Original Article

# Increased expression of ABO blood group antigens secretion phenotype with O blood group and age advances

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## ABSTRACT

**الأهداف**: يرتبط النمط الظاهري لفصيلة الدم ABO وحالة الإفراز بشكل كبير بقابلية الإصابة ببعض الأمراض. يعد تحديد مدى انتشار الحالة الإفرازية لأي مجموعة سكانية أمرًا بالغ الأهمية. ولذلك سعت الدراسة الحالية إلى التأكد من مدى انتشار إفرازات المستضدات ABH بين اليمنيين. بالإضافة إلى استكشاف العوامل التي قد تؤثر على التعبير الجيني للإفراز.

**المنهجية**: أجريت هذه الدراسة المقطعية في الفترة ما بين مايو وسبتمبر 2022م على 215 فردًا يمنيًا يتمتعون بصحة جيدة. تم اختبار المشاركين لمعرفة مستضد فصيلة الدم في عينات الدم الخاصة بهم باستخدام طريقة أنبوب الاختبار القياسي باستخدام الأمصال المضادة ل ABH. تم جمع اللعاب واختبار إفرازه باستخدام طريقة تثبيط التراص الدموي باستخدام الأمصال المضادة المناسبة A وB وH. قبل جمع عينات الدم، تم الحصول على موافقة مستنيرة من كل مشارك وتم جمع البيانات الكاملة من قبل فريق البحث.

**النتائج**: بشكل عام، وجد أن 78.1% من المشاركين اليمنيين هم من المفرزين، و 80% من الذكور و 73.3% من الإناث. ارتفعت هذه النسبة ضمن فصيلة الدم O (95%)، وانخفضت ضمن فصيلة الدم AB (54%). أظهرت كل من فصائل الدم O و AB ارتباطًا ذو دلالة إحصائية مع سمة الإفراز. كما لوحظ أن التقدم في العمر يزيد من التعبير لجين *Se*. بالإضافة إلى ذلك، و زادت حالة الإفراز بين الأشخاص الذين ليس لديهم عامل Rh.

**الخلاصة**: بلغت نسبة إفرازات ABH بين سكان محافظة إب في اليمن 78.1%. وكان الافراز أكثر بين من يحملون فصيلة الدم O (95%)، في حين أظهرت فصيلة الدم AB أقل إفراز (54%). زاد ايضا التعبير الجيني للإفراز مع التقدم في العمر ثم نقص.

**Objectives:** To ascertain the prevalence of ABH antigen secretors and non-secretors among Yemenis. In addition to explore the factors that may affect the expression of the secretion phenotype.

**Methods:** This cross-sectional study was carried out between May and September 2022 on 215 healthy Yemeni individuals at the International Malaysian University, Ibb, Yemen. The participants were tested for blood group antigen on their blood samples using standard test tube method using the suitable ABH antisera. Saliva was collected and tested for secretion using hemagglutination inhibition test with suitable A, B, and H antisera. Before collecting the blood samples, informed consent was obtained from each participant and complete data and history questionnaire were collected by the research team.

**Results:** In general, 78.1% of Yemini participants were found to be secretor (80% men and 73.3% females). This percentage increased within O blood group (95%) and decreased within AB blood group (54%) individuals. Both O and AB blood groups showed statistically significant association with secretor trait. Also, it was noticed that age advance increases the expression of *Se* gene. In addition, the secretor state increased among Rh-negative people.

**Conclusion:** The frequency of ABH secretors was 78.1% among Ibb province population in Yemen. Blood group O revealed the greatest frequency (95%), whereas blood group AB showed the lowest secretor frequency (54%). The secretor phenotype was highly expressed gradually with advance age then decline.

**Keywords:** secretors, ABO system, ABH antigens, hemagglutination inhibition method, saliva, Yemen

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ABO blood group antigens A, B, and H are expressed on red blood cells as well as on epithelial cells, lymphocytes, platelets, and some organs. Three genes A, B, and H control the expression of A, B, and H antigens.[1,2] These genes are coded for glycosyletransferase enzymes that add fucose and other immunodominant sugar to the precursor substance chain type II on red blood cells to give one's blood group trait. H antigen is the precursor of the A and B blood group antigens.[1] ABO blood group antigens may be secreted by many people in their saliva, tears, milk, and other body fluids.[3] Secretor individuals secrete ABO antigens according to their blood group phenotype. Secretion is controlled by *Se* gene of *SeSe* and *Sese* genotypes of people. Secretor's glycosyletransferase enzyme adds the immunodominant sugar on the precursor substance chain type I.[4] Type 3 and type 4 chains precursors of ABH antigens are tissue restricted.[5]

The importance of secretion state is attributed to its effect on individual susceptibility to infection. One of the suggested mechanisms is the advantage of ABO antigen as a receptor for some pathogens.[4] It was found that the saliva of ABH secretors contains carbohydrate compounds that aggregate certain bacteria and decrease their activity and infectivity.[6] In addition, it was reported that non-secretors had a higher incidence of mouth diseases, esophageal cancer, and epithelial dysplasia in comparison to secretors.[7]

In the gastrointestinal tract, the microbial content growth is affected by the secretor state.[8] Microbium content is crucial for gastrointestinal tract functioning.[9] The vulnerability of secretors and non-secretors to viral infection was also investigated; for instance, norovirus infection was discovered to be inhibited in homozygous non-secretor for ABH and Le antigens individuals.[10] Secreted antibodies of ABO system also may contribute in prevention against bacterial infection.[11] Another benefit of secretion is its use in forensic laboratories, which identify criminals and victims for their blood group from saliva or semen.[12]

The purpose of this study was to ascertain the frequency of secretors and non-secretors of the ABO blood group system among Yemeni people and investigate the variables that could influence the expression of the secretion phenotype in this population.

**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.

**Methods.** This study is a cross-sectional study carried out on 215 healthy Yemeni people between May and September 2022 at the International Malaysian University, Ibb, Yemen.

Inclusion criteria included healthy individuals with age ranged between 10-60 years. Pregnant women and cancer patients were excluded, because they may produce little antigens.

Participants' demography and medical history were obtained using a questionnaire that was filled out by the research team. Also, dental examination and history were obtained with the help of dentists at the Outpatient Dental Clinic of International Malaysian University, Ibb, Yemen. Crooked teeth, loose teeth, bad breath, sensitive teeth, or toothache are the important problems reported and scored accordingly.

Ethical approval was obtained from the research ethics committee of the Faculty of Medical Sciences at the International Malaysian University, Ibb, Yemen, under approval number: 26-4/2022. Informed consent was acquired from each participant prior to the collection of blood samples in accordance with the international biomedical research standards. For each voluntarily participating individually, the research team filled out a history questionnaire and documented all pertinent data.

ABO blood group was determined from a blood sample with a standard tube test using anti-A, anti-B, and anti-Rh reagents (LORNE LABORATORIES LTD, Berks, RG6 4U.UK) by using the agglutination method.[13]

Ethylenediaminetetraacetic acid (EDTA)-blood sample was washed with 0.9% NaCl, 3 times and suspended in saline to make 5% suspension. Approximately 2 drops of suspended cells were added to 3 tubes specified for A, B, and Rh antigen testing, to which one drop of anti-A, anti-B, and anti-Rh were added. The tubes were mixed and immediately spun for one minute. Agglutination develops on examination indicates the presence of corresponding antigen.

Secretion status was determined in saliva by hemagglutination inhibition tests with ABH antisera to demonstrate the presence of H, A, or B antigens after optimization of the method.[4,13]

Briefly, approximately 1 mL of saliva was collected in a clean new test tube after mouth cleaning with neutral water. The test tube was put in a boiling water bath for 10 minutes to inactivate innate salivary enzyme, which may interfere with subsequent testing. After centrifugation for 10 minutes at high speed, the clear supernatant saliva was transferred into a sterilized disposable glass tube to be used for secretor testing.

For each antigen testing, one drop of the appropriately diluted antiserum (1:9) was used. Previous optimization with different antisera dilutions was carried out. The highest dilution of antisera that agglutinate red cell suspension of 8% was selected as an appropriate dilution used. One drop was added to a new test tube. To this tube, one drop of saliva was added, mixed thoroughly and incubated at room temperature for at least 10 minutes. Then, one drop of a 5% saline suspension of appropriate indicator cells (corresponding to the tested antisera) was added, mixed, and incubated for 60 minutes at room temperature. Then, the tube was centrifuged at 1,000g for 30 seconds and the cells were gently resuspended and examined for the presence or absence of agglutination.

***Statistical analysis.*** Descriptive data of categorical variables were expressed as frequencies and percentages (%). The statistical analysis was carried out using the Statistical Package for the Social Sciences software, version 21.0 (IBM Corp., Armonk, NY, USA). Non-parametric Chi-square test was used for difference analysis of categorical data. Association analyses were carried out using 2x2 Chi-square test and odds ratio (OR) at 95% confidence interval (CI). Reference group was used for OR and 95% CI calculation of the ordinal data. A *p*-value of <0.05 was considered significant.

**Results.** Most of the participants in this study were males 140 (65.1%) compared with females 75 (34.9%). The age average for both males and females was 34.6 years. They were distributed for age groups between 10 and 60 years old. The age group from 21-30 years had the highest percentage of participants 116 (53.9%), while the age ranges from 41-60 years had the lowest percentage of participation 17 (7.9%).

Table 1 displays the frequencies of ABO blood groups among participants. Blood groups A (35.4%) and O (33%) showed the highest frequencies, followed by B (19.5%) and AB (12%). In the current study, 81.9% of participants had RhD positive, whereas only 19.1% had RhD negative. As listed in Table 1 also, the findings of the secretor examination utilizing the hemagglutination inhibition test on participant saliva showed that 78.1% of participants were secretors and 21.9% were non-secretors.

At the same time, the number of participants who had a past history of oral problems was 58.6%. In addition, approximately 18.2% brushed their teeth daily, and 41.4% have never brushed their teeth. Only 21.4% of the participants were smokers, and 76.7% chawed Qat (local habit of chawing Qat; a stimulant plant for getting euphoria). In terms of chewing gum, 34.4% were doing so, compared to 65.6% who were not (Table 2).

Association analysis between secretor state with gender reveal male affection without statistical significance (OR=1.46, 95% CI: [0.75-2.81], *p*=0.344) as shown in Table 3. Secretion frequency was increased with increased age then declined at more advanced age (above 50 years old). The only statistically significant

**Table 1 -** Healthy Yemeni participant's gender, age, ABO phenotype, Rh groups, and secretor status.

| Variables | n (%) |
|---|---|
| *Gender* | |
| Male | 140 (65.1) |
| Female | 75 (34.9) |
| *Age (years)* | |
| 10-20 | 47 (21.9) |
| 21-30 | 116 (53.9) |
| 31-40 | 35 (16.3) |
| 41-60 | 17 (7.9) |
| *ABO blood group* | |
| A | 76 (35.4) |
| B | 42 (19.5) |
| AB | 26 (12.1) |
| O | 71 (33.0) |
| *Rh blood group* | |
| D positive | 174 (81.9) |
| D negative | 41 (19.1) |
| *Secretor state* | |
| Secretor | 168 (78.1) |
| Non-secretor | 47 (21.9) |

Values are presented as numbers and percentages (%).

**Table 2 -** Mouth and teeth health data among healthy Yemeni participants.

| Variables | n (%) |
|---|---|
| *Periodontal or teeth problems* | |
| Yes | 126 (58.6) |
| No | 89 (41.4) |
| *Brush teeth* | |
| Several times per day | 12 (5.6) |
| Daily | 27 (12.6) |
| Weekly | 45 (20.9) |
| Monthly | 42 (19.5) |
| No | 89 (41.4) |
| *Gum consumption* | |
| Yes | 74 (34.4) |
| No | 141 (65.6) |
| *Smoking* | |
| Yes | 46 (21.4) |
| No | 169 (78.6) |
| *Qat chawing* | |
| Yes | 165 (76.7) |
| No | 50 (23.3) |

Values are presented as numbers and percentages (%).

age group odds in reference to the lowest age group was that of the age group 31-40 years old (OR=3.63, 95% CI: [1.09-12.16], $p$=0.032).

Secretors' prevalence within O blood group was 95%, 72% within A blood group, 71% within B blood group, and 54% within AB blood group. ABO secretor trait was statistically higher within Rh-negative participants (83%) and Rh-positive (76%) compared with non-secretors which constitute 17% and 24% for both Rh-negative and Rh-positive. The statistically significant association, calculated using 2x2 Chi-square test, was reported for blood group O, where the secretor trait increased with O phenotypes by 7.4 times compared to non-O phenotypes (OR=7.37, 95% CI: [2.53-21.47], $p$<0.001). In addition, the secretion trait decreased within AB phenotype to 0.28 times compared to non-AB phenotypes (OR=0.28, 95% CI: [0.12-0.64], $p$=0.004) as listed in Table 4. Association with other ABO phenotypes were non-significant.

The secretor status was increased within an acidic and more sticky saliva as reported in Table 5, association between these physical properties with secretion was statistically nonsignificant. Associations analysis of secretor state with the teeth problems score revealed no statistically significant association (Table 6).

**Discussion.** Investigation of the secretor status is one of the crucial survey studies that were scanty for the developing countries. These studies will establish a basic data these populations lake. It is worthy to mention that the prevalence of antigenic phenotypes of ABO and Rh in this study resembled that obtained from the registries of the Ministry of Interior, Civil Affairs administration, Yemen Republic (the obtained data was for approximately 3000 individuals).

The results obtained have demonstrated that the large majority of the people examined in the Yemeni healthy people were secretors (78.1%). This result was

**Table 3 -** Secretor prevalence and its association with Yemeni participant's gender and age.

| Variables | Secretors | Non-secretors | ORs | 95% CIs | *P*-values |
|---|---|---|---|---|---|
| *Gender* | | | | | |
| Male | 112 (80.0) | 28 (20.0) | 1.46 | 0.75-2.81 | 0.344 |
| Female | 55 (73.3) | 20 (26.7) | | | |
| *Age groups* | | | | | |
| 10-20 | 32 (68.1) | 15 (31.9) | - | - | - |
| 21-30 | 90 (77.6) | 26 (22.4) | 1.62 | 0.76-3.44 | 0.205 |
| 31-40 | 31 (88.6) | 4 (11.4) | 3.63 | 1.09-12.16 | 0.026 |
| 41-50 | 12 (85.7) | 2 (14.3) | 2.81 | 0.56-14.18 | 0.172 |
| 51-60 | 2 (66.7) | 1 (33.3) | 0.94 | 0.08-11.17 | 0.695 |

Values are presented as numbers and percentages (%). ORs: odds ratios, CIs: confidence intervals

**Table 4 -** Association between secretion status with ABO and Rh blood group phenotypes.

| Secretion status | Event blood group | Non-event blood group | ORs | 95% CIs | *P*-values |
|---|---|---|---|---|---|
| | **A** | **Non-A** | | | |
| Secretor | 55 (72.0) | 112 (81.0) | 0.63 | 0.33-1.22 | 0.226 |
| Non-secretors | 21 (28.0) | 27 (19.0) | | | |
| | **B** | **Non-B** | | | |
| Secretor | 30 (71.0) | 137 (79.0) | 0.66 | 0.31-1.41 | 0.380 |
| Non-secretors | 12 (29.0) | 36 (21.0) | | | |
| | **AB** | **Non-AB** | | | |
| Secretor | 14 (54.0) | 153 (81.0) | 0.28 | 0.12-0.64 | 0.004 |
| Non-secretors | 12 (46.0) | 36 (19.0) | | | |
| | **O** | **Non-O** | | | |
| Secretor | 67 (95.0) | 100 (69.0) | 7.37 | 2.53-21.47 | <0.001 |
| Non-secretors | 4 (5.0) | 44 (31.0) | | | |
| | **Rh positive** | **Rh negative** | | | |
| Secretor | 131 (76.0) | 36 (83.0) | 0.62 | 0.26-1.50 | 0.390 |
| Non-secretors | 41 (24.0) | 7 (17.0) | | | |

Values are presented as numbers and percentages (%). ORs: odds ratios, CIs: confidence intervals

**Table 5 -** Secretor frequency and its association with potential of hydrogen and consistence properties of saliva.

| Saliva characteristics | Secretors | Non-secretors | ORs | 95% CIs | *P*-values |
|---|---|---|---|---|---|
| *pH* | | | | | |
| Acidic | 92 (82.2) | 20 (17.8) | 1.72 | 0.90-3.29 | 0.140 |
| Alkalin | 75 (72.8) | 28 (27.2) | | | |
| *Consistency* | | | | | |
| Normal watery clear | 97 (75.8) | 31 (24.2) | - | - | - |
| Frothy bubbly | 34 (79.1) | 9 (20.9) | 1.21 | 0.52-2.79 | 0.659 |
| Sticky frothy | 36 (81.8) | 8 (18.2) | 1.44 | 0.61-3.42 | 0.409 |

Values are presented as numbers and percentages (%). ORs: odds ratios, CIs: confidence intervals

**Table 6 -** Secretor status frequency and association with teeth problems history.

| Total teeth score | Secretors | Non-secretors | ORs | 95% CIs | *P*-values |
|---|---|---|---|---|---|
| 0 | 68 (76.4) | 21 (23.6) | - | - | - |
| 1 | 49 (80.3) | 12 (19.7) | 1.26 | 0.57-2.80 | 0.712 |
| 2 | 26 (76.5) | 8 (23.5) | 1.01 | 0.40-2.55 | 0.818 |
| 3 | 11 (78.6) | 3 (21.4) | 1.13 | 0.29-4.44 | 0.871 |
| 4 or more | 13 (76.5) | 4 (23.5) | 1.01 | 0.30-3.41 | 0.760 |

Values are presented as numbers and percentages (%). ORs: odds ratios, CIs: confidence intervals

close to the study carried out on 740 participants from Osogbo, Southwestern Nigeria, where the secretors percentage reached 78.1%.[14] Jaff[15] showed a frequency of secretors 76.1% among people in Kurdistan Region, Iraq. The Lower prevalence reported was 64.4% in Karachi, Pakistan.[16] Meanwhile, the higher prevalence rate reported were 70.3% in Kabul, Afghanistan, 84.9% in Calabar Municipal, Nigeria, and 86.7% in Narketpally, India.[17-19] This wide variation of the secretor trait reported earlier was attributed to different geographic regions, genetics, and racial factors. Secretor people have *Se* (FUT2) gene. Previous findings linking host genetic variation in FUT2 to gut microbial composition, that directly correlated with feeding habits of each population.[20,21] Gut microbiota changes with age, this explains the difference in secretor prevalence among different age groups.[22] Natural selection is another plausible cause of variation in secretor prevalence among different ethnic groups, this was evident in polymorphism of the FUT2 promoter, and loss of function mutation in FUT2 gene that make the individual non-secretor.[20,23]

Out of 140 participant males, 112 (80%) were secretors, and out of 75 participant females, 55 (73.3%) were secretors. Jaff[15] in Iraq showed the same prevalence rate of secretors among males as well as females (76%). Distributions of secretors state within different ABO groups were 72% for A blood group, 71% for B blood group, 46% for AB blood group, and 95% for O blood group. These values are comparable with data obtained by Igbeneghu et al,[14] who report percentages of 72.6% among A blood group, 66.4% Among B blood group, 52.8% among AB blood group, and 86.3% among O blood group. Higher secretion phenotype expression with advanced age suggests the possible age effect on *Se* (FUT2) gene expression. As stated above, this effect may be attributed to gut microbiota composition change which is age-related, further genetic studies focus on the *Se* gene polymorphism and its regulation are needed.[22] Regarding Rh positive, approximately 76% were secretors, and 82% of Rh negative were secretors. Increased number of secretors within Rh negative is consistent with another study that reported secretor percentages for the same groups of 76% and 77%.[15]

Advanced age association with ABH secretion exhibits a gradual non statistically significant OR of increase to reach maximum frequency and statistically significant odds of secretion by 3.34 times at the age group 31-40 years (OR=3.63, 95% CI: [1.09-12.16], $p$=0.032), this association declines with higher age and also with no statistical significance. With a large sample size, this association will be significant. Epigenetic causes may lie behind age change expression of ABH antigens secretion.

Association between ABO blood group phenotypes and the secretor trait exhibited only statistically significant contrary associations with O and AB blood groups. However, the secretion was increased with O blood group phenotype by 7.37 times compared with non-O phenotypes (OR=7.37, 95% CI: [2.53-21.47],

$p$<0.001). In contrast, decreased secretion status was significantly associated with AB phenotype compared with non-AB phenotypes (OR=0.28, 95% CI: [0.12-0.64], $p$=0.004). Regarding association between O blood group and secretor trait, it may be attributed to the high H antigen concentration in O blood group people in comparison with others. The reverse will be correct, the lowest H antigen number on red cells of AB phenotype confirms our suggestion. Molecular analysis for the expression of H (FUS1) gene and FUS2 gene will confirm or exclude that.

ABH secretor status is important for the normal flora growth, which is consequently responsible for the normal functioning of the gastrointestinal tract. It has been found that some bacteria in the gastrointestinal tract produce enzymes that degrade ABH antigens because ABH substances are used for their nutrition. Bacteria capable of degrading B antigen produce enzymes that detach the terminal alpha-D-galactose, meanwhile, that degrade A antigen produce enzymes detach the terminal N-acetylgalactoseamine.[24] Consequently, ABO blood groups and secretor status have some relevance to certain diseases. ABH antigen on the epithelial cells of the intestinal and urogenital tract allows microorganisms adherence and increases the risk of duodenal ulcer, celiac disease, urinary tract infections, and persistent candida infections. In this context, the total scores of teeth problems reported for participants of this study showed no statistically significant association, such association was not our main task in this study, further research specific for this task will elucidate such association. Nevertheless, the results of D'adamo et al's[8] study found decreased secretor prevalence with increased patients oral problems. However, Al-Sihli et al[25] disagreed with this conclusion, where they showed 63.3% secretors and 36.7% non-secretors. This denotes the importance of ABH substances found in saliva for teeth health.[25] In agreement with this result, related work showed that secretion of ABH antigens is risk factor for the progression of periodontal diseases.[26]

***Study limitations.*** The size of the sample in this work was small, but it was compensated by randomization. Another limitation is the lack of advanced molecular techniques in our restricted resources country that can be used for robust analysis.

In conclusion, frequency of ABH secretors was 78.1% among Ibb province population, Yemen. Blood group O has the highest secretor frequency of 95%, while blood group AB has the lowest frequency (54%). More secretion frequency increased to reach maximum at mid-age then declined after that. Correlation studies between ABH secretion and liability to different infections will be established upon further studies.

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