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# PATHOLOGY MATTERS

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## Role of Thyroid Antibodies in Autoimmune Diseases

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Autoimmune diseases (AD) are a spectrum of disorders arising from inflammation of organs due to antibody production against self-structures and cytotoxic action of T cells (Figure 1). Data from Asia, Middle East, Caribbean and South America reported the following prevalence (cases/100,000 individuals) of the more common AD[1]: Graves' disease (GD: 20), Hashimoto's thyroiditis (HT: 350), rheumatoid arthritis (RA:120–550), Crohn's disease (CD: 6–113), multiple sclerosis (MS: 4–101), and Sjögren disease (SD: 330–1,560).

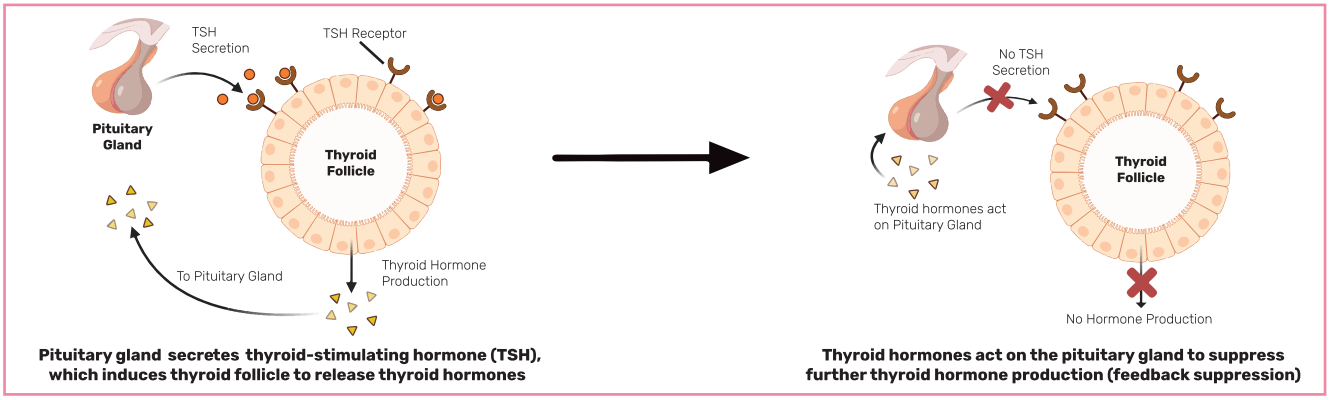


Figure 1: Normal thyroid hormone secretion[16].

Autoimmune thyroid diseases (AITDs) include several inflammatory thyroid diseases with GD and HT (Figure 2) being the most frequent of them[2]. AITDs are usually accompanied by the presence of antibodies such as thyroid peroxidase antibody (TPO-Ab), thyroglobulin antibody (Tg-Ab), and thyroid-stimulating hormone receptor antibody (TRAb). They have been included in the diagnostic and prognostic tools of AITDs.

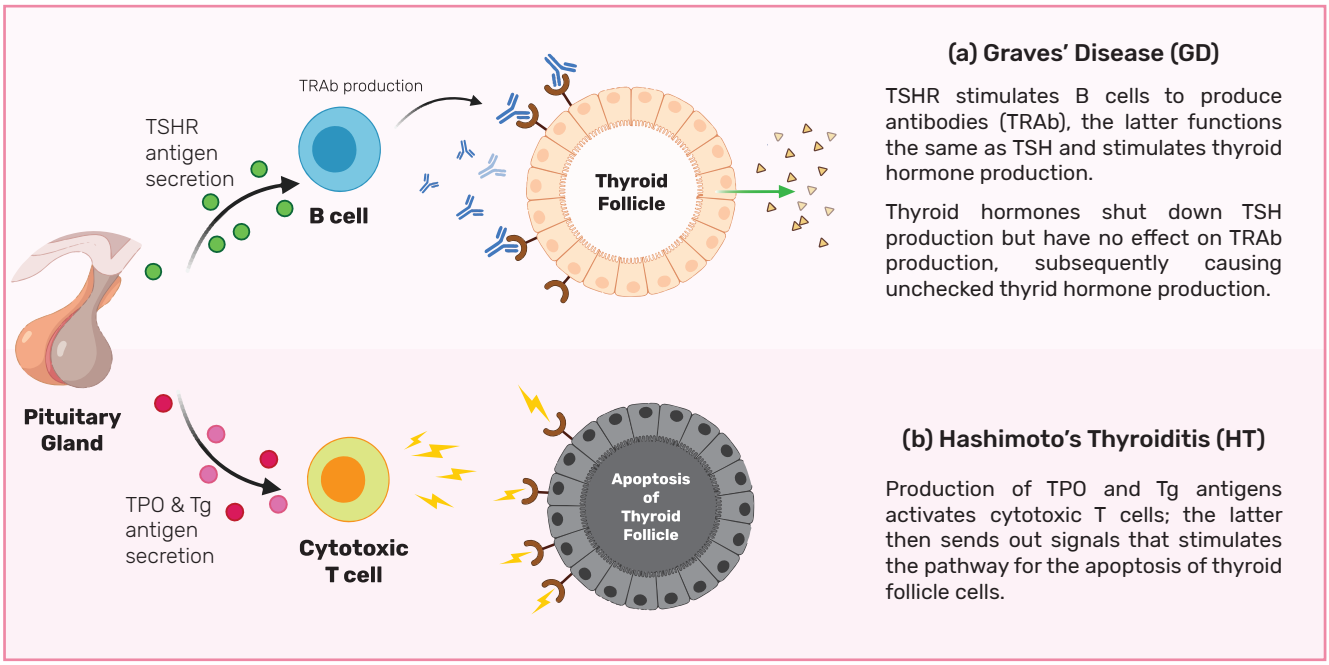


Figure 2 : Pathogenesis of Autoimmune Thyroid Diseases (AITDs)[16]. a) Graves' Disease; b) Hashimoto's Thyroiditis

## Thyroglobulin antibodies (Tg-Ab)

Serum Tg-Ab is a marker of thyroid autoimmunity. It is elevated in 10% of the general population (especially in women), and therefore does not make it a sensitive or specific thyroid biomarker compared to its counterparts, thyroid peroxidase antibodies (TPO-Ab) or TSH receptor antibodies (TRAb)[3]. In the absence of TPO-Ab, Tg-Ab is not significantly associated with thyroid disease[4]. The main clinical utility of Tg-Ab test is to determine the reliability of serum Tg as a marker to monitor patients with differentiated thyroid carcinoma (DTC). For patients with elevated Tg-Ab (in which case this renders serum Tg unreliable as a tumor marker), Tg-Ab itself can serve as a surrogate tumor marker for DTC[3, 5-8].

## Thyroid peroxidase antibodies (TPO-Ab)

TPO-Ab is found in 5–20% of the general population and is nearly always elevated in patients with Hashimoto's thyroiditis[3]. In addition to aiding the diagnosis of Hashimoto's thyroiditis, TPO-Ab also has a role in the management of subclinical hypothyroidism. Based on a 20-year prospective UK study, progression to overt hypothyroidism occurred at 4.3% per years among patients with elevated TPO-Ab, measured as antimicrosomal antibodies, compared with 2.6% per years in those that were TPO-Ab-negative[9]. These findings are consistent in a US-based study[10]. In an Australian study using contemporary TPO-Ab assays[11], women with elevated TPO-Ab and TSH between 2.5 and 4.0 mIU/L progressed to subclinical and overt hypothyroidism after 13 years. This suggests that patients with subclinical hypothyroidism and an elevated TPO-Ab may need close monitoring or even be considered thyroid hormone replacement. Guidelines have also recommended close monitoring with TSH (either monthly or 3-monthly) among pregnant euthyroid women with elevated TPO-Ab[12,13].

## TSH receptor antibodies (TRAb)

TRAb are specific biomarkers to diagnose GD. It binds to the TSH receptors and there are three types of TRAb: stimulating, blocking, or neutral, of which thyroid-stimulating antibodies are the most common[14]. TRAb can be measured by two types of assays: competitive TSH-binding inhibition (TBI) or thyroid-stimulating immunoglobulin (TSI) assays[15]. The former measures TRAb in serum samples based on its ability to inhibit the binding of TSH receptors with known TSH receptor ligands. This assay only detects the concentration of TRAb but is unable to differentiate between the function of the different types of TRAb[14]. The TSI assay employs cAMP production in cells incubated with patient serum. This assay can identify only stimulating TRAb[14]. As TRAb is not present in the general population, it is specific for the diagnosis of GD. They are also useful in the differential diagnosis of hyperthyroidism, prediction of remission after treatment of Graves' hyperthyroidism, prediction of fetal/neonatal thyrotoxicosis, and assessment of ophthalmopathy[15].

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# Understand the Human ABO blood group system


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Human blood group system is usually determined by the individual's combination of one or more red cell surface antigens. As of June 2021, the International Society of Blood Transfusion (ISBT) Working Party for Red Cell Immunogenetics and Blood Group Terminology has recorded a total of 43 recognized blood group systems containing 345 red cell antigens[1] (Figure 2). These 43 systems are genetically determined by 48 genes.

These red cell antigens are important as they are unique to an individual, they are recognized as foreign if transfused into another individual. Most of these blood group system except for ABO, may stimulate an individual to develop the red cell antibody to the foreign antigen when exposed through blood transfusion or pregnancy and these antibodies may pose a problem in future blood transfusion of the individual.

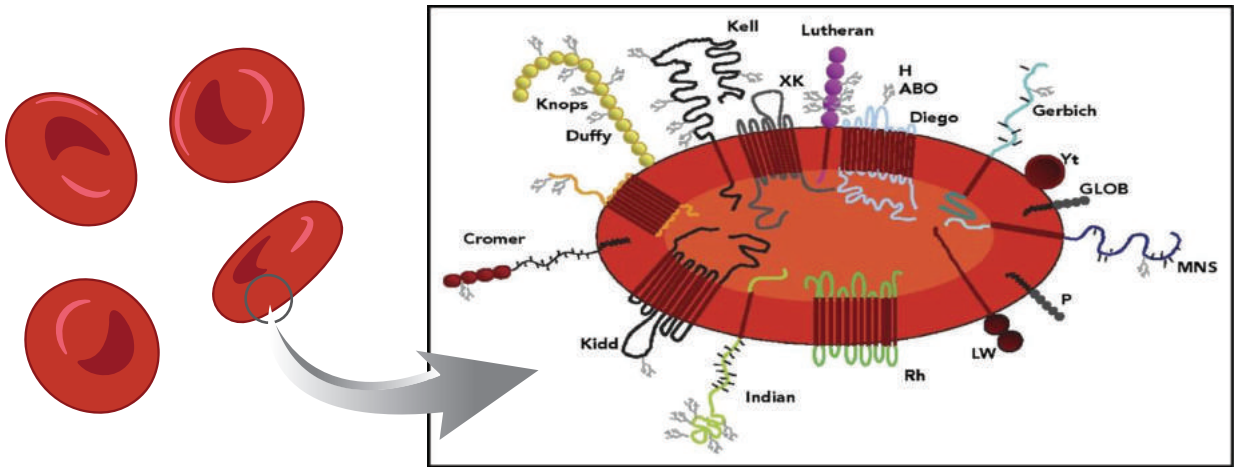


Figure 3: Red Blood Cell (RBC) membrane with representative blood group antigens[2]

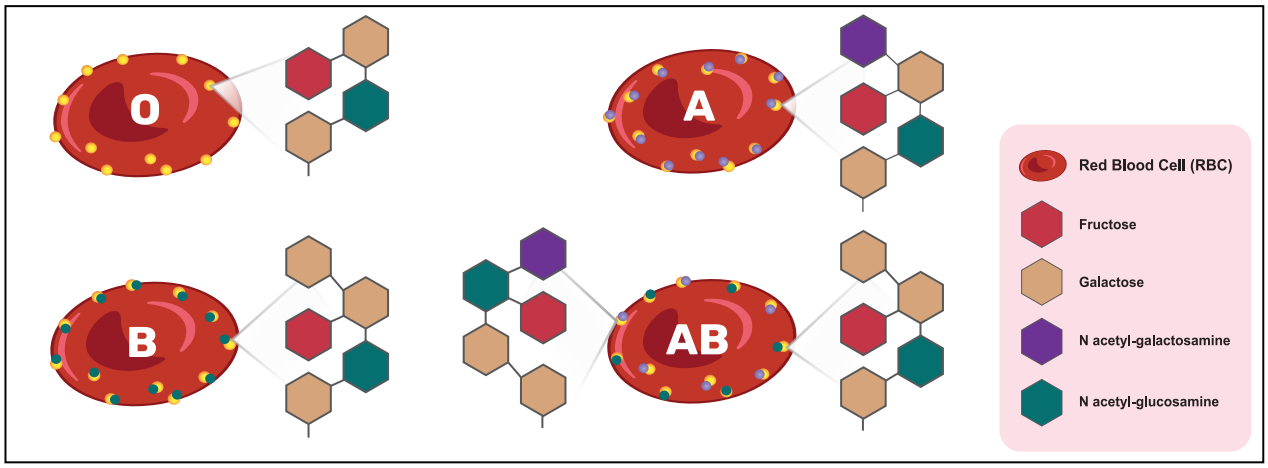


Figure 4: Schematic diagram showing the immunodominant sugars responsible for the ABO antigen specificity[2]

### ABO Blood Group System

The most well known and clinically important blood group system in human blood transfusion is ABO system. It was discovered by Karl Lansteiner in 1900. The genes that determine the ABO blood groups are ABO gene and H gene (Figure 3). The H gene form the basic structure called H antigen. With the inheritance of A and/or B gene, one will form A antigens or B antigens or both A and B antigens, thus leading to blood types, namely A, B, AB. For individuals who do not inherit A or B gene, no A or B antigens formed, thus they are grouped as O.

## ABO Blood Group System

The ABH antigens developed very early in fetal life but do not increase much in strength during gestational period. In newborn, the red cells carry only about 25-50% of the number of antigen sites found in adult red cells. The A and/or B antigen expression are only fully developed at 2-4 years of age, and may remain constant throughout life.

The reciprocal ABO antibodies are not present in the newborn, it is formed "naturally" when the immune system encounters the "missing" ABO blood group antigens in foods or in micro-organisms. It is usually happens at early age around 4-6 months of life, because the sugars that are identical to, or very similar to the ABO blood group antigens are found in nature.[3] The antibody level will reach the adult level at 5-10 years of age, and decreases in the elderly.

| Phenotype | Antigens on RBCs | Antibody in plasma/serum | Genotype (s) |
|---|---|---|---|
| A | A | Anti-B | AA or AO |
| B | B | Anti-A | BB or BO |
| AB | AB | None | AB |
| O | O | Anti-A, Anti-B | OO |

Table 1 - This shows the corresponding antigen - antibody presence in the four different phenotype of ABO blood groups.

## Testing of ABO blood group in the laboratory

The standard procedure to determine the ABO blood group (Table 1) in the laboratory consists of two parts i.e testing the antigens on the red cells (forward grouping) and the reciprocal antibody in the serum/plasma (reverse grouping). The blood group will only be confirm if the forward and reverse grouping are consistent. Any discrepancy detected between the forward and reverse grouping, further investigations need to be carried out to confirm the blood group before issuing blood for transfusion except for emergency situations.

## Conclusion

ABO blood group system is of prime importance in transfusion medicine. The correct typing of the ABO blood group, resolving any discrepancies between forward and reverse grouping before supplying ABO and cross match compatible blood for one's transfusion is required to ensure safe transfusion practices.

**SAFE TRANSFUSION**

**RIGHT BLOOD, RIGHT PATIENT, RIGHT TIME AND RIGHT PLACE**

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