

Higher frequency of secretor phenotype in O blood group – its benefits in prevention and/or treatment of some diseases

Mohamad Salih Jaff

Pathology Department, Hawler Medical University (Formerly Salahaddin University), Erbil, Kurdistan Region, Iraq

Abstract: ABO blood groups and secretor status are important in clinical and forensic medicine and in relation to some diseases. There are geographic and racial differences in their frequencies, but the frequency of secretor status in different ABO blood group systems has not been determined yet. Therefore, the aim of this study was mainly to determine this point. Blood and saliva from 762 randomly selected apparently healthy adult individuals (480 men and 282 women) were examined to determine their ABO and Rhesus blood groups by standard conventional methods, and their secretor status by using Lewis blood grouping and/or hemagglutination inhibition test of saliva. Results showed that 76.1% of the study population were ABH blood group antigens secretors and 23.9% were nonsecretors. The frequencies of secretor status in different ABO blood groups were 70.1% in group A, 67.8% in group B, 67.9% in group AB, and 88.3% in group O. In conclusion, blood group O individuals have significantly higher frequency of secretor status than non-O blood group individuals. This finding would be beneficial to them, protecting them, at least partially, from certain malignancies or allowing them to have less aggressive disease, and this finding might be useful in enhancing further studies and research in this direction.

Keywords: blood group O, ABO blood groups, secretor phenotype, frequency, malignancies, prevention and/or treatment

Introduction

In 1930, it was found that individuals could be classified as ‘secretors’ and ‘nonsecretors’ according to their ability to secrete ABO blood group antigens in saliva.¹ ABO blood group antigens (A, B, and H), in addition to their presence on blood cells and platelets, are also present on other tissue cells and are variably expressed through body fluids, such as saliva, tears, semen, urine, gastric juice, and breast milk, depending on whether the individual possesses the secretor gene or not, the inherited A, B, O genes, and Lewis blood group system.²

In addition to ABO blood group applications in blood transfusion and forensic medicine, numerous studies have found strong relations between individuals’ susceptibilities to some diseases and their ABO blood groups,³ as well as their secretor status.⁴

The secretor gene encodes for enzymes (glycosyltransferases), which become active in mucin-secreting cells like goblet and mucous cells of mucous membranes and different glands, resulting in the secretion of the corresponding blood group antigens in the body fluids.⁵ H antigen that is present on the cells of individuals with O blood group is the base for A and B antigens, but A and B antigens differ only in their added terminal sugars, which are controlled by specific enzymes called transferase enzymes. These enzymes are under the control of inherited genes, which are A, B, H (*FUT1*) genes and secretor

Correspondence: Mohamad Salih Jaff
Pathology Department, Hawler Medical University (Formerly Salahaddin University), P.O.B. 0845/14, Engineering College Houses, No. 25, Kirkuk Street, Erbil, Kurdistan Region, Iraq
Tel +00964 0750 4777683
Email msjaff@yahoo.com

(*FUT2*) genes.⁶ H (*FUT1*) and secretor (*FUT2*) genes are separate but closely linked. Lewis blood group phenotypes are also important in determining the secretor status of an individual, as Lewis genes (*FUT3*) are closely linked to secretor (*FUT2*) and H (*FUT1*) genes.^{7,8} Subjects are either Lewis negative or Lewis positive. In Lewis-negative individuals, the secretor genotype does not affect the Lewis phenotype. However, in Lewis-positive individuals, the secretor genotype generates either the nonsecretor phenotype Le(a+b-) or the secretor phenotype Le(a-b+), or the partial secretor genotype, which gives rise to a transient Le(a+b+) phenotype.⁹ Therefore, practically, there are only three Lewis phenotypes: Le(a+b-), Le(a-b+), and Le(a-b-).

The frequencies of different Lewis-secretor phenotypes vary markedly among different ethnic populations.¹⁰ It is generally known that about 80% of the world's population are secretors of ABH antigens and only 20% are nonsecretors but with some racial differences.⁸ One of the studies in our region showed that 78% of Kurds are secretors and 22% of them are nonsecretors.¹¹

Because most secretors have a Lewis blood group of Le(a-b+) phenotype and most nonsecretors have a Lewis blood group of Le(a+b-) phenotype, Lewis blood grouping is used to detect the secretor status of most of the population. Only a minority of the population (5%–10%)^{12,13} have Le(a-b-) phenotype, ie, Lewis double negative (LDN). For these people, as the standard Lewis blood grouping cannot be used to determine their secretor status, saliva testing by the standard hemagglutination inhibition test is used.¹⁴

To the best of our knowledge, there are no reports on the incidence of secretor status in different ABO blood groups (A, B, AB, and O), and to investigate this point we planned this study.

Materials and methods

Seven hundred and sixty-two apparently healthy unrelated adults (480 men and 282 women) were randomly selected and asked to volunteer for this study, after they were informed about its aim. This study was carried out in Hawler Teaching Hospital Laboratory, Erbil, Kurdistan Region, Iraq, in the period between January 2008 and May 2010.

From each individual, 3 mL of blood was taken into sterile plain tubes. Subjects were informed to rinse their mouth with water prior to saliva collection. After chewing a piece of paraffin wax, to stimulate secretion of saliva, 5 mL of saliva was collected in sterile plain glass tubes. Saliva samples were tested within 2 h of collection.

ABO and Rhesus blood grouping was performed on saline-washed red blood cells using commercial antisera kits: monoclonal anti-A, anti-B antisera (Plasmatec Laboratory Products Ltd., Bridport, Dorset, UK), and monoclonal anti-H antiserum (Seraclone, Biotest, Dreieich, Germany) by the standard conventional hemagglutination technique.

Lewis blood group phenotype was also performed on the saline-washed RBCs by the standard hemagglutination technique using monoclonal anti-Le(a) and anti-Le(b) (Lorne Labs, Reading, Berkshire, UK) according to the manufacturer's instructions. Individuals with Le(a-b+) were assigned as secretors, those with Le(a+b-) were assigned as nonsecretors, and those with Le(a-b-), ie, LDN, were assigned unknown secretor status, for whom saliva was used to determine their secretor status by the standard hemagglutination inhibition test.

Statistical analysis was performed using Windows software, Microsoft Office Excel 2003. χ^2 tests and *t*-test were used to determine the significance of the influence of sex, Rh type, and different ABO blood groups on the frequency of secretor status among the study population. *P* values <0.05 were regarded as significant.

Results

The total number of participants in this study was 762 (480 men and 282 women). Their age ranged between 19 and 45 years with a median of 34 years. The frequencies of Lewis blood group phenotypes Le(a+b-), Le(a-b+), and Le(a-b-) are shown in Table 1. Saliva test was done on 84 individuals with Le(a-b-) phenotype and showed that 60 (71%) of them were secretors and 24 (29%) were nonsecretors. Secretor and nonsecretor status formed 76.1% and 23.9% of the study population, respectively. In men, 75.6% were secretors and 24.4% were nonsecretors, while in women 74.1% were secretors and 25.9% were nonsecretors (Table 2). In Rh(D)-positive individuals, 76% were secretors and 24% were nonsecretors, while in Rh(D)-negative individuals 77% were secretors and 23% were nonsecretors (Table 3). Statistically, no significant differences were found in the secretor status between men and women (*P* > 0.05) as well

Table 1 Frequency of Lewis blood group phenotype in the study population

Lewis phenotype	Secretors	Nonsecretors	Total
Le(a+b-)	0	158	158
Le(a-b+)	520	0	520
Le(a-b-)	60	24	84
Total	580	182	762

Table 2 Distribution and comparison of secretor status prevalence in men and women

Gender	Male	Female	Total	P
Secretors	368 75.6%	212 74.1%	580 76.1%	>0.05
Nonsecretors	112 24.4%	70 25.9%	182 23.9%	–
Total	480 36.0%	282 37.0%	762 100%	–

as between Rh(D)-positive and Rh(D)-negative individuals ($P > 0.05$).

The distribution of ABO blood groups in the study population and the incidence of secretor status in different ABO blood groups are shown separately in Table 4. There was a highly significant increase in the incidence of secretor status in O blood group individuals when compared with A, B, and AB blood group individuals separately ($P < 0.0001$, $P < 0.0001$, $P = 0.0003$, respectively) and collectively ($P < 0.0001$). However, there were no significant differences in the incidence of secretor status in A, B, and AB blood groups when compared with each other ($P > 0.05$ for all comparisons) (Table 5).

Discussion

The incidence of secretor status in men and women and in Rh(D) group was in concordance with our previous study¹¹ and similar to many other studies.¹⁵ This significant increased incidence of secretor status in blood group O individuals in this study was not, to the best of our knowledge, recorded in the literature reviewed. This may at least, to some extent, explain the low incidence of certain diseases in blood group O individuals. Many published data from large cohort studies from different parts of the world suggest low incidence of many malignancies¹⁶ in group O compared with group A, eg, gastric carcinoma,¹⁷ oral cancerous lesions,^{18,19} lung,^{20,21} colon,²² ovarian cancer,²³ pancreatic carcinoma,^{24,25} prostatic carcinoma,²⁶ bladder cancer,²⁷ breast cancer,²⁸ and acute leukaemia.²⁹

Blood group O also appears to exert a protective effect by preventing the growth and spread of tumors and being associated with longer survival times in cancer patients.³⁰ The following will correlate our finding to, and might explain, the above finding. Thomsen-Friedenreich antigen

Table 3 Distribution and comparison of secretor status frequency in Rh(D)-positive and Rh(D)-negative individuals

Rhesus type	Rh-positive	Rh-negative	Total	P
Secretors	532 76%	48 77%	580 76.1%	>0.05
Nonsecretors	168 24%	14 23%	182 23.9%	–
Total	700 91.8%	62 8.1%	762 100%	–

Table 4 Frequency of secretor status in A, B, AB, and O blood group individuals

Blood group	Secretors	Nonsecretors	Total
A	171 70.1%	73 29.9%	244 32.0%
B	124 67.8%	59 32.2%	183 24.0%
AB	36 67.9%	17 32.1%	53 7.0%
O	249 88.3%	33 11.7%	282 37.0%
Total	580 75.1%	182 23.9%	762 100%

(TF), which was discovered in the late 1920s,³¹ is the core disaccharide structure of ABO blood group (H) substance. It is cryptic on cell membranes of various normal cells, including epithelial cells, red blood cells, and lymphocytes. During carcinogenesis, it appears with several other different tumor-associated glycol antigens. It is expressed in many carcinomas, including those of the breast, colon, bladder, and prostate (pan-carcinoma marker), and becomes immunoreactive.³²

It has been postulated that TF has a role in adhesion and metastasis through tumor–endothelial-cell interactions, which is the key role in cancer metastasis,³³ and through binding ligands such as galectins or other lectins³⁴ in sites of metastatic tumor growth, ie, in the vascular endothelium, liver, bone marrow, and lymph nodes.³⁵ Due to antigenic similarity of TF to A antigen, blood group A individuals have the least aggressive humoral immune response against the TF than group O individuals, so it might be readily confused by the immune system of blood group A individuals.³²

Humans normally possess natural anti-TF antibodies (IgM), which are commonly induced in the gut, as many gram-negative organisms carry TF antigen, and people recovering from *Escherichia coli* enteritis and after infection with *Helicobacter pylori* apparently have higher levels of anti-TF antibodies.³⁶

Table 5 Comparison of blood group O secretor status prevalence with A, B, and AB blood groups separately and collectively

Blood groups, secretors/totals (%)	A (171/244) (70.1%)	B (124/183) (67.8%)	AB (36/53) (67.9%)	A + B + AB (331/480) (69.0%)
A (171/244) (70.1%)	–	$P = 0.074$	$P = 0.122$	$P = 0.065$
B (124/183) (67.8%)	$P = 0.074$	–	$P = 0.133$	$P = 0.071$
AB (36/53) (67.9%)	$P = 0.122$	$P = 0.133$	–	$P = 0.122$
O (249/282) (88.3%)	$P < 0.0001$	$P < 0.0001$	$P = 0.00031$	$P < 0.0001$

Interestingly, these bacteria grow more readily in blood group O individuals and secretors than non-O individuals, which means that they have more natural anti-TF IgM and IgG antibody production and probably are less susceptible to cancer or have less aggressive disease.³⁷ Higher levels of naturally occurring anti-TF antibody also appear to confer better prognosis.³⁸ Studies have also shown that secretors have the highest natural anti-TF IgM level irrespective of ABO phenotype.

Passive transfer of an anti-TF-Ag monoclonal antibody in animal experimental trials has significantly resulted in extending the median survival time of animals bearing metastatic 4T1 breast tumors and caused more than 50% inhibition of lung metastasis.³⁹

This means that individuals with O blood group, secretors, and postinfection with *E. coli* are strong responders of anti-TF antibody production together or independently, whether they are normal or cancer patients.

Von Willebrand factor (vWf) serves as an adhesive link between platelets and the endothelium. Several reports have demonstrated increased vWf antigen levels in the plasma of patients with ovarian, bladder, and colon cancers, with increased vWf antigen correlating with more metastasis and poor prognosis.⁴⁰

In fact, secretor genetics appears to interact with ABO genetics to influence the plasma levels of vWf, with non-secretors and non-O blood groups having the highest vWf concentrations, and the group O secretors having the lowest concentration of vWf:Ag and VIII:Ag.⁴¹

All these findings, collectively, lead us to the hypothesis that these tumors have more chance to thrive in A blood group patients and be more aggressive than in O blood group patients. In addition to the contribution of the above findings to the explanation of less aggressiveness of these malignancies in O blood group patients, it might also contribute to the explanation of the association of blood group O with other diseases.

In conclusion, blood group O individuals have significantly higher incidence of secretor status than non-O blood group individuals. Therefore, it is speculated that with the help of this finding and the above information from other studies, blood group O individuals with higher natural anti-TF IgM, lower levels of vWf, and higher susceptibility to infection by *H. pylori* and gram-negative intestinal flora are benefited and protected, at least partially, from certain malignancies or have less aggressive diseases. Also, we might be able to speculate that this finding might be useful in enhancing further studies and research in this direction.

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Disclosure

The author is the principal investigator and takes primary responsibility for the paper, as he was in charge of sample collection, performed the laboratory work, and wrote the paper.

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