

# Total immunoglobulin E: clinical utility and measurement

## Abstract

Total Immunoglobulin E (tIgE) is still being ordered alone or along with allergen specific IgE as first line test to diagnose allergic diseases in primary care settings. It has been well established that elevated serum tIgE levels are of very limited clinical utility in allergy as it does not give any information of sensitizing allergens in an individual. tIgE levels are shown to be useful to screen for presumptive diagnosis of IgE myeloma (myeloma that selectively produce IgE par protein). Though tIgE immunoassay are one of the most well standardized assays with high precision and reproducibility, its main utility appears to be limited to evaluate and monitor patients as candidates for the receiving anti-IgE therapy. tIgE is a non-specific allergy marker and is replaced by more specific and sensitive markers as specific-IgE (sIgE) and component-resolved diagnostics.

**Keywords:** immunoglobulin E, total IgE, clinical utility, allergy

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**Abbreviations:** IgE, immunoglobulin E; tIgE, total IgE; sIgE, specific IgE

## Introduction

Immunoglobulin E (IgE) is normally present at very low levels in plasma and primarily produced by plasma cells in mucosal associated lymphoid tissue. IgE is the antibody isotope that contains the  $\epsilon$  (epsilon) heavy chains and it is a monomer with five domains in the immunoglobulin structure and has a half-life of about 1-5 days.<sup>1-3</sup> IgE as a fifth immunoglobulin class was announced by WHO International Reference Center in 1968.<sup>4</sup> IgE mediates its response by binding to Fc $\epsilon$ R receptors which are mainly of two types. High sensitivity receptors (Fc $\epsilon$ RI) found on mast cells, basophiles, antigen presenting cells<sup>5-7</sup> whereas low affinity receptors (Fc $\epsilon$ RII) are found to be expressed on B-cells, monocyte and dendritic cells.<sup>8</sup> Binding of antigen to IgE cross-links these receptors and this causes the release of chemical mediators from the mast cells, which may lead to the development of a type I hypersensitivity reaction. As basophils and activated eosinophils also express Fc $\epsilon$ RI; therefore display surface-bound IgE and also take part in the production of Type I hypersensitivity reaction.<sup>9</sup> The concentrations of serum tIgE are highly age-dependent. Mean serum tIgE levels progressively increase in healthy children up to the age of 10 to 15 years and then decline in an age-dependent manner from the second through eighth decade of life. Therefore, the serum tIgE levels should always be evaluated to the reference intervals established from age-stratified healthy (nontoxic) population.<sup>10-12</sup> IgE is expressed as kU/L or IU/mL to alleviate the inconvenience in expressing very low serum levels<sup>13</sup> tIgE Measurement.

Currently tIgE is measured in serum by commercially available immunoassays on automated platforms. Historically IgE has been measured by using number of competitive and non-competitive, solid and liquid phases, isotopic and non-isotopic immunoassays that used antibodies specific to human IgE as either capture and/or detection reagent. These antibodies were insolubilized on a solid phase (capture Ab) and/or directly conjugated with the label (radio-nuclide, enzyme or fluorophor). Current most commonly used immunoassays for tIgE are non-isotopic based on sandwich principle. These immunoassays assays are one of the most well standardized immunoassays with

improved precision, reproducibility with good sensitivity and specificity. Though different manufacturers may use different solid phases for antibody attachment and detection methods, all assays are standardized to a common primary human IgE standard (WHO 75/502)<sup>14</sup> and most are cross standardized to a common secondary IgE reference preparation.<sup>15,16</sup> This has resulted to highly reproducible and agreeable results between manufacture. College of Pathologist conducts PT survey which involves 5-6 sera three times a year for which about 150 laboratories participate worldwide, the data demonstrates high inter-assay precision and analytical accuracy and agreement between different methods with CV <10%.<sup>17</sup>

## Clinical utility

Elevated serum tIgE levels can be detected in subjects sensitized to allergens as well as non-allergic diseases. Serum tIgE levels are shown to be associated and significantly higher in atopic disorders as allergic rhinitis, extrinsic asthma and atopic dermatitis than age-adjusted, healthy (nontoxic) population.<sup>11,18,19</sup> Serum tIgE levels are also shown to be significantly increased in parasitic infections, especially helminthes infection thus people living in helminthes endemic areas have significantly higher levels of tIgE despite being non-atopic and most of these IgE are nonspecific thus limiting its use as an allergic marker.<sup>20,21</sup> Extreme elevations of tIgE concentrations are observed in myeloma that selectively produce IgE par protein called IgE myeloma, hyper IgE syndrome (Joe syndrome) and some disorders of vacuities, although these conditions are rare but should be considered in the differential diagnosis if significantly elevated tIgE levels are observed.<sup>22</sup> A recent study conducted in children in the age group of 6 months to 12 years showed strong association of tIgE to environmental factors like passive smoking, cold, pollen and pets but was not statistically significant to systemic allergy, skin allergy, food allergy, allergic sinusitis, allergic rhinitis and allergic conjunctivitis. Elevated tIgE levels were strongly associated with bronchial asthma and its severity.<sup>23</sup> Normal or low tIgE levels in asthmatic individuals could suggest that IgE-mediated mechanism may play only an insignificant role in the pathogenesis of disease and would support the diagnosis of non-allergic (intrinsic) asthma.<sup>24</sup> However, low or normal levels of tIgE do not eliminate the possibility of IgE-mediated allergic disease.<sup>25</sup>

Serum tIgE measurement is commonly requested as one of the first allergic marker to diagnose allergy along with allergen specific IgE. The observation led to identifying cut-off levels for the diagnosis of allergy. A cut-off of >200 kU/L has been proposed to have high probability in predicting the presence of allergy. Several studies have however, shown that there is a considerable overlap with serum tIgE for both allergic and control population which minimizes the clinical utility of tIgE in diagnostic work up of an allergic patient thus tIgE is relatively a non-specific marker in detecting allergic disorders.<sup>26,27</sup> Therefore, the serum tIgE should be interpreted carefully within clinical context for each patient. In recent years tIgE assays are being used to evaluate patients as candidates for the receiving anti-IgE therapy as Omalizumab, which is used to treat allergic asthma. Omalizumab is a humanized IgG1 anti-human IgE Fc that binds to an epitope on the epsilon-heavy chain. Administration of this drug leads to reduction in allergic symptoms following allergen exposure due to down regulation of number of high affinity IgE receptors on mast cells and basophils.<sup>28,29</sup> Serum tIgE levels between 30 – 700 IU/mL are candidates for the therapy and thereafter to monitor and ensure optimal treatment efficacy.<sup>29,30</sup>

tIgE and sIgE do not have same sensitivity and specificity to an allergic disease. The tIgE is the sum of all the sIgE. It is not IgE directed against a specific allergen, but is the measurement of all the allergen-specific IgE. sIgE on the other hand refers to IgE which is directed against a specific allergen, e.g. specific IgE may be the amount of IgE that is directed against peanut. The presence of sIgE indicates sensitization to a specific allergen and does not necessarily means allergic disease. In vitro measurement of sIgE combined with skin tests has become the cornerstone in the diagnosis of allergic disease. The first assay designed to identify sIgE was the radioisotope-based radioallergosorbent test commonly referred as RAST.<sup>31,32</sup> In recent decade however, the development of new immunoenzymatic methods as ELISA and fluorometric assays have replaced the radioisotope based assays which offer technical advantage of increased accuracy, sensitivity and fast turnaround time.<sup>33</sup> However, a marked variability in quantitative estimates of sIgE between different methods is a cause for concern. Molecular Allergology or component-resolved diagnostics is now an emerging diagnostic tool that quantifies the allergen specific IgE antibodies to single, pure allergen molecules. This technique offers enhanced diagnostic accuracy in polysensitized patients and strengthens the clinical utility of IgE testing.<sup>33,34</sup>

## Conclusion

Elevated serum tIgE levels can be detected in subjects sensitized to allergens as well as non-allergic diseases. tIgE level alone therefore, is of limited clinical utility as a marker for allergy as it does not give any information to sensitizing allergens in an individual. Studies have shown that there is a considerable overlap between serum tIgE in both allergic and control population and atopic subjects show an irregular distribution for tIgE. tIgE is thus a non-specific marker in detecting allergic disorders, therefore, should be interpreted carefully within clinical context for each patient. tIgE immunoassays though one of the most well standardized assays with high precision and reproducibility, have limited utility to evaluate and monitor patients as candidates for the receiving anti-IgE therapy.

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## Conflicts on interest

The author declares that there is no conflict of interest.

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