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), inducing 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 phosphate buffer.
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 administered. 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].

| 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.COVID2.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 |

Table 1 Characteristics of the primary COVID-19 vaccines
| 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 |
The 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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