlying pathogenic mechanisms.

The type of Covid-19 vaccines

Multiple vaccines with varying efficacy and safety have been developed against COVID-19. In Table 1, we summarized the data on the vaccines approved and recommended by World Health Organization. SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA, encoding the viral spike glycoprotein (glycoprotein S), induce host cells to build the spike protein, eliciting protective immune responses [14]. mRNA-based vaccines are encapsulated in lipid nanoparticles to transport mRNA encoding viral proteins to the cell membrane of host cells, and may include inactive ingredients such as buffer or salts. Adenovirus-based SARS-CoV-2 vaccines are designed to invade cells but not replicate, and carry genes for the full-length glycoprotein S of SARS-CoV-2 [15, 16]. Ad5, Ad26, and ChAdOx1 act as a delivery vehicle for DNA instructions to produce glycoprotein S in the body. The inactivated vaccine is harvested after isolated SARS-CoV-2 virus infection in Vero cells. It has been chemically inactivated by β-propiolactone and formulated with alum adjuvant. The aluminum hydroxide complex is then diluted in sodium

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Table 1 Characteristics of the primary COVID-19 vaccines

Name of vaccine	Organization	Type of vaccines	Target antigen	Common side effects
BNT162b2	Pfizer-BioNTech USA, Germany	mRNA	S protein	Short-term, mild-to-moderate pain at the injection site, fatigue, and headache
mRNA-1273	Moderna, USA	mRNA	S protein	Transient local and systemic reactions, fever, fatigue, headache
CoronaVac	Sinovac Biotech, China	Inactivated virus	Whole virus	Injection site pain, headache, fatigue
Covaxin	Bharat Biotech, India	Inactivated virus	Whole virus	Injection site pain, headache, fatigue, fever, and nausea or vomiting
AZD1222	Oxford-AstraZeneca, University of Oxford, England	Chimpanzee adenoviral vector	S protein	Injection site pain, fever and headache
Sputnik V	Gamaleya, Russia	Human rAd26 and rAd5 vector	S protein	Injection site pain, hyperthermia, headache, asthenia, muscle and joint pain
Ad26.COV2.S	Janssen Biotech, USA	Human rAd26 vector	S protein	Injection site pain, headache, fatigue, nausea and myalgia
NVX-CoV2373	Novavax, USA	Recombinant SARS CoV-2 nanoparticle glycoprotein vaccine with adjuvant matrix M	S protein	Injection site pain, tenderness, fatigue, headache, and myalgia

chloride, sterile phosphate-buffered saline, and water before administration [17, 18].

According to the Vaccine Adverse Event Reporting System of US Centers for Disease Control and Prevention (www.cdc.gov), as of March 28, 2022, more than 550 million doses of SARS-CoV-2 vaccines have been administrated. A small number of recipients (more than 0.0042%) experienced serious adverse events, including serious anaphylaxis, thrombotic events and thrombocytopenia, Guillain-Barre' syndrome, myocarditis, and even death.

The side effects of the endocrine system following SARS-CoV-2 vaccination

At present, the endocrine dysfunction reported in the literature after SARS-CoV-2 vaccination mainly involves the thyroid gland, islets, pituitary gland, and adrenal gland (Table 2). In thyroid gland, the most common disorder was subacute thyroiditis (SAT), more than a hundred cases have been reported. The onset of symptoms such as neck pain and swelling ranged from 4 to 21 days after the vaccination. Clinical laboratory results and cytological findings were associated with subacute thyroiditis [19–21]. SAT is generally a mild and self-limiting course after vaccination, the recovery time may be less than post-viral cases [22, 23], symptomatic management was only required for this process. As for autoimmune thyroid diseases, several cases of newly diagnosed or recurrent Graves' disease (GD) have been reported with clinical manifestations of thyroid hyperactivity, increased thyroid hormone levels, suppressed thyroid-stimulating hormone (TSH), and elevated antithyroid antibodies [24, 25]. Thyroid ultrasonography revealed enlargement and hypervascularity. Co-occurrence of SAT and GD can also be encountered [26]. In addition. cases of painless thyroiditis after adenovirus-vectored vaccine have also been reported [27]. Physical examination revealed no abnormal findings, with elevated thyroid hormones and suppressed TSH. Thyroid scintigraphy showed decreased uptake and thyroid ultrasound showed diffuse hypoechoic echotexture of the thyroid gland with reduced blood flow.

Hyperglycemia exacerbation after COVID-19 vaccines has been revealed by flash glucose monitoring in type 1 diabetes and self-monitoring of blood glucose in type 2 diabetes, which mainly occurs within 1 week after vaccination and generally settles within a few days after an increased antidiabetics drugs dose or without intervention [28, 29]. However, severe hyperglycemic emergencies, including diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome, may also be triggered by COVID-19 vaccination [30–32]. These patients show a subacute onset of osmotic symptoms within 1 week of vaccine administration, with a history of T2DM or pre-diabetes or newly diagnosed with T2DM in the hospitalization. All patients presented to hospital within 3–5 weeks and remained well controlled on oral antidiabetic medications within 2 months of discharge.

As for the pituitary gland, a case of hypopituitarism related to COVID-19 immunization has been described [33]. The

Table 2 Adverse events of the endocrine system after SARS-CoV-2 vaccination

Author reference	Type of vaccine	Time of symptoms onset	Main symptoms	Complications	Treatment
Thyroid-Subacute Thyroiditis (SAT)					
Sözen et al. [51]	BNT162b2 (Pfizer-BioNTech)	mainly 4–20 days after 1st dose	neck pain, fatigue, palpitation	None	Acetylsalicylic acid, propranolol, and Ibuprofen
Bornemann et al. [52]	Spikevax (Moderna Biotech, Spain) and Vaxzevria (AstraZeneca, Sweden)	mainly 14 days after 1st dose	cervical pain that radiated to both ears, fever chills, and headache	None	Ibuprofen diclofenac, prednisolone
Oyibo et al. [41]	ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	21 days after 1st dose	neck pain and swelling, headache, sore throat, generalized aches and palpitations	None	Propranolol, ibuprofen and paracetamol
Thyroid- Graves' disease (GD)					
Vera-Lastra et al. [43]	BNT162b2 (Pfizer-BioNTech)	mainly 2–3 days after 1st dose	nausea, vomiting, fatigue, anxiety, insomnia, palpitations, and a distal tremor	sinus tachycardia and episodes of paroxysmal atrial fibrillation	Propranolol, diltiazem, ivabradine, and thiamazole
Sriphrapradang et al. [53]	ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	4 days after the booster dose	palpitations and loss weight	hyperthyroidism	Methimazole and propranolol
Bostan et al. [54]	inactivated COVID-19 vaccine (CoronaVac®; BNT162b2 (Pfizer-BioNTech)	mainly 4–30 days after 2nd dose	excessive sweating, palpitation, and fatigue hand tremors	rapidly developing Graves' ophthalmopathy was detected in one patient.	Methimazole and propranolol
Thyroid-Painless thyroiditis (PT)					
Siolos et al. [27]	ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	21 days after 1st dose	None	None	No specific treatment
Pancreas-Hyperosmolar hyperglycemic state (HHS)					
Abu-Rumaileh et al. [31]	BNT162b2 (Pfizer-BioNTech)	2 days after 2nd dose	increased nocturia, polyuria, polydipsia, worsening mental status, and weight loss	new-onset T2DM	Intravenous fluids with insulin drip
Lee et al. [32]	BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)	mainly 2 days after 1st dose	fatigue, blurry vision, polyuria and polydipsia	one patient was diagnosed with T2DM and nonketotic HHS without coma	Intravenous hydration and an insulin infusion, and metformin
Pancreas-Diabetic ketoacidosis (DKA)					
Lee et al. [32]	mRNA-1273 (Moderna)	10 days after 1st dose	weakness and altered mental status, fatigue and myalgias	aspiration pneumonia and a lower extremity deep	Normal saline hydration, continuous insulin infusion, antibiotics and enoxaparin
Edwards et al. [30]	ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	20 days after 1st dose	subacute onset of osmotic symptoms	pre-diabetes	Amlodipine, indapamide

Table 2 (continued)

Author reference	Type of vaccine	Time of symptoms onset	Main symptoms	Complications	Treatment
Pancreas-High glucose (HG)					
Mishra et al. [28]	Covishield (ChAdOx1 nCoV-19)	mainly 1–6 days after 1st dose	higher SMBG values	T2DM	Metformin or without intervention
Pituitary- Hypophysitis					
Murvelashvili et al. [33]	mRNA-1273 (Moderna)	3 days after 2nd dose	headache, nausea, vomiting, malaise, and diffuse arthralgias	low libido and erectile dysfunction	Steroids and thyroid hormone
Adrenal-Hemorrhage					
Taylor et al. [34]	ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	8 days after 1st dose	severe abdominal pain and vomiting	VITT	Hydrocortisone, Plasma exchange, fludrocortisone
Adrenal-Primary adrenal insufficiency					
Varona et al. [35]	ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	10 days after 1st dose	headache, somnolence, mild confusion, and progressive abdominal discomfort	VITT	Hydrocortisone

VITT vaccine-induced thrombosis and thrombocytopaenia

patient suffered from headache, nausea, vomiting, malaise, and diffuse arthralgias 3 days after his second mRNA-1273 SARS-CoV-2 vaccination, with secondary adrenal insufficiency, central hypothyroidism, and hypogonadism. Magnetic resonance imaging (MRI) revealed a diffusely enlarged pituitary gland consistent with acute hypophysitis. The patient responded well to glucocorticoid and thyroid hormone supplementation. After 1 month, follow-up MRI of the pituitary revealed markedly diminished enlargement of the gland with a mostly empty sella. Plasma testosterone level normalized without testosterone replacement therapy.

In addition, adrenal gland-related disorders have also been reported, including bilateral adrenal hemorrhage [34] or primary adrenal insufficiency [35]. These two cases were due to vaccine-induced thrombosis and thrombocytopaenia 8–10 days after receiving the adenoviral vector-based vaccines. Laboratory tests showed a substantial increase in D-dimer, profoundly decreased platelet count, and positive platelet-factor-4 antibody. As for the bilateral adrenal hemorrhage, computed tomography abdomen showed retroperitoneal fat stranding and high-density fluid surrounding the adrenal glands. Plasma exchange and maintenance on hydrocortisone and fludrocortisone were eventually undertaken. As for the primary adrenal insufficiency, abdominal MRI showed bilateral adrenal nodular enlargement with hyperintense peripheral halo and hypointense center. In hormonal laboratory testing, low levels of cortisol, DHEA and aldosterone, and high ACTH levels confirmed primary adrenal insufficiency. These patients were treated with hydrocortisone as hormone replacement therapy.

The possible mechanisms

1) Autoimmune/inflammatory syndrome induced by vaccine adjuvants (ASIA) [36]. Adjuvants have been widely used in human vaccines to enhance the immune response to vaccination [37]. In genetically susceptible individuals, ASIA may develop by disrupting the immunological balance of the host, by molecular mimicry, triggering polyclonal activation of B lymphocytes or other similar etiopathogenetic mechanisms [38]. Previously, type 1 diabetes mellitus, primary ovarian failure, adrenal insufficiency, and thyroiditis (mostly SAT) have been reported to be related to ASIA syndrome after human papillomavirus, hepatitis B virus, and influenza vaccination [38, 39]. As for the COVID-19 vaccines, aluminum salts, emulsions, oils, toll-like receptors, AS01B, four lipids of the mRNA vaccine and polyethylene glycol might induce an immune response in susceptible individuals [39, 40].

2) Immune system hyper-stimulation and molecular mimicry [27]. It is worth noting that the thyroid peroxidase

peptide sequence in thyroid tissue is similar to SARS-CoV-2 spike protein, nucleoprotein, and membrane protein [21, 41]. The cross-recognition between the modified SARS-CoV-2 proteins in vaccines and the thyroid target protein due to molecular simulation results in autoimmune thyroiditis. The symptoms of thyroiditis appear in the first few days after vaccination in most cases. A probable reason may be that the concentration of viral proteins peaked within a few days post-vaccination and triggered the autoimmunity [42, 43].

3) Systemic inflammatory response and "cytokine storm" [44, 45]. Transient hyperglycemia following COVID-19 vaccination could result from a systemic inflammatory response [46] or a personalized reaction to vaccine components, e.g., the adenovirus system or encoded SARS-CoV-2 spike protein immunogen, the adjuvant, or the adjuvant excipients/impurities [30]. Furthermore, COVID-19 infection could cause islet cell degeneration [47]. SARS-CoV-2 may impair insulin receptor signaling through increased renin-angiotensin system activation via ACE receptor downregulation [48]. SARS-CoV-2-induced pro-inflammatory cytokine reactions may directly result in impaired insulin receptor signaling and islet cell damage [49]. Thus, it is reasonable that SARS-CoV-2 antigen presentation also exhibited similar responses.

Clinicians should inquire about the recent COVID-19 vaccination in patients with endocrine disorders. The overall benefits of COVID-19 vaccination outweigh the risk of side effects [50], especially in individuals at higher metabolic risk. However, in case these presentations do reflect a causative association between vaccines and endocrine alteration, it may be prudent to screen at-risk individuals for endocrine dysfunction. Whether the COVID-19 vaccine-related complications on endocrine system are more common in patients with endocrinopathy? Whether the type of COVID-19 vaccine is associated with differences in the development of endocrinopathy-associated complications? These unresolved issues need further investigation.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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