Metabolic and Immunologic Consequences of ABH Secretor and Lewis Subtype Status

Peter J. D'Adamo, ND, and Gregory S. Kelly, ND

Abstract

Determining ABH secretor phenotype and/or Lewis (Le) blood group status can be useful to the metabolically-oriented clinician. For example, differences in ABH secretor status drastically alter the carbohydrates present in body fluids and secretions; this can have profound influence on microbial attachment and persistence. Lewis typing is one genetic marker which might help identify subpopulations of individuals genetically prone to insulin resistance, autoimmunity, and heart disease. Understanding the clinical significance of ABH secretor status and the Lewis blood groups can provide insight into seemingly unrelated aspects of physiology, including variations in intestinal alkaline phosphatase activity, propensities toward blood clotting, reliability of some tumor markers, the composition of breast milk, and several generalized aspects of the immune function. Since the relevance of ABH blood group antigens as tumor markers and parasitic/bacterial/viral receptors and their association with immunologically important proteins is now well established, the prime biologic role for ABH blood group antigens may well be independent and unrelated to the erythrocyte.

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Functional and Genetic Factors Involved in ABH Secretion

The term "ABH secretor," as used in blood banking, refers to secretion of ABO blood group antigens in fluids such as saliva, sweat, tears, semen, and serum. A person who is an ABH secretor will secrete antigens according to their blood group; for example, a group O individual will secrete H antigen, a group A individual will secrete A and H antigens, etc. Soluble (secreted) antigens are called substances. To test for secretor status, an inhibition or neutralization test is done using saliva. The principle of the test is that if ABH antigens are present in a soluble form in a fluid (e.g., saliva) the antigens will neutralize their corresponding antibodies, and the antibodies will no longer be able to agglutinate red cells possessing the same antigens.

One of the primary differences in physiology between secretors and non-secretors involves qualitative and quantitative differences in components of their saliva, mucus, and other

Peter D'Adamo, ND – Private practice, Stamford, CT. Author of Eat Right 4 Your Type. Correspondence address: 2009 Summer Street, Stamford, CT 06905.

Gregory S. Kelly, ND – Associate Editor, Alternative Medicine Review.

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bodily secretions. ABH secretion is controlled by two alleles, Se and se. Se is dominant and se is recessive (or amorphic). Approximately 80 percent of people are secretors (*SeSe* or *Sese*).

In the most rudimentary sense, it is the secretor gene (FUT2 at 19q13.3) that codes for the activity of the glycosyltransferases needed to assemble aspects of both the ABO and Lewis (Le) blood groups. This is accomplished in concert with the gene for group O, or H (FUT1) and the gene for the Lewis phenotype. These enzymes are then active in places like goblet and mucous gland cells, resulting in the presence of the corresponding antigens in bodily fluids.[1]

The H antigens are indirect gene products expressed as fucose-containing glycan units, residing on glycoproteins or glycolipids of erythrocyte membranes or on mucin glycoproteins in secretions. They serve as the fucosylated-glycan substrates for glycosyltransferases that give rise to the epitopes for the A, B, and Lewis blood group antigens. The major difference between the two genes is in their pattern of expression. The FUT1 (H) gene is expressed predominantly in erythroid tissues giving rise to FUT1 (H enzyme) whose products reside on erythrocytes, whereas the FUT2 (Secretor) gene is expressed predominantly in secretory tissues giving rise to FUT2 (Secretor enzyme) and to products that reside on mucins in secretions.[2]

When alleles of both genes fail to express active enzymes, individuals bearing them in homozygous state lack the substrates for the A or B glycosyltransferases and do not express the A and B epitopes.

Relationship of ABH Secretor Status and Lewis System

Two broad categories of Lewis blood type exist. These are the Lewis positive (either Le (a+b-) or Le (a-b+)) and Lewis negative (Le (a-b-)) phenotypes. Since FUT1 provides the glycans necessary for glycosyltransferase conversion into the Lewis antigen in addition to ABH, the Lewis blood group determinants are structurally related to determinants of the ABO and the H/h blood group systems and the outcome of Lewis typing can be used for the *de facto* determination of ABH secretor status among Lewis positive

Table 1. Lewis Blood Types and their Relationship to ABH Secretors/Non-secretor Status

LEWIS PHENOTYPE	ABH SECRETOR STATUS
Le (a+b-) which has Lewis a antigen but not Lewis b	Always ABH non-secretor
Le (a-b+) which has Lewis b antigen but not Lewis a	Always ABH secretor
Le (a-b-) having neither Lewis a nor Lewis b	Lewis outcome not a determinant of ABH secretor status. However, this variant is associated with its own unique metabolic consequences.

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individuals (Table 1). In the presence of FUT2 alleles that express type 1 H determinants, the phenotype will be Le (a-b+), but individuals in whom the FUT2 gene is not expressed will be Le(a+b-).

Among Lewis positive individuals, ABH secretors are always Le (a-b+) since they convert all their Lewis(a) antigen into Lewis(b). Conversely, among Lewis positives, ABH non-secretors are always Le (a+b-) since they lack the FUT2 dependent glycosyltransferase to accomplish this. A small segment (1-8 percent of the population, dependent on race) will be Lewis negative and Lewis typing cannot be used to determine ABH secretor status. In these individuals determination via saliva is necessary to determine ABH secretor status. It can be quite useful to determine both ABH secretor status and Lewis blood group phenotype, since secretor status provides some degree of generalized information regarding disease states but Lewis negative individuals also appear to have unique interactions with certain disease states.

Although ABH secretor status is often thought of as an all-or-none situation, this is generally not the case. In some ABH non-secretors (known as partial or weak secretors) there will often be some form of active A or B blood group substance in the saliva; however, the quantity and quality of these substances is greatly reduced, predisposing them to similar functional problems as other non-secretors.[3,4]

Antigenic Structures in Fluid Secretions

There are several advantages to having large quantities of blood type antigens (both ABO and Lewis) secreted into saliva. First, salivary carbohydrate structures found in mucins can aggregate some oral bacteria and constituents of pellicle and plaque. Since saliva of secretors contains substantially more diversity and total carbohydrate than non-secretor mucins, this places secretors at a slight advantage. Second, these same blood type carbohydrate structures, due to the known "sweet tooth" (carbohydrate avidity) of many dietary lectins, may place secretors at an advantage with respect to the binding of blood type specific dietary lectins prior to any disruptive interaction of lectins with cell surface glycoproteins.

In the gastric mucosa of healthy individuals the normal mucosa of secretors is characterized by a uniform distribution of blood type antigens in the pits. Healthy mucosa of non-secretors shows little staining for these blood type antigens, but instead, demonstrates significant quantities of the I(Ma) antigen. This tendency to express the I(Ma) antigen will subsequently have an impact on antibody capabilities, as will be evidenced when immunity is discussed.[5]

Physiological Manifestations

Brush-Border Hydrolases

ABO blood group determines much of the enzyme activity in the tissue (brush-border) of the intestine. At least six intestinal hydrolases have ABO blood group antigenic determinants directly related to ABO blood group. Basically, the intestinal glycoproteins of blood group A and B individuals express A or B antigens, while blood group O subjects express the H determinant. The expression of these ABH antigens is under the control of the secretor gene; so these ABH antigens are not detected in the hydrolases of non-secretor subjects.[6] ABH secretors have greater quantities of free ABH antigens in the makeup of their intestinal secretions, which has significant effects on bacterial and lectin adherence to the gut microvilli.

Intestinal Alkaline Phosphatase Activity

The activity of intestinal alkaline phosphatase and serum alkaline phosphatase is strongly correlated with ABH secretor

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phenotypes. Independent of ABO blood group, ABH non-secretors have lower alkaline phosphatase activity than ABH secretors. It has been estimated that the serum alkaline phosphatase activity of non-secretors is only about 20 percent of the activity in the secretor groups.[7-10]

The intestinal component of alkaline phosphatase is involved with both the breakdown of dietary cholesterol and the absorption of calcium. The differences in intestinal alkaline phosphatase are almost exclusively related to one fraction of this enzyme. Normal molecular mass intestinal alkaline phosphatase (NIAP) is present in the serum of both secretors and non-secretors, regardless of ABO blood group. However, the high molecular mass intestinal alkaline phosphatase only appears in serum of Le (a-b+) blood group secretors.[11]

In addition to ABH secretor status, ABO polymorphism is also linked to the levels and persistence of intestinal alkaline phosphatase.[12] Numerous studies have associated group O individuals with the highest alkaline phosphatase activity, and group A the least.[13]

These findings suggest the link between group O individuals and adaptation to cholesterol-containing foods in the diet (such as meats) reaches its greatest accommodation in group O secretors. Conversely, group A non-secretors would have the lowest levels of intestinal alkaline phosphatase and the greatest difficulties in handling dietary fat. In addition, one study has implied the group A antigen itself may inactivate NIAP.[14]

Bacterial Flora

The role of the ABO blood group in determining the bacteria making up a healthy gastrointestinal ecosystem is particularly strong in ABH secretors. Since ABH secretor status and ABO blood group dictate the presence and specificity of A, B, and H blood group antigens in human gut mucin glycoproteins, this can influence the populations of bacteria capable of taking up local residence. This occurs because some of the bacteria in the digestive tract are actually capable of producing enzymes that allow them to degrade the terminal sugar of the ABH blood type antigens for a constant food supply.[15]

For example, bacteria capable of degrading blood group B antigen produce enzymes that allow them to detach the terminal alpha-D-galactose and use this sugar for food. Blood group A degrading bacteria would have similar capabilities with respect to N-acetylgalactosamine. Group B secretors produce greater levels of B-degrading than A- or H-degrading activity, and A secretors produce greater levels of A-degrading than B- or H-degrading activity. Because of this capability, the bacteria that use ABH antigens for food have a competitive advantage and can thrive in the environment created by the preconditioning of ABH secretions.[16]

Although comparatively small populations of bacteria produce blood group-degrading enzymes (estimated populations are 10^8 per g), the quantity of these bacteria are several orders of magnitude greater in different blood types and are much more stable residents. For example, B-degrading bacteria have a population density about 50,000-fold greater in blood group B secretors than in other subjects. Similar bacterial specificity and enzyme activity is found among other blood types.[15,16]

Breast Milk Components

Significant variations in the carbohydrate residues in human breast milk are found depending on the mother's ABO, Lewis, and Secretor blood types (Table 2). During the first week of lactation the ability to produce neuraminyloligosaccharides is linked to the ABH secretor groups. And the ability to produce oligosaccharides with Le(a) or Le(b) characteristics is linked to Lewis and Secretor systems. The consequences of this are that

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Table 2. Differences in Carbohydrate Composition by ABO and Lewis Blood Groups and ABH Secretor Status

MATERNAL ABO BLOOD GROUP, ABH SECRETOR STATUS AND LEWIS PHENOTYPE	COMPOSITION OF BREAST MILK
A or O, Secretors, Lewis (a-b+)	High amounts of N-acetylneuraminic acid and N-acetylglucosamine Lower levels of galactose Higher Fucose Lower lactose Presence of Le(b) and either A or O substances
B or AB, Secretors, Lewis (a-b+)	High amounts of N-acetylneuraminic acid Lower N-acetylglucosamine Moderate galactose Higher Fucose Lower Lactose Presence of Le(b) and either B or AB substances
ABO non-secretors, Lewis (a+b-)	Highest galactose Lowest amounts of N-acetylneuraminic acid Higher fucose Lower lactose Presence of Le(a) and absence of ABO substances
ABO, Lewis negative, Lewis (a-b-)	No Lewis substances Highest Lactose Quantities of ABO substances, galactose, N-acetylneuraminic acid, and N-acetylglucosamine can not be estimated

secretors will produce higher levels of N-acetylneuraminic acid and lower levels of galactose in their breast milk than non-secretors. In the ABH secretor groups, blood type A and O secretors also have higher N-acetylglucosamine contents than B and AB secretors ($p < 0.001$), while the A and B secretors have higher galactose levels. The Lewis secretor groups are also distinguished by a significantly higher level of fucose. The ABH (+), Le (a-b-) group had higher lactose contents than the other groups.[17]

Blood Clotting

ABO blood group impacts the clotting ability to a significant degree. In fact, it has been estimated that a significant fraction (30%) of the genetically determined variance in plasma concentration of the von Willebrand factor antigen (vWf) is directly related to ABH

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Table 3. Lewis Blood Type and Clotting Factors

LEWIS PHENOTYPE	CLOTTING CHARACTERISTICS
Le (a- b-) highest activity of factor VIII and vWf	Shortest bleeding times (especially in A, B and AB)
Le (a+ b-) intermediate activity	Shorter bleeding times (especially for O)
Le (a- b+) lowest activity of factor VIII and vWf	Longest bleeding times (especially for O)

determinants. As a rule, it is blood group O individuals who have the lowest amount of this clotting factor.[18]

ABH non-secretors are reported to have shorter bleeding times and a tendency toward higher factor VIII and vWf. This relationship appears to be another example of blood type synergy between ABO and Secretor/Non-secretor phenotypes. In fact, secretor genetics appear to interact with ABO genetics to influence as much as 60 percent of the variance of the plasma concentration of vWf, with secretors (Le(a-b+)) having the lowest vWf concentrations.[19,20]

Among persons belonging to blood group O (the blood type most likely to have problems with clotting), the lowest concentrations of vWf:Ag and VIII:Ag are found in the group O secretors. On the other hand, blood group O non-secretors will have higher concentrations of both vWf:Ag and factor VIII antigen (VIII:Ag), providing them with a better capability for clotting.[18]

Among blood groups A, B, and AB, also having the Le (a-b-) phenotype is associated with the highest degree of clotting factors (Table 3). In white men with these blood types, the Le (a-b-) phenotype implies significantly higher levels of factor VIII and von Willebrand factor. Among black men with blood type A, B, or AB, and phenotype Le (a-b-), a similar trend is found with these individuals having the highest values for factor VIII and von Willebrand factor. In women with blood type A, B, or AB, and phenotype Le (a-b-) a correlation exists for higher levels of factor VIII.[18]

Researchers have suggested the Le (a-b-) phenotype (and blood groups A, B, and AB especially), by virtue of their association with raised levels of factor VIII and von Willebrand factor, might be at a higher risk for future thrombotic and heart disease.[21]

Dental Cavities

In all blood groups the average number of cavities is lower for ABH secretors than for non-secretors. This difference is most significant for smooth surface areas of the teeth. Also, secretors of blood group A have been shown to have the lowest numbers of cavities.[22]

Diabetes, Heart Disease, and Syndrome X

Diabetes

Lewis negative individuals are at a greater risk of developing diabetes (especially type 2 diabetes) and they might be at a greater risk of developing complications from diabetes. Findings also suggest a greater proportion of non-secretors are found among patients with diabetes, particularly of the type 1, or insulin-dependent type.[23-24]

The Le(a-b-) red blood cell phenotype appears to confer the greatest risk of

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developing diabetes. This blood type is observed greater than three times more frequently (29%) in diabetics irrespective of their clinical type. Non-diabetics categorized as low insulin responders to glucose are also significantly more likely to be Lewis negative.[25] Among individuals with type 1 diabetes, the prevalence of severe retinopathy as a complication of diabetes is lower in ABH secretors than in the ABH non-secretor group.[26]

Heart Disease

Data suggests that ABH non-secretor phenotype might be a risk factor for ischemic heart disease (IHD) while ABH secretor status might confer a degree of genetic resistance. Evidence also suggests that the Lewis negative phenotype might be an even more important genetic marker for increased risk of heart disease among males. This finding was reported in the Copenhagen Male study and replicated in the NHLBI Family Heart Study.

Eight percent of men with the Le (a-b-) phenotype had a history of nonfatal myocardial infarction (among Lewis-positive men the frequency was only 4%). Even more serious is research showing that men with Le (a-b-) had an increased risk of death from heart IHD (IHD case fatality rate (RR = 2.8 (1.5-5.2), p = 0.01)) compared with others. Adjusted for age, relative risk climbed even higher to 4.4 ((1.9-10.3), $p < 0.001$), and for all causes of mortality RR = 1.6 ((1.0-2.6), $p < 0.05$).[27]

Results from the NHLBI Family Heart Study also showed a higher risk of coronary heart disease (odds ratio was 2.0 (95% confidence interval = 1.2 to 3.1)) for Le (a-b-) versus other Lewis groups. Triglycerides were significantly higher in the Le (a-b-) subjects. Among women, there was also a trend towards increased risk of IHD among Lewis-negative phenotypes; however, the trend was dramatically weaker than among male subjects.[28]

Additional research has also duplicated these results, supporting and adding to the weight of evidence linking Le (a-b-) with high risk for the development of ischemic heart disease. Even excluding the Lewis-negative phenotype, the secretor phenotype Le (a-b+) was found to be a genetic marker of resistance against the development of IHD, while ABH non-secretor status is a risk factor predisposing individuals towards heart disease.[29,30]

Effects of Alcohol

In men, Le (a-b-), a group genetically at high risk of IHD, alcohol consumption seems to be especially protective. In the Copenhagen study, researchers found that drinking alcohol was the only risk factor that had an interaction with Lewis-negative blood type and that alcohol could strongly modify risk in an inverse (hence positive) manner. There was a significant inverse dose-effect relationship between alcohol consumption and decreasing risk.[31]

Paradoxical with the cardiovascular benefits of alcohol in Lewis-negative individuals, several large studies have associated alcoholism with ABH non-secretor status and the Lewis-negative phenotype.[32,33]

Metabolic Syndrome X

Data suggest that Le (a-b-) men exhibit features of insulin resistance syndrome or syndrome X, including a tendency to prothrombic metabolism, higher body mass index levels, elevated triglycerides, fasting levels of serum insulin and plasma glucose. These same relationships do not appear to hold true for Le (a-b-) women.

A group of metabolic problems comprised of insulin resistance, elevated plasma glucose, lipid regulation problems (elevated triglycerides, increased small low-density lipoproteins, and decreased high-density lipoproteins), high blood pressure, a prothrombic state, and obesity (especially central obesity or a predisposition to gaining weight in the abdomen) combine to form

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"metabolic syndrome X" (MSX). This cluster of metabolic disorders seems to promote the development of type 2 diabetes, atherosclerosis, and cardiovascular disease. And while insulin resistance might lie at the heart of the problem, all of these metabolic disorders appear to contribute to health problems.

Because of the associations with non-secretor status and both diabetes and heart disease, many different researchers have explored the connection between MSX and Lewis and non-secretor blood types. Similar to diabetes and heart disease, individuals with Le (a-b-) phenotype are most predisposed to MSX. It has even been hypothesized that Le (a-b-) men and syndrome X share a close genetic relationship on chromosome 19 and that the Le (a-b-) phenotype is a genetic marker of insulin resistance syndrome.[34]

As was discussed in the prior section on clotting, non-secretors and especially Lewis-negative individuals, are particularly prone to prothrombic metabolism (a tendency to form clots more readily and to have slower bleeding times). The tendency to higher triglycerides was mentioned in the discussion on heart disease.[35]

Researchers have also investigated Lewis blood types as part of the Copenhagen Study and have found very supportive evidence of trends toward metabolic differences. Compared to all other men, the Le (a-b-) men had a significantly higher systolic blood pressure (6 mm Hg; $p = 0.0024$). They also had higher values of body mass index (8%; $p = 0.016$), total body fat mass (25%; $p = 0.015$), fasting values of serum insulin (32%; $p = 0.006$), serum C-peptide (20%; $p = 0.029$), and plasma glucose (8%; $p = 0.003$). These trends, while consistent for men, did not hold true for women.[36,37]

Immunological Consequences

Basic Functions

Evidence suggests that ABH non-secretors have lower levels of IgG.[38,39] Tests of 202 Caucasian researchers found IgA concentrations to be significantly lower in non-secretors than in secretors.[40,41] This seems to imply that the ABH non-secretor state is associated with a "Defense In Depth" strategy (i.e., let the invader in and attempt to destroy it internally) versus the ABH secretor state, which implies a "Preclusive Strategy" (i.e., wall out the invader and don't allow entrance in the first place). For example, the free ABH antigen on the mucosa barriers of ABH secretors acts as an effective anti-adhesive mechanism against ABH specific bacterial fimbriae lectins.

On the other hand, the ability to secrete relatively different concentration of the components of the blood group substances as determined by secretors/non-secretor genetics seems to affect phagocytic activity of the leukocytes in a manner that actually places non-secretors at somewhat of an advantage. In general, leukocytes of non-secretors have substantially greater ingestion power as compared to secretors. Although this ability appears to be across the board for all non-secretors, blood group O and B non-secretors have the greatest advantage and highest phagocytic activity.[42] Perhaps this is a compensatory mechanism for their more limited antigenic barrier in their body fluids and secretions.

Pathologic cold agglutinins are produced either in response to infection or by paraneoplastic or neoplastic growth of a single immunocyte clone. In either case, they generally share the same immunochemical characteristics and polysaccharide specificities. Cold agglutinins regularly occur in the course of *Mycoplasma pneumoniae* (primary atypical pneumonia) where they are usually specific for the I antigen. Data are suggestive that the level of the anti-I cold agglutinin in the serum of

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normal individuals may be affected by the donor's ABO group, secretor status, and gender. For individuals with blood group O, B and AB, secretors have higher levels of an antibody presumed to be auto-anti-I (cold hemagglutinin). The level of this antibody is usually even higher among non-A female secretors than for males.[43]

Diabetic non-secretors appear to have lower levels of some complement fractions when compared to diabetic secretors. Researchers have found that in individuals with type 1 diabetes mellitus, the mean level of complement fraction C3c for non-secretors is significantly lower than that found for secretors. The level of fraction C4 among ABH non-secretors was also significantly lower than that of ABH secretors.[44]

Helicobacter pylori

The genetics of the ABH secretor/non-secretor system interact to alter an individual's risk for ulcers. In several studies, non-secretors of ABH substances have been found to have a significantly higher rate of duodenal and peptic ulcers.[45,46]

The Copenhagen study found the lifetime prevalence of peptic ulcer in men who were ABH non-secretors was 15 percent (statistically 15 percent of ABH non-secretors will have an ulcer at some point in their lives). And, the attributable risk of peptic ulcer in men who were Le (a + b-) or ABH non-secretors, with blood group O or A phenotypes was 37 percent.[47]

Overall, the relative risk of gastroduodenal disease for non-secretors compared with secretors is 1.9 (95% confidence interval). Duodenal ulcer patients are more likely to be non-secretors, and being a non-secretor acts as a multiplicative risk factor with the gene for hyperpepsinogenemia I to impact the risk of duodenal ulcer.[48,49]

Because of the increased prevalence of ulcers among non-secretors, researchers have suggested that secretor status might influence bacterial colonization density or the ability of *H. pylori* to attach to gastroduodenal cells. Regarding the overall interaction with *H. pylori* infection, non-secretor status is generally considered to be a separate independent risk factor for gastroduodenal disease in addition to *H. pylori* infection; however, there is more to this story involving some interesting interactions between secretor status, Lewis genetics, and *H. pylori*.[48]

Because non-secretors are limited in their ability to secrete the Le(b) blood group antigen into the mucus secretions of their digestive tract, it has been proposed that they are at a competitive disadvantage from preventing *H. pylori* attachment. In fact, the Le(b) antigens have been found to act as somewhat of a preferential target for *H. pylori* attachment. Thus, lack of Le(b) in mucosal fluids of ABH non-secretors might indirectly contribute to colonization by *H. pylori*.[50-52]

In a simplified sense, when the Le(b) antigen is free floating in the mucus, it probably acts to bind up some of the *H. pylori* before it can contact and attach to host tissue. In essence, being an ABH secretor provides an ability to put some biological decoys or metabolic chaff out into the gastric secretions that is very specific for *H. pylori*. Also, in ABH non-secretors the immune response against *H. pylori* appears to be lower and *H. pylori* appears to attach with higher aggressiveness and cause more inflammation.[53]

Individuals with Le (a+b-) ABH non-secretor phenotype also show a significantly higher proportion of the *H. pylori*-seronegative subjects and a lower IgG (*H. pylori* immunoglobulin G (IgG) antibody) immune response to *H. pylori* antigens as compared with the individuals of Le (a-b+)/secretor phenotype.

Evidence also indicates that 100 percent of non-secretors with duodenal ulcers culture positive for *H. pylori* infection. However, among non-secretors with gastric ulcer,

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H. pylori is found in only about 12.5 percent of the cases. This is not observed among secretors, who are nearly equally likely to have *H. pylori* infection in either gastric or duodenal ulcer.[54]

Bacterial Urinary Tract Infections

ABH non-secretors are at a greater risk for recurrent urinary tract infections (UTI) and are much more likely to develop renal scars. This susceptibility is even greater among the Lewis negative subset. The ABH secretor phenotype conveys a measure of protection; cutting the risk of recurrent UTI by greater than 50 percent and dramatically decreasing the likelihood that renal scars will develop.

ABH non-secretors appear to be at extra risk for recurrent urinary tract infections. In one study of women with recurrent UTI, 29 percent of the women were the Le (a+ b-) non-secretor phenotype, while another 26 percent of the women were Le (a- b-) recessive phenotype. When the women with ABH non-secretor and recessive phenotypes were combined and considered collectively, the odds ratio (an estimate of relative risk of recurrent urinary tract infection) for those without the secretor phenotype Le (a-b+) was 3.4.[55-58]

A form of synergy also appears to exist between UTI risk, secretor status, and the lack of ability to create anti-B isohemagglutinin. Essentially, blood groups B and AB and the non-secretor phenotype seem to work together to increase the relative risk of recurrent UTI among these women.[59] Evidence also indicates that women and children with renal scarring subsequent to recurrent UTI and pyelonephritis are more likely to be ABH non-secretors.[56,60,61] As many as 55-60 percent of all ABH non-secretors have been found to develop renal scars, even with the regular use of antibiotic treatment for UTI, whereas, as few as 16 percent of ABH secretors will develop similar renal scarring.[62]

This tendency to scarring does not seem to be dictated as much by the aggressiveness of the bacterial infection as by the more aggressive inflammatory response created by ABH non-secretors against the bacterial infection. The levels of C-reactive protein, erythrocyte sedimentation rate, and body temperature are significantly higher in non-secretors than in secretors ($p < 0.04$) with recurrent UTI. As a consequence, in non-secretors the renal scarring seems to be secondary to their acute phase inflammatory response.[63]

Neisseria sp.

The genetically determined inability to secrete the water-soluble glycoprotein form of the ABO blood group antigens into saliva and other body fluids is a recognized risk factor for Neisseria meningococcal disease. ABH non-secretors are consistently over represented among individuals contracting this infection. This overrepresentation is even greater among individuals who are carriers of the infection.[64] Secretory immune capabilities and other factors appear to contribute to the relative protection against colonization by meningococci enjoyed by ABH secretors. ABH non-secretors typically have lower levels of anti-meningococcal salivary IgM. And, to add insult to injury, both the IgA and IgM antibodies produced by ABH secretors are more effective at providing protection against this microorganism.[65]

Candida sp.

ABH non-secretors are much more likely to be carriers of Candida sp. and to have problems with persistent Candida infections. Blood group O non-secretors are the most affected of the non-secretor blood types. One of the innate defenses against superficial infections by Candida species appears to be the ability of an individual to secrete the water-soluble form of his ABO blood group antigens into body fluids. The protective effect afforded by the secretor gene might be due to the ability of glycocompounds in the body fluids of

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secretors to inhibit adhesins (attachment lectins) on the surface of the yeast. In attachment studies, preincubation of blastospores with boiled secretor saliva significantly reduced their ability to bind to epithelial cells. ABH non-secretor saliva did not reduce the binding and often enhanced the numbers of attached yeast colonies.[66-67] In one study, among individuals with type 2 diabetes, 44 percent of ABH non-secretors were oral carriers of this yeast.[68]

Although non-secretors make up only about 26 percent of the population, they are significantly over represented among individuals with either oral or vaginal Candida infections, making up almost 50 percent of affected individuals.[66] The inability to secrete blood group antigens in saliva also appears to be a risk factor in the development or persistence of chronic hyperplastic candidosis. In one study, the proportion of non-secretors of blood group antigens among patients with chronic hyperplastic candidosis was 68 percent.[69]

Women with recurrent idiopathic vulvovaginal Candidiasis are much more likely to be ABH non-secretors. Combining both ABH non-secretor phenotype and absence of the Lewis gene Le (a- b-), the relative risk of chronic recurring vulvovaginal Candidiasis is 2.41-4.39, depending on the analysis technique and control group.[70]

Oral carriage of Candida is also significantly associated with blood group O ($p < 0.001$) and, independently, with non-secretion of blood group antigens ($p < 0.001$), with the trend toward carriage being greatest in group O non-secretors.[71]

Autoimmune Disease

ABH non-secretors appear to have an increase in the prevalence of a variety of autoimmune diseases including ankylosing spondylitis, reactive arthritis, psoriatic arthropathy, Sjogren's syndrome, multiple sclerosis, and Grave's disease. This susceptibility toward autoimmune problems appears to be most pronounced among Le (a-b-) phenotypes. Among individuals with spondyloarthropathies, non-secretors are reported to make up 47 percent of the patient population. In the subgroup of these patients suffering from ankylosing spondylitis, ABH non-secretors account for 49 percent of patients. Since the control population has a prevalence of non-secretors of 27 percent (consistent with the expected percent in the general population), it appears that in spondyloarthropathies in general, and ankylosing spondylitis specifically, non-secretors are dramatically over represented,[39,72] although this association has not gone uncontested.[73]

Among individuals with primary Sjogren's syndrome, Lewis blood group frequency differs from that of the general population, due mainly to an increased Le (a-b-) frequency.[74]

The inability to secrete the water-soluble glycoprotein form of the ABO blood group antigens into saliva is significantly more common in patients with Graves' disease than control subjects (40% versus 27%: $p < 0.025$), but not among those with Hashimoto's thyroiditis or spontaneous primary atrophic hypothyroidism.[75]

ABH non-secretors with Grave's disease were found to produce higher levels of antitubulin antibodies, while levels of other antibodies were similar to secretors.[75]

Celiac Disease

ABH non-secretors are at an increased risk for development of celiac disease. One study found 48 percent of patients with celiac disease were reported to be ABH non-secretors.[76] This appears to be especially true for the recessive Le (a-b-) phenotype. Evidence suggests an increased prevalence of complications and celiac-associated abnormalities in the non-secreting and Lewis-negative celiac patients.[77]

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Pulmonary Considerations

ABH secretors are significantly over represented among patients with influenza viruses A and B (55/64, 86%; $p < 0.025$), rhinoviruses (63/72, 88%; $p < 0.01$), respiratory syncytial virus (97/109, 89%; $p < 0.0005$), and echoviruses (44/44, $p < 0.0005$). Why this increased risk appears in secretors has not been clearly established.[78]

Among coal miners, asthma has been related significantly to non-secretor phenotype. In this population, significantly lower lung function and higher likelihood of wheezing is found among Lewis-negative or non-secretor subjects with blood group O.[79] Independent findings suggest that the ability to secrete ABH antigens might decrease the risk of COPD. Non-secretors have been found to have significantly greater impairment of forced expiration. ABH non-secretors have lower mean values of forced expiratory volume in one second as a percentage of forced vital capacity (FEV1/FVC%) and a significantly larger proportion of them had aberrant values, defined as FEV1/FVC% less than 68.[80] ABH non-secretor status also offers a slight increase risk for habitual snoring.[81]

Neoplasia and Malignancy

Secretor and Lewis Phenotypes and Tumor Markers

Accurately predicting the relevance of some tumor markers for diagnosis of cancer appears to be dependent on both secretor status and Lewis blood group. As an example, some researchers have suggested that taking into account aspects of Lewis and/or secretor status in order to establish reference ranges might actually be a way to increase the clinical utility of the CA 19-9 tumor marker (Table 4).[82]

There is a substantial difference in levels of this tumor marker under the control of secretor and Lewis genetics. Individuals having homozygous inactive Se alleles (*sese*) and homozygous active Le alleles (*LeLe*), exhibited the highest mean CA19-9 value. All of the Lewis-negative individuals consisting of an *lele* genotype had completely negative CA19-9 values, irrespective of the Se genotype.

On the other hand, Lewis-negative individuals showed a higher mean DU-PAN-2 value than did the Lewis-positive individuals. Among patients with colorectal cancer, the Lewis-negative patients (*lele*) with colorectal cancer showed undetectable CA19-9 values (i.e., less than 1.0 unit/mL), but many of them exhibited highly positive DU-PAN-2 values. In contrast, many of the Lewis-positive patients (*LeLe* or *Lele*) had positive CA19-9 values; whereas, very few of them exhibited positive DU-PAN-2 values.[83]

The implication is that the CA19-9 measurement is not a useful tumor marker for

Table 4. CA19-9 and DU-PAN-9 Expression in Colorectal Cancer Correlated to Lewis Subtype

LEWIS PHENOTYPE	CA19-9	DU-PAN-9
Le (a+b-)	Highest levels	Lower levels
Le (a-b+)	High levels	Lower levels
Le (a-b-)	None to very low levels	Highest levels

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Lewis-negative individuals, although DUPAN-9 appears to be. Lewis-negative individuals do not express any kinds of type 1 chain Lewis antigens (Le (a), Le (b), and secretory Lewis(a)) in their digestive organs. It is, therefore, not useful to measure the CA19-9 titer of the Lewis-negative cancer patient.[84]

Preneoplastic Changes and Cancer

As a general rule, a higher intensity of oral disease is found among ABH non-secretors. So it is not surprising that when it comes to precancerous or cancerous changes to tissue of the mouth and esophagus, ABH non-secretors seem to fair worse than ABH secretors. This oral disease susceptibility is reflected in the occurrence of epithelial dysplasia, for example, which is found almost exclusively in the non-secretor group.[85]

Barrett's esophagus, a condition often preceding the development of esophageal cancer, and esophageal cancer also show a positive association with Le (a+b-) non-secretor phenotypes.[86]

Conclusion

Determining ABH secretor phenotype and/or Lewis blood group status may be useful as risk factor determinates for a number of conditions including heart disease, diabetes, insulin resistance, certan types of cancer, Candida, *H. pylori*, autoimmune diseases, celiac disease, chronic urinary tract infections, and others.

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