



Trends in gluten research and its relationship to autoimmune and allergic diseases



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ABSTRACT

Introduction: Gluten is a protein found in certain grains, and causes an autoimmune response in celiac disease patients. Although the subject of considerable research, gluten research foci and future directions are largely unknown.

Methods: The MEDLINE search tool was used to evaluate research trends. For perspective, yearly publications on gluten and other celiac disease reactive proteins were compared to food allergy proteins research. Then the relationship of gluten publications to affiliated keywords was determined. The affiliated keywords belonged to one of several groups: grains, vitamins and minerals, interaction, autoimmunity, genetics, or enzymes. The yearly number of publications in the peer-reviewed medical literature was determined for each relationship from years 1960–2013. The relationships were graphed, and linear regression analysis was used to determine the rate of change in publications per year, and the coefficient of determination.

Results: Among celiac disease reactive proteins (gluten, gliadin, and glutenin) and selected food allergy proteins (ovalbumin, lysozyme, ovomucoid, and Ara h), gluten showed the greatest rate of increase in published medical research (+20.01 studies/year since 1996, $r^2=0.97$). Additionally, there were sharp increases in the rate of gluten research publications per year in association with keywords 'autoimmunity' (+7.69 studies/year since 1997), 'wheat' (+6.08 studies/year since 1999), and 'transglutaminase' enzyme (+5.05 studies/year since 1995). The longest running moderate trend was research on 'gluten' and 'antibodies' (+2.50 studies/year, $r^2=0.92$ since 1971).

Conclusions: Research on gluten as a reactive protein is of rapidly growing interest in the medical literature. MEDLINE is helpful to determine foci and future directions.

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1. Introduction

Celiac disease is a common health concern throughout the world, affecting approximately 1% of the population [1]. It is an autoimmune disease [2], with the reactive substrate being specific proteins found in the grains wheat, rye, and barley. When these grains are consumed, there is an autoimmune response, at the level of the small intestinal mucosa, to the protein gluten, and its component proteins gliadin and glutenin [3]. Research on gluten and celiac disease is important to determine the mechanisms of the disease and possible treatments [4].

In prior work we have used the MEDLINE search tool to determine research directions and foci in the area of celiac disease from the peer-reviewed medical literature [5]. In the current study we analyze the major reactive protein in celiac disease, gluten, to determine the foci and future directions of the research, with respect to other facets of celiac disease. This is done by pairing keyword ‘gluten’ with associated keywords used in celiac disease research. For perspective, the published literature on gluten is compared with its component proteins which are also reactive in celiac disease (gliadin and glutenin) and to selected proteins reactive in food allergies, which are an increasing clinical problem and of increasing interest in medical research.

2. Method

The MEDLINE search tool was used for all comparisons and analyses [6]. The search checks the title of the paper, the abstract, and the keywords selected by the authors of the paper. The MEDLINE tool was initialized to include multimedia references, and so as not to map the term to the subject heading. The limits used involved only the publication year. First the total number of publications from the years 1960–2015 inclusive was determined, for the following keywords (each noted by single quotation marks):

- Proteins reactive in celiac disease - ‘gluten’, ‘gliadin’, ‘glutenin’
- Proteins reactive in selected food allergies - ‘ovalbumin’, ‘lysozyme’, ‘ovomucoid’, and ‘Ara h’

‘Ara h’, a protein reactive in peanut allergy, was searched as: (‘Ara h’ or ‘Ara h1’ or ‘Ara h2’ or ‘Ara h3’).

MEDLINE treats each of these as distinct entities. The number of research publications per year for all reactive proteins was then determined via a MEDLINE search for each year, and graphed for the years 1960–2013. The year 2013 was used as an endpoint because it was the last year at the time of the study for which all research publications had been accounted for. Once the graphs of reactive protein publications were constructed, linear regression analysis (SigmaPlot, 2013, Systat Software, San Jose, CA) was used to determine the rate of change in the number of publications per year, i.e., the slope of the regression line, and also the coefficient of determination or r^2 value (fit to a straight line). The first data point in each keyword graph used for regression analysis was the last year in which the number of publications which included the keyword was equal to zero. If for a particular keyword, there were research publications for all years from 1960 to 2013, then the year 1960 was used as the starting point for regression analysis. An r^2 value of less than 0.8 was used to indicate a lesser fit to the straight line. For any such keywords, if a later portion of the graph in time had an evident better fit to a straight line, it was used as a separate linear regression model for analysis.

The degree of cross-publication between major reactive protein keywords was also determined, i.e., the following searches were made for the years 1960–2013:

Table 1
Total number of studies involving reactive protein and their association with terms used in celiac disease.

Protein	Total	Wheat	Rye	Barley	Oats	Rice	Vitamins	Calcium	Iron	Def.	Sensitivity	Intolerance	Allergen	Inflammation	Antibodies	Autoimmune	B cell	T cell	IgA	IgE	tTG	Enzyme	HLA
Gluten	8078	1704	295	340	135	136	96	230	325	911	561	305	851	2019	1589	87	663	991	104	906	923	840	
Gliadin	3082	944	157	152	62	39	10	43	73	555	143	194	299	1650	716	38	331	866	143	605	696	423	
Glutenin	614	547	32	37	6	28	0	0	1	18	2	46	5	57	20	3	17	6	40	13	56	13	
Ovalbumin	21,468	101	8	7	2	18	20	478	32	744	21	5674	5371	6236	5889	996	5191	492	2774	18	2651	108	
Lysozyme	20,477	61	2	21	1	27	33	546	60	1035	4	198	1129	2484	2029	548	821	518	102	19	4066	139	
Ovomucoid	835	42	1	4	0	2	2	18	0	34	0	145	7	131	46	7	15	7	103	1	243	4	
Ara h	393	1	0	0	0	3	0	2	2	53	0	265	6	115	49	6	27	4	252	2	77	4	

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