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Foods Causing Highest IgG Immune Response in Saudi Arabia

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Background: Type III hypersensitivity caused by immunoglobulin G (IgG) to food has elicited plenty of scholarly attention in recent years. Opinions continue to be divided regarding the linkage between IgG reactivity to food and chronic inflammatory diseases.
Objective: To identify foods that cause the maximum amount of IgG immune reaction in patients throughout Saudi Arabia from a standardized food panel and to identify any difference caused by age or gender.
Methods: We used a pre-existing database for patients who participated in the standardized panel of 268 foods ELISA-based IgG to conduct a food allergy test referred to as ImuPro™ Complete. The data in the database was prepared by the database provider through the utilization of established procedures from R-Biopharm AG using standard ELISA plates. Meanwhile, the samples were processed in ELISA Washer and Reader machines. Readings were analyzed using R-Biopharm's standard ImuPro™ software and then fed into the database used by us.
Results: A total of1644 patients (913 males and 731 females=55.5% male, 44.5% female) were tested. IgG reactivity was predominant in eight foods (3%) in at least three-quarters of the studied population. These included Oats (82.5%), Barley (79.1%), Rye (76.1%) Cow's Milk (75%), Wheat (74.9%), Kamut (74.6%), Spelt (74.6%) and Gluten (73.9%). The IgG immune response of males and females to each food type was found to be almost the same. Children have a significantly different IgG food profile in comparison to adults (p-value =0.024). Cow's milk was found to induce

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the highest IgG immune response among children below five years of age (95.74%), followed by oats (92.2%).

Conclusion: To the best of our knowledge**,** this is one of the largest studies to have been conducted worldwide that involves the IgG immune response of patients to food. The top-most foods were 'mainstream' foods consumed almost daily, which include gluten and dairy products. No significant difference was found between males and females. A clear difference can be seen between children and adults when it comes to the IgG immune reaction to different food items. Further investigations are recommended to determine the food characteristics and eating habits that cause these IgG immune responses.

Keywords: Chronic illness; chronic inflammation; food allergy; IBS; IgE; IgG; immunoglobulin E; immunoglobulin G; immunoglobulin.

1. INTRODUCTION

Allergy is known to affect millions of people worldwide. In this context, Immunoglobulin E (IgE) allergy, which is also known as type I allergy, has been extensively studied [1,2,3,4]. Allergies can be classified into two major groups: inhalant and food allergies. About 4-8% of the population suffers from food allergy [4,5]. There is a smaller subclass called "Monoallergy", which denotes allergy to different drugs and medications, including those for insect bites. Although this is an IgE-mediated hypersensitivity, the total IgE is not increased. This type of allergy can be acquired anytime during the life of the patient and is not known to have any inducing factors [1].

In addition to IgE mediated allergy, a second type of immune response may occur against food. This type of response is categorized as Type III IgG food sensitivity [6,7,8], which has recently gained a lot of attention from the medical community. It is assumed to affect up to 20% of the population suffering from chronic inflammatory diseases. The IgG-mediated hypersensitivity is mostly a delayed-type of allergy, with symptoms usually appearing hours or up to three days after the consumption of concerned food [9,10]. This makes it practically impossible to identify such foods without testing them. The objective of this study is to determine the foods that caused the maximum IgG immune response in patients that underwent the ImuPro Complete test against all the 268 foods. In addition, it aims to examine whether there is any difference in the above response between males and females, and between children and adults. According to the findings, most of the foods causing this response are mainstream foods. For this reason, it is interesting to study the causes of this type immune response.

The presence of IgG against food is a contentious issue [11,12] Some authors believe that it is normal to have IgG antibodies to food that are regularly consumed, and that the presence IgG is a marker of contact and tolerance, rather than hypersensitivity. However, this viewpoint has been contradicted by a study [13] carried out in Germany in which volunteers who were IgG negative to soy, cow's milk, or eggs were required to follow a 3-week provocation diet containing in addition to their daily intake: either 750 ml of soy milk, 750 ml of cow's milk, or two eggs. After four and seven weeks, IgG titers were measured, and none showed any elevated IgG to the consumed foods. Moreover, it is impractical for any individual to possess antibodies to all foods, including beef, chicken, rice, potatoes, and vegetables. It is noteworthy that less than 5% of people are allergic to beef, although millions of people globally consume beef once per week. Humans have developed a high degree of tolerance against food [14], which implies an absence of immune reaction. This is the normal situation. We only develop antibodies to a particular type of food when our immune systems react to it and tag it as something potentially dangerous. An IgG-mediated immune response is triggered every time someone consumes food that the body's IgG immune system considers as a threat.

Thousands of patients have undergone and benefitted from the IgG test. In general, these patients suffer from chronic medical conditions such as irritable bowel syndrome (IBS) [15,16], migraine [16,17], psoriasis, joint pains, Crohn's disease [18,19], hypertension [20], and asthma [21], to name a few. Many of them have even taken medical treatments without positive outcomes. In addition, a number of these patients carry on with their lives by taking medications that treat the symptoms but do not

address the root cause of the problem. Food might not be the primary cause for their ailments, but IgG marked food antigens may indeed be fixed by a sensitized organ, attract phagocytes, and get destroyed locally. This action will inflame the tissue before increasing the progression of the disease. In order to stop this process, one needs to identify and remove individual triggers.

However, it is observed that patients who take the IgG test, either because their doctor advise them to do so, or because they stumble upon it while searching the internet for a cure to their pain and suffering, get cured of their problems by excluding these foods from their diet [10,17].

IgE-mediated food allergy is a prevalent type of sensitivity reaction that can occur anytime or anywhere. These allergies are quite difficult to avoid and are usually treated by some medicines, such as antihistamines [22]. However, preventing these allergies may become difficult since they can occur due to everyday food items such as, milk, chicken, eggs, and peanuts [23]. These foods, along with many other common food items, can cause life-threatening anaphylaxis [24,25].

IgG food hypersensitivity occurs when the immune system recognizes food as a foreign invader. As a result, the immune system produces IgG antibodies that attack the foreign food items. The four subclasses of IgG are: IgG1, IgG2, IgG3 and IgG4. IgG1-3 are pro-inflammatory antibodies, while IgG4 has anti-inflammatory properties [26,27,28,29,30]. IgG4 is regarded as the antidote to IgE, as the liberation of histamine is strongly reduced, and allergic symptoms can be avoided. IgG4 is the type of antibody that is produced during desensitization of type 1 allergy. IgG4 cannot induce an allergy or inflammatory response, which is considered to be protective and induce tolerance. IgG4 only constitutes 5% of total IgG in serum and its concentration is much lower than the other subclasses. In the test used for this study, only 1% of the reactions can be attributed to IgG4. In contrast IgG1-3 have strong pro-inflammatory properties, they can activate the complement system; they are opsonizing and induce chemotaxis, which results in the destruction of the formed immune complex by phagocytosis. The main white blood cells involved are neutrophils. In case of injected allergens, the mechanism leading to IgG mediated immune reactions and anaphylaxis were published by Jönsson et al. [31]. They found that neither IgE, histamine, basophiles, normastocytes were involved, but that IgG, IgG receptors, and neutrophils were responsible for the observed anaphylaxis. Furthermore, PAF (platelet activating factor) was observed to be one of the most potent cytokines involved. As observed in this study, food is ingested instead of being injected, which leads to the destruction of epitopes, a dilution and delayed uptake from the gut to the blood. For these reasons, IgG reaction to food doesn't lead to anaphylaxis or immediate reaction such as IgE. Instead, it causes the onset of delayed milder symptoms. This inflammatory or hypersensitivity reaction, in turn, may produce various other symptoms such as constipation, tiredness, bloating, irritable bowel syndrome (IBS), diarrhea, migraines, eczema, and headaches [32,33].

It is notable that IgG I, IgG II, or IgG III reaction to certain kinds of food is found to occur every time the patient consumes the affecting food item. As a matter of fact, everyday consumption of these foods induces this inflammatory process on a daily basis. This is when the useful IgG reaction may become harmful since the immune system treats these foods as a threat in such cases and reacts accordingly.

Studies have shown that an increase of inflammation markers such as serum CRP, white blood cell counts, Calprotectin could be observed within a short time after consumption of IgG positive foods [19,20].

There are several types of food testing, but the most common method is to test or screen the patient against an innumerable number of food additives and items. Consumers are then provided with a list of food items that they are intolerant to.

In this regard, IgG (immunoglobulin G) testing is one of the most useful methods for food intolerance testing [20,34,35]. The test is used in various kinds of conditions where diet elimination and preventing allergies is deemed mandatory. Such conditions can include movement disorders, gastrointestinal, and neurological conditions [36]. IgG testing is not intended to confirm any diagnosis. Instead, it is used as a guide to identify the foods that cause elevated IgG levels in the blood. The next step is to follow the gold standard for diagnosing food allergy, which to eliminate these foods [37] from the diet followed by a provocation diet where these foods are reintroduced one at a time to determine the foods that actually cause the symptoms to reappear [38].

In order to resolve this problem, food specific IgG testing helps identify the food items that cause IgG hypersensitivity reactions before eliminating them from the individuals'dietary intake [8]. By doing so, a variety of medical conditions such as epilepsy, rheumatoid arthritis [39], cystic fibrosis, autism, AD(H)D, and IBS can disappear or be be effectively addresses [15,40].

2. METHODS

For this study, a preexisting database for patients in Saudi Arabia underwent the ImuPro™ food allergy test between 2011 and 2016 was used. This test was devised by R-Biopharm AG from Germany and is an enzyme-linked immunosorbent assay (ELISA). It is used a standardized panel of 268 foods ELISA-based IgG food allergy test. The database provider had all the samples processed by CTL laboratory, Germany, and 5 ml of blood was extracted from each patient, before being centrifuged and collecting the serum. Standard procedures from R-Biopharm AG using standard ELISA plates for performing the ImuPro™ food allergy test were then adhered to. In addition, all the samples were sent across to CTL laboratories in Germany with a view to processing the samples in an ELISA Washer and Reader machines. The measurements were analyzed by R-Biopharm's standard ImuPro™ software and the results were put in the database used by us.

Only numerical test results, as well as patient age and gender data, were used in this study. No patient identifying information was used. Inclusion criteria included patients who were part of a pre-existing database and took the aforementioned test in Saudi Arabia between 2011 and 2016. A total of 1644 patients (913 males and 731 females of different ages) were analyzed. The large size of this sample made it possible to represent all patients and no exclusion were made. Some patients were referred by physicians, while others opted to perform the test on their own accord. In other words, the sample was representative of all patients.

Patients signed a consent form, which allowed their data to be used for research purposes.

3. RESULTS AND DISCUSSION

This section explains the findings based on actual measurements involving 1644 patients (913 males and 731 females) of all ages ranging from 1 year up to 80 years old in Saudi Arabia who were tested for the same 268 food types.

Fig. 1 shows the topmost food groups that induced an IgG immune response. The size of the circle indicates the percentage of the population affected by this food group. Evidently, milk products, eggs, yeast, cereals, and seeds emerged as the biggest contributors to the IgG immune response.

Fig. 2 (a) uses a Box and Whisker plot to display the distribution of foods, thus inducing an IgG immune response in the population tested. As shown by the above figure, the majority of foods (243 foods = 91%) tested affected less than 30% of the population. In addition, it can also be seen that 25 outliers affect more than 70% of the population. Fig. 2(b) shows the outliers and the percentage of the population affected.

Shakoor et al. [9] performed a similar study using a microarray test and tested 223 food types. Their study involved 71 patients (49 males and 22 females) between the ages of 6 and 80 years. They excluded patients with IgE symptoms and elevated IgE levels, as well as those with positive skin prick test and any disorders other than allergies including IBS, food enzyme deficiency, and celiac disease. Our study is different in that we intentionally did not have any exclusion criteria to obtain a global view of the society IgG profile. We included 1-year old children and older, used an ELISA test, tested 268 different food types, and had 1644 patients (913 males and 731 females). Meanwhile, our panel includes several types of beans (cocoa bean, green bean, soybean, broad bean, and mung bean), but excludes cola bean and red kidney beans. It is interesting to compare some of their results to ours for similar foods, as shown in Table 1. It can be seen that we have a close match for wheat and egg white. The difference in results is actually quite interesting and opens up further research opportunities to investigate the underlying reason for these differences, be it due to the age difference, the exclusion criteria used by Shakoor et al. [9], the different sensitivities of microarray and ELISA, or some other factors. Another reason for the difference between our results and that of Shakoor et al. [9] is that our study used different test technologies from different companies, which could include different sources of antigens and a unique chemistry behind each testing system.

Fig. 1. Food groups causing IgG immune reaction. The size of the circle indicates the percentage of the population affected by this food group

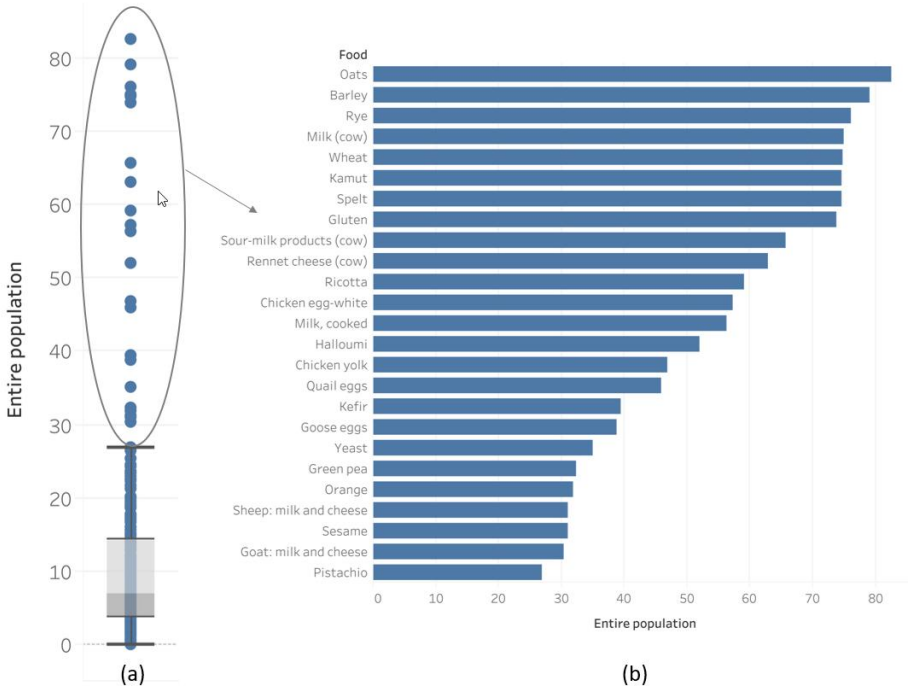

Fig. 2(a) Box and Whisker plot of the entire data with outliers. (b) Outlier foods with the percentage of the population they affected

Table 1. Comparison with the results of Shakoor et al. [9]

Food tested	Our results	Shakoor et al. [9]
Yeast	35.0%	78.9%
Wheat	74.9%	77.5%
Pea	32.4%	63.4%
Corn	10.6% (maize)	62.0%
Egg white	52.3%	62.0%
Barley	79.1%	57.7%
Pistachio	26.9%	56.3%
Cow's milk	75.0%	56.3%

Fig. 3 (a) illustrates the same data shown in Fig. 2(a), albeit in a histogram plot. It plots the percentage of patients affected by each food type. For analogy purposes, the curve shown in Fig. 3(a) denotes an exponential probability density random function. We can determine the probability characteristics for any region by means of probability rules.

Fig. 3(b) shows the foods affecting over 50% of the population. The size of the circle reflects the percentage of the population affected. A comparison between the data in Fig. 2(b) and Fig. 3(b) clearly reveals the presence of a well-defined prevalence of IgG allergic response to foods. Meanwhile, Table 2 shows that 26 foods (9.7% of the foods tested) caused an IgG reaction in 26% of the population, whereas 14 foods (5.2% of the foods tested) triggered an IgG reaction in 51% of the population. However, only eight foods (3% of the foods tested) were found to trigger an IgG immune response in more than 73% of the tested patients.

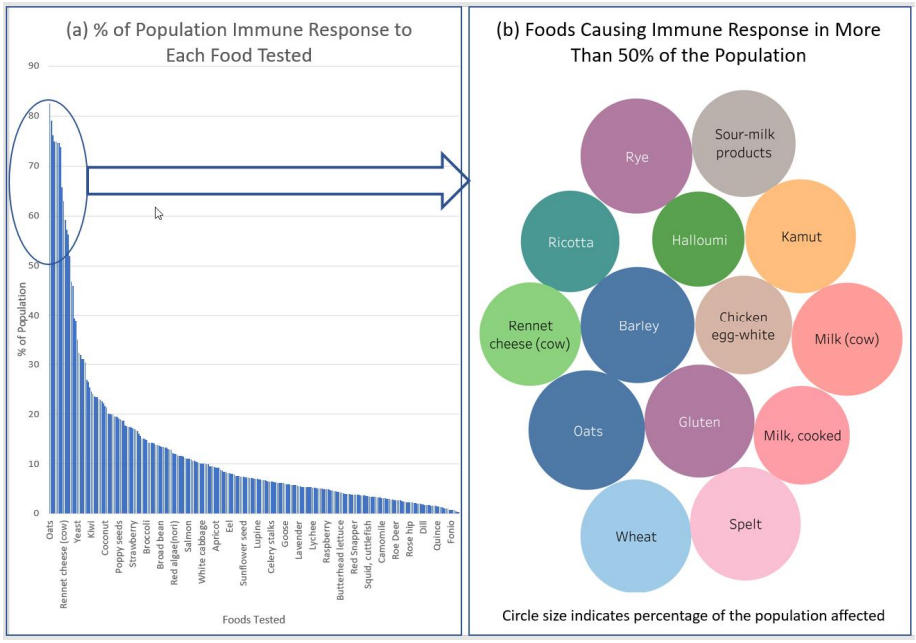

Fig. 3. % of patients with IgG levels above the cut-off threshold for each food tested in descending order

Table 2. Number of foods causing the most IgG immune response

# of Foods	% Compared to total foods tested	% of Population affected
26	26 / 268 = 9.7%	> 26.5%
14	14 / 268 = 5.2%	> 51.2%
8	8 / 268 = 3.0%	> 73.8%

Fig. 2(b) shows that the outlier foods exhibit an overlapping trait:these 'mainstream' foods are consumed by the majority of people almost on a daily basis, forming part of the majority of our diets. These primarily include wheat, gluten, cow's milk, and eggs. This is further clarified if we study Fig. 3(b) where it can be seen that the 14 foods affecting more than 50% of the population are actually mainstream foods consumed on a regular basis. It is also pertinent to look at the other end of the spectrum and analyze the ten food items that cause the least IgG allergic response in the population tested.

Table 3 lists ten foods causing the least IgG response in the descending order. Notably, although cow's milk affects 75% of the population and is consumed directly or indirectly on a daily basis as an ingredient used in various food recipes, there are other foods that are consumed almost as frequently, but induce almost negligible IgG immune response. For example, our results show that black tea and green tea have a very low effect on IgG immune response, affecting only 1.58% and 0.72% of the participants, respectively. Although people drink tea and cow's milk almost on a daily basis, the former impacts less than 2% of the population tested, while the latter affects 75% of the population tested. Some of the other foods that are consumed almost every day include chicken, beef, and rice; however, they impact only 11.98%, 5.42%, and 4.89% of the population, respectively. Thus, it can be concluded that merely eating a particular food on a regular basis and in large quantities alone is not a strong enough reason to cause a large percentage of the population to develop an IgG immune response to it. It is important for the foods to have some intrinsic properties that cause many people to develop an IgG immune response to these items when consumed frequently and in large quantities. This point is an interesting topic for further research.

Since all the patients were tested for the same 268 food items, their median is 134 foods. The five foods that fall above and below the median are depicted in Table 4. It is evident that most foods around the medial induced an IgG response in only about 7% of the population tested.

Table 3. Ten foods causing the least response in the population

	Food	% of Population
1	Tannin	1.07
2	Lemon balm	1.07
3	Teff	1.07
4	Fonio	0.77
5	Carrageenan (E407)	0.77
6	Goat meat	0.72
7	Tea, green	0.72
8	Nettle	0.42
9	Moluchia	0.36
10	Saffron	0.30

Table 4. Ten foods around the median

	Food	% of Population
129	Rosemary	7.33
130	Bamboo shoots	7.15
131	Sunflower seed	7.39
132	Sea bass	7.09
133	Thyme	7.21
134	Amaranth	7.15
135	Cauliflower	6.97
136	Lupine	6.97
137	Pectin (E440)	6.85
138	Oysters	6.73
139	Nutmeg	6.79

It is also interesting to compare the results of male and female participants. Fig. 4 illustrates the percentage of males and females who reported an IgG immune response to each food tested. It was observed that the majority of these foods induced almost the same effect on both males and females.

Fig. 5 plots the percentage of population affected by each food for children below the age of five against the percentage of the population above the age of 15 years that were affected by the same food. An analysis of these foods reveals a clear difference. Some foods were found to affect the majority of children below five years much more than the remainder of the population above the age of 15. While other foods were observed to have a minor effect on children below the age of five, they had a stronger impact on the remainder of the population above 15 years of age. In general, Fig. 5 demonstrates that children are affected by more types of foods than adults. This becomes evident from the prevalence of more data points to the right-hand side of the 45-degree line.

Fig. 6(a) illustrates a Box and Whisker plot to display each food and subtracts the percentage of the children population below the age of five from the percentage of the remainder of the population above 15 years of age who developed an IgG immune response to that same food. It can be seen that there are 22 foods in the upper outlier (foods that affected children much more than adults) and there are three foods in the lower outlier are listed in Fig. 6(b). This clearly shows that a major change occurs in the immune profile of children and adults. For example, 60% more children below the age of five years showed an IgG immune reaction to coconut as compared to adults older than 15 years. Contrastingly, more than 30% of adults reported an IgG immune response to black pepper in comparison to children below the age of five.

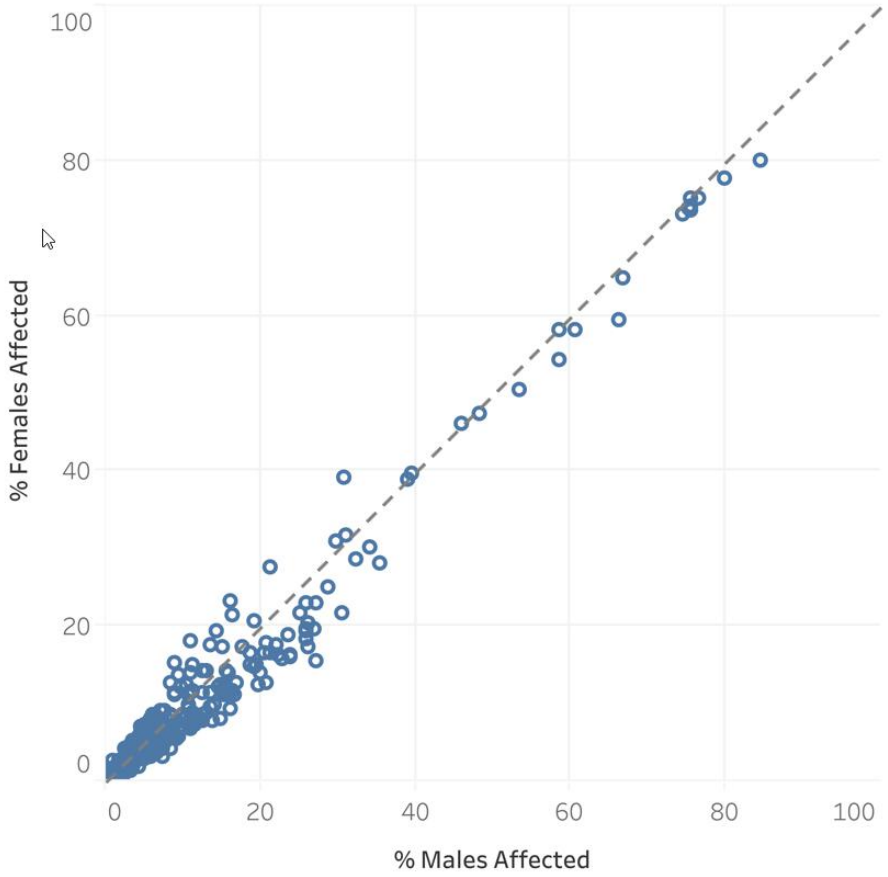

Fig. 4. Comparing male and female Immune response to all foods tested

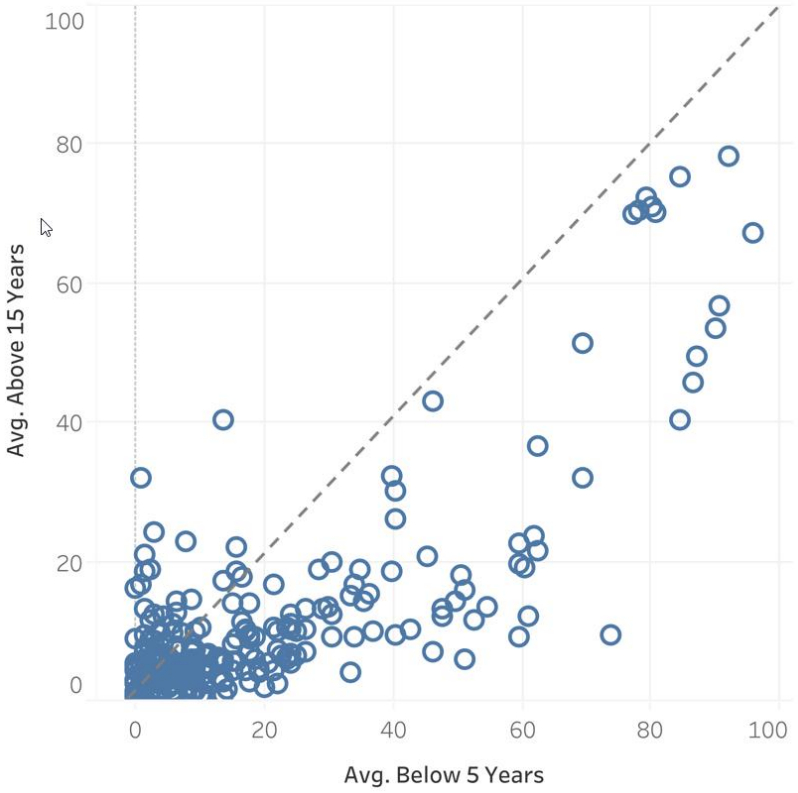

Fig. 5. Comparing IgG induced immune response for each food in children below five years old and the remainder of the population above 15 years of age

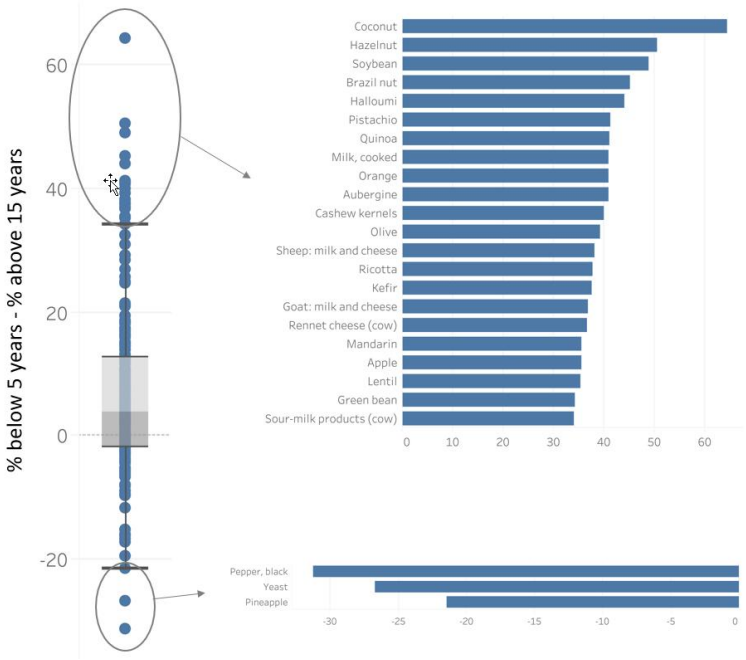

Fig. 6(a). Box and Whiskers plot showing for each food tested the % affected children below five years - % affected for those above 15 years, (b) outliers

Table 5. List of foods where the difference between the % affected Adults and children was the greatest

Food	% Affected below five years	% Affected above 15 years	Difference
Coconut	73.76	9.45	64.31
Hazelnut	59.57	9.11	50.46
Soybean	60.99	12.11	48.88
Brazil nut	51.06	5.93	45.13
Halloumi	84.4	40.38	44.02
Pistachio	60.28	18.99	41.29
Quinoa	54.61	13.49	41.12
Milk, cooked	86.52	45.62	40.9
Orange	62.41	21.56	40.85
Aubergine	52.48	11.68	40.8
Cashew kernels	59.57	19.59	39.98
Sheep: milk and cheese	61.7	23.54	38.16
Ricotta	87.23	49.57	37.66
Kefir	69.5	31.96	37.54
Goat: milk and cheese	59.57	22.68	36.89
Rennet cheese (cow)	90.07	53.44	36.63
Apple	49.65	14.18	35.47
Lentil	51.06	15.81	35.25
Sour-milk products (cow)	90.78	56.7	34.08
Pepper, black	0.71	31.96	-31.25
Yeast	13.48	40.21	-26.73
Pineapple	2.84	24.31	-21.47

Table 5 Compares the foods that caused an IgG immune response in 50% or more in the children's population below the age of five (141 children), as well as the corresponding percentage of affected population above 15 years of age (1164 persons) to the same food. The data is sorted in a descending order for % of children affected.

In this analysis, we determined the allergic level of food items versus the individual's age, starting from a very early age. Our results were compared based on the foods triggering an IgG immune response in children aged under five years (141 children compared with the rest of the population above 15 years of age (1164 persons). The selection of these age groups is intended to emphasize the role of age with regards to the IgG immune response. This approach facilitates an understanding of the nature of IgG food Immune response in human beings. Table 5 shows different results for both children and adults. The most interesting result seen in the table is that cow's milk has the highest indication of IgG response for children below five years of age. This food item is followed by oats, cow sour-milk, rennet cheese, ricotta cheese, and cooked milk, respectively. However, the order and prevalence of the same foods on individuals above the age of 15 years for the same foods was observed to change. This result leads to the conclusion that the foods derived from cow's milk induce the strongest IgG allergic response in children below five years of age. This effect continues to reduce with age.

4. CONCLUSION

This study obtained and compared the results from 1644 patients in Saudi Arabia who underwent the ELISA-based ImuPro IgG test (from R-Biopharm AG – Germany) on 268 food items. According to the findings, eight foods representing 3% of the tested foods affected 73.4% of the population. Notably, all the topmost type III IgG allergy-causing foods are essentially 'mainstream' foods that are consumed by the majority of people almost on a daily basis. They primarily comprise of wheat, gluten, cow's milk, and eggs. Contrastingly, other common foods such as beef, and rice and drinks such as tea, elicited very little IgG response in the population. Foods were also found to affect both males and females almost equally.

Most crucially, the most significant foods for children below the age of five include cow's milk, oats, sour cow's milk, rennet cheese, ricotta

cheese, and cooked milk. For those older than 15 years, the sequence of the same food items is 8, 1, 9, 10, 12, and 13, respectively. Thus, it can be inferred that cow's milk causes the strongest IgG allergic response in children younger than five years of age, because children have a significantly different IgG food profile as compared to adults ($p<.05$ i.e. p-value =.024). With the increase in age, a gradual change is observed in the foods that cause IgG allergic responses.

In summation, it can be concluded that IgG induced immune response for some foods can be eradicated or reduced drastically with time. At the same time, the IgG induced immune response for some foods can appear or even radically increase with time. These findings reinforce the belief that the adverse of type III IgG food immune response can be reduced or even completely cured, and that the method used for testing IgG immune response is far more effective than traditional methods. These results are valid for Saudi Arabia, and may vary from one continent to another due to cultural and/or genetic factors. It would be interesting to conduct further investigations provided the same testing system is used to compare the results.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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